Luc Téot
Thomas A. Mustoe
Esther Middelkoop
Gerd G. Gauglitz
Editors

Textbook on Scar Management

State of the Art Management and Emerging Technologies

G-ScarS
Global Scar Society

Springer

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This book is an open access publication.
ISBN 978-3-030-44765-6 ISBN 978-3-030-44766-3 (eBook)
https://doi.org/10.1007/978-3-030-44766-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The interest in wound healing goes back to the beginning of history and has not diminished throughout the centuries also because practical implications of wound healing studies have remained very relevant for public health. During the last century, much progress has been made in the understanding of basic mechanisms of skin wound healing, and it has been realized that healing processes evolve similarly in various organs. It has been established that fibrotic diseases are regulated by analogous mechanisms, albeit less controlled, compared to those regulating wound healing. Moreover, many advances, such as the use of antiseptics and, later, of antibiotics, as well as the introduction of skin transplants have facilitated the treatment of wounds. It has been shown that wound healing evolution depends on several factors including the type of injury causing the damage, the tissue and/or organ affected, and the genetic or epigenetic background of the patient.

This Compendium has the merit of discussing a broad spectrum of topics, including the general biology of wound healing, modern diagnostic approaches, and therapeutic tools, applied to many different clinical situations. It should be of interest to teachers, students, and clinicians working in different aspects of wound healing biology and pathology. I am sure that it will rapidly become an important reference book in these fields.

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Preface

Scars represent the indelible cutaneous signature of aggression, surgery, traumas, and other events occurring during life. Most of them cause no problem, but some of them become sources of social exclusion, especially in a world where beauty is glorified. The psychosocial aspects surrounding culture, religion, and uses may be determinant. Even a transient redness may become source of suffering. Paradoxically, major keloids or massive contractures cause definitive loss of function or social problems leading to exclusion in developing countries, whereas simultaneously, we assist a rapid extension of laser technology indications for minor scar problems in the same countries. When we founded the Scar Club in 2006 together with Prof. Tom Mustoe, the aim was and still is the diffusion of knowledge and the development of all types of mechanical devices and antiscarring drugs.

Important financial support for researches in the field of growth factors and antiscarring agents was recruited, aiming at controlling cell proliferation and secretion using chemical compounds, but the results were modest. Mechanical control of keloids or hypertrophic scars is proposed and reimbursed in some countries, applying medical devices capable to exert forces over the suture during the post-operative period or over post-burn scars.

This small group formed the Scar Club, composed of passionate colleagues who attracted surgeons and dermatologists, researchers, and physiotherapists, becoming an upmost scientific biannual rendezvous attracting colleagues from all over the world. The Scar Club group is built like a club, focusing on researches, new organizations and collaborations, new strategies, and development of guidelines.

The need for a larger educational initiative appeared since 2015 and the GScarS was founded in 2016. In October 2018, the first GScarS meeting was held in Shanghai with a successful event, grouping more than 600 colleagues. The idea came from the Board to provide an educational book free of charge, open source, and downloadable from anywhere. Patients and caregivers suffer most of the time from an insufficient professional training, and scar science is poorly represented in teaching courses at universities. Most of the proposed treatments are still based on cultural or anecdotal medicine. It is time to propose a structuration of the scar knowledge based on evidence-based medicine, consensus, guidelines, and key opinion leaders' expertise.

This Compendium on scar management proposes a synthesis of the basic principles in scar management, including the large armamentarium of medical devices having proven efficacy and considered as the standards of care, and also the most recent techniques accessible in scar management, provided by the most prominent specialists coming from all over the world. It will be completed by a series of illustrations, schematic strategies, and clinical cases accessible on the Springer website.

Luc Téot
Montpellier, France

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Biology and Scar Formation

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Fetal Wound Healing

Magda M. W. Ulrich

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_1

1

1.1 Background

Wound healing is a complex and tightly regulated process and can be divided in three different overlapping phases: the inflammatory phase, the proliferation phase, and the remodeling phase. The first phase begins directly after wounding and is characterized by hemostasis and inflammation. Platelets play an important role in the formation of the blood clot to stop the bleeding, and through the secretion of chemokines, they recruit different inflammatory cells such as neutrophils and monocytes to the wound. The inflammatory cells clean the wound by phagocytosis of invading microorganisms and damaged tissue. The inflammatory cells also secrete chemotactic signals which attract fibroblasts and endothelial cells to the wound which, together with the inflammatory cells, form the granulation tissue. This is the proliferation phase during which the destroyed tissue is replaced. During this phase, the keratinocytes migrate over the granulation tissue to form a new epidermis to close the skin defect.

The last phase in wound healing is the remodeling phase which is characterized by a decrease in cellularity and vascularity by apoptosis and an increase of synthesis and deposition of the components of the extracellular matrix (ECM). In adults, this process results is scar formation, whereas in fetal skin, complete regeneration of the skin, including the formation of skin appendices such as hairs and sebaceous and sweat glands, takes place.

Since the 1950, studies on scarless healing in fetal skin in animals have been published, and in the late 1970s of the last century, the first publications appeared describing scarless healing of fetal skin wounds in humans. Since then, several experimental studies on this subject have been published. From experimental animal and human studies it is known that scarless healing only occurs during the first period of gestation. Human fetuses lose the ability of skin regeneration around 22 weeks of gestation.

Animal experiments in which adult, late gestational, and early gestational fetal skin were transplanted on early gestational fetuses showed clear differences in wound healing outcome. Incision wounds created in these transplants showed scar formation in adult and late gestational fetal skin, whereas the wound created in the fetal skin resulted in complete regeneration [1]. These experiments show not only that this phenomenon is an intrinsic property of the fetal skin itself but also that scarless healing is not triggered by the intrauterine environment. Interestingly, the wounds at the fetal-adult interface also healed without scar formation implicating that direct contact of a wound with fetal skin is sufficient to induce regeneration of the tissue [2].

Several mechanisms have been suggested to be responsible for the scarless healing in fetal skin, e.g., a diminished inflammatory reaction, differences in composition and architecture of the extracellular matrix, and mechanical load in fetal skin. Furthermore, fetal skin differs from adult skin in many factors commonly associated with scar formation such as proteolytic activity and TGF-β secretion and sensitivity. This chapter will discuss the different mechanisms during the three phases of wound healing proposed in the literature to be involved in scarless healing.

1.2 Inflammation

Several studies have shown that the inflammatory response to injury is strongly reduced in fetal skin wounds, and induction of the local inflammation causes scar formation in early fetal skin.

The inflammatory reaction involves recruitment of inflammatory cells which produce inflammatory mediators such as growth factors and cytokines. The growth factors and cytokines subsequently recruit more inflammatory cells.

Inflammation in adult wound healing starts off with a pro-inflammatory cytokine and immune cell response and the activation of the acute phase response. During this period, invading microorganisms and injured tissue are cleared from the wound bed. Subsequently, the inflammatory reaction is skewed to an anti-inflammatory profile which initiates the healing response. Although the exact role of inflammatory cells in scar formation is not entirely elucidated, it is evident that they play an important role in the derailed wound healing process leading to scar formation. It was shown that in severely scarred wounds such as burn wounds, the acute (pro-) inflammatory status is continued for a very long time.

Cells involved in the pro-inflammatory reaction are neutrophils and the M1 subtype macrophages, while macrophages of the M2 subtypes and regulatory T cells are anti-inflammatory, pro-healing cells.

Platelets are the first cells involved in the induction of the inflammatory reaction. The platelets are activated and aggregate during the coagulation phase forming the hemostatic plug. The activated platelets release cytokines such as platelet-derived growth factor (PDGF), interleukins (IL) 1 and 6, and transforming growth factor beta (TGF-β) into the wound environment. It was shown that fetal platelets aggregate poorly when exposed to higher levels of hyaluronic acid, a component of the extracellular matrix, which is more abundantly expressed in fetal skin than in adult skin, and subsequently release lower levels of platelet-derived cytokines.

The lower platelet-derived cytokines are most likely responsible for the reduced inflammatory cell infiltration, such as neutrophils, macrophages, and lymphocytes, seen in fetal wounds at early gestational age [3].

Not only recruitment of inflammatory cells from the circulation to the fetal wound is reduced, but also the number of resident macrophages, mast cells, Langerhans cells, dendritic cells and T cells in uninjured fetal skin is reduced. Moreover, the immune cells present in the fetal skin have the anti-inflammatory, pro-healing phenotype as fetal skin contains higher numbers of regulatory T cells and macrophages of the M2 phenotype. In addition, chemoattractant cytokines such as CCL17, CCL21, and CCL27 involved in recruitment of T cells and dendritic cells are reduced in fetal skin [4].

Although the inflammatory growth factor TGF-β plays an important role in scar formation, it is also involved in the resolution of the inflammatory reaction. In fetal skin, high levels of all the components of the TGF-β pathway are present, and moreover, the pathway seems to be highly activated. This highly activated TGF-β pathway might also result in fast suppression of the pro-inflammatory reaction in fetal wounds [4].

These findings indicate that indeed the (pro-)inflammatory immune reactions is reduced in fetal wound healing. However, the inflammatory component cannot be the key link to scarless healing since wounding of transplanted adult sheep skin to a sheep fetus resulted in scar formation despite the diminished inflammatory state of the fetus itself and the intrauterine environment.

1.3 Extracellular Matrix

The extracellular matrix of fetal skin is distinctly different than adult skin matrix. Early gestational fetal skin contains higher amounts of collagen type III, fibronectin EIIIA, and hyaluronic acid (HA) and is deficient in elastin. Similar expression profiles for ECM components were demonstrated for the (adult) oral mucosa, a tissue also known for reduced scar formation.

Although collagen type I is the major component in both adult and fetal skin, in fetal skin, collagen type III/collagen type I ratio is higher compared to adult skin. The higher levels of collagen type III have effects on the ECM organization and collagen fiber diameter. Downregulation of collagen type III expression results in increased scar formation and differentiation of fibroblasts into myofibroblasts, the main cell type involved in scar formation [5].

The properties of the ECM network do not depend only on the presence and percentage of the different collagen subtypes and other ECM components but also on cross-linking of the ECM components. Increased cross-linking results in ECM accumulation and increased rigidity. In fetal skin, most of the collagen fibers are not cross-linked [5]. One of the enzymes involved in collagen and elastin cross-linking is lysyl oxidase (LOX). Early gestational fetal wounds show reduced LOX expression in comparison to late gestational wounds.

Other important components of the ECM which are differentially expressed between fetal and adult skin are glycosaminoglycans (GAGs) and proteoglycans. The GAGs like hyaluronic acid (HA) contain long polysaccharide chains which can absorb large amounts of water and are important for hydration of the skin and determine the viscoelasticity of the skin. HA is thought to play an important role in regulation of the inflammatory reaction during wound healing. However, its effect is dependent on the length of the polysaccharides. High-molecular-weight (HMW) HA suppresses the inflammatory reaction, while low-molecular-weight (LMW) HA fragments are immunostimulatory and induce the inflammatory reaction [6].

Expression of HA in fetal skin is high and during wound healing the expression is induced in adults. The positive effect in fetal wound healing might be related to the balance between HMW and LMW HA, which may be caused by differential expression of enzymes synthesizing HA (hyaluronan synthases) and enzymes degrading HA (hyaluronidases) between adult and fetal tissue. It was shown that addition of hyaluronidases to fetal wounds can induce fibroplasia, collagen deposition, and neovascularization, processes involved in scar formation.

Besides the abovementioned component, elastin is also an important component of the ECM. This protein is responsible for connective tissue pliability in the adult dermis; however, it is absent in early gestational skin, and its role in scarless wound healing is not clear [7] (Fig. 1.1).

1.4 Angiogenesis

Several studies have shown that reduced angiogenesis during adult wound healing reduces scar formation. However, indisputable evidence that this also plays a role during fetal wound healing has not been provided although several studies suggested lack of strong neovascularization and reduced proangiogenic factors in fetal wounds.

Angiogenesis is much more prominent in adult wound healing compared to fetal wound healing. Early in adult wound healing, a dense capillary bed is created. However, this capillary tangle lacks the assembly of a functional network which is able to provide nutrition and oxygen to the wound bed [8].

It was shown that HA degradation products induce angiogenesis; therefore, the reduced synthesis of hyaluronidases not only has a positive effect on suppression of the inflammatory reaction but also reduces the exaggerated neovascularization seen in adult wounds.

However, this could also be attributed to reduced levels of angiogenic growth factors such as basic fibroblast growth factor and PDGF. Addition of angiogenic factors such as hyaluronidase and PDGF to fetal wounds was shown to induce angiogenesis and lead to scar formation.

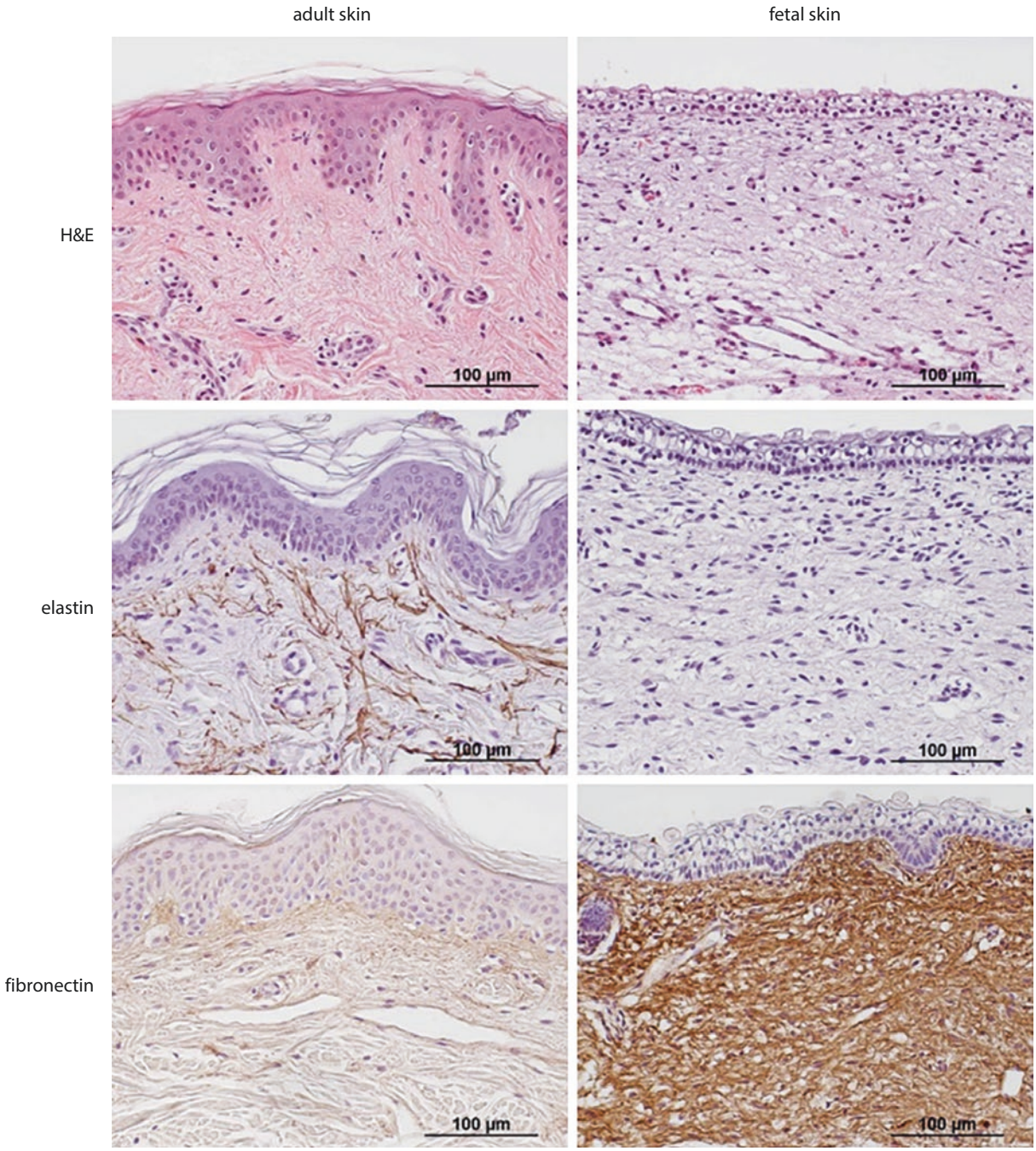

Fig. 1.1 Expression of different ECM components in adult and fetal skin. The specific ECM components are stained in brown

1.5 Keratinocytes

One of the factors thought to play a role in scar formation is delayed wound closure by reepithelialization. Wound closure in fetal wounds is much faster in comparison to adult wounds.

Fetal keratinocytes not only have a higher proliferation rate; also the mechanism of reepithelialization was found to be distinctly different between adult and fetal wounds. In adult wound healing reepithelialization, the basal keratinocytes at the wound edge undergo morphological changes. They form actin containing cytoplasmic elongations called lamellipodia through which they crawl over the extracellular matrix of the wound bed. To be able to migrate, the cells lose their ECM binding structures (hemidesmosomes) and the cell-cell binding sites (desmosomes). Fetal keratinocytes do not form lamellipodia but form an actin myosin II containing

cables through the front keratinocytes at the wound edge [9]. This cable runs from cell to cell most likely through the adherens junctions, another form of cell-cell junction similar to the desmosome. The cable is formed within hours after wounding and by contraction pulls the keratinocytes together to close the wound.

Integrins may also play a role in faster reepithelialization in fetal wound healing. Integrins are heterodimeric transmembrane receptors which can bind to specific ECM components. Different combinations of the subunit determine the specificity for the different ECM components, and they determine cellular processes like cell proliferation and migration. In the fetus, it was shown that specific integrins were rapidly upregulated upon wounding and that this occurred much faster than in adult keratinocytes.

It is evident that there is an interaction between keratinocytes and fibroblasts in the dermis. In vitro experiments have shown that fetal keratinocytes suppress proliferation, myofibroblast differentiation, and ECM production, in fibroblasts derived from hypertrophic scar, whereas fetal keratinocytes promote proliferation and migration in fetal and adult healthy skin-derived fibroblasts.

1.6 Fibroblasts

Fibroblasts are the main cell type of the dermis; they produce the ECM and therefore play an important role in wound healing and scar formation. During wound healing, this cell type differentiates into myofibroblasts. These latter cells produce high levels of ECM components and contain the contractile protein alpha smooth muscle actin (αSMA) which is involved in tissue contraction seen in scar formation. The transition to a myofibroblast population in the wound healing environment and especially the persistence of this cell population are seen as the most important contributor to scar formation. Transforming growth factor beta (TGF-β) plays an important role in this process. However, TGF-β also plays an important role during embryonic and fetal development and thus is abundantly present in the fetus. TGF-β is stored as an inactive compound in the ECM. In order to execute its role in the many processes this growth factor is involved in, it has to be activated which ultimately leads to the induction of various genes including genes involved in fibrosis and the process of scar formation. It was shown that all of the components are abundantly present in the fetal skin. In addition, the TGF-β pathway was also shown to be highly activated in healthy fetal skin in comparison to adult skin, but this does not result in fibrotic skin or scar formation. It was suggested that differential expression in TGF-β isoforms plays a crucial role in this. TGF-β1 and TGF-β2 are thought to be profibrotic, whereas TGF-β3 has antifibrotic properties. However, this segmentation is not completely indisputable. The balance between the profibrotic and antifibrotic TGF-β isoforms in fetal skin is shifted in comparison to adult skin: 99.5%:0.5% in adult to 97.4%:2.6% in fetal skin. However, the absolute concentrations of all TGF-β isoforms are much higher in fetal skin in comparison to adult skin.

Several differences were observed between fetal skin fibroblasts and adult dermal fibroblasts: The fetal cells migrated much faster than adult fibroblasts and exhibited a "hyperactive morphology." They produced higher amounts of extracellular matrix components. Furthermore, fetal cells produced a larger contraction effect when cultured in fibroblast-populated collagen lattices compared to adult fibroblasts.

As in fetal keratinocytes, it was shown that fetal fibroblasts express different integrins which results in higher proliferation and migration rates. Inhibition of one of the specific fetal integrins resulted in a more adultlike fibroblast phenotype.

Stimulation of fetal fibroblasts in vitro also induced myofibroblast differentiation and shows higher contraction of fibroblast-seeded collagen matrices [4].

Studies in which fetal skin cells have been applied to burn wounds show improved wound healing. Since it was shown that the fetal cells were not incorporated into the newly formed skin, it is thought that the cells secrete growth factors or in any other form interact with the host organism to accelerate wound healing.

1.7 Mechanical Forces

Mechanical forces, extracellular as well as intracellular, play an important role in skin homeostasis as it directs cell function and activity through a process called mechanotransduction. In this process, the composition, viscoelasticity, and stiffness of the ECM play an important role. Adult skin contains thick collagen bundles mainly consisting of type I fibrils, whereas fetal skin contains thin collagen fibers which are high in collagen type III fibrils and show reduced resting stress.

Through adhesion molecules on the surface of the skin, the integrins, the ECM is connected to the cytoskeleton of the cell. The link between the ECM and the cytoskeleton is a dynamic complex, called focal adhesions (FA), which are constantly assembled and disassembled. The FA are able to direct not only cell function such as gene expression but also cellular adhesion and cell migration. Fibroblasts exposed to mechanical stress form supermature FA displaying a specific composition of FA proteins such as paxilin (Pax). Fetal fibroblasts

were shown to have reduced FA protein expression among which Pax and different integrin subunits [4].

Also from clinical data, there is evidence that mechanical stress plays an important role in scar formation. Collagen fibers in the ECM of the skin are aligned in a specific pattern depending on the location of the body. This pattern forms the so-called Langer lines and determines the direction of the tension in the skin. From surgery, it is known that incisions made parallel to these lines heal with less scar formation than incisions perpendicular to the Langer lines, suggesting that mechanical load to the wound influences scar formation [10]. In fetal skin, the ECM is organized in a loose reticular network of collagen, while in adult skin, there are thicker more compact collagen fibers. In fetal wound healing, the same reticular ECM network is formed indistinguishable from the unaffected surrounding, whereas in adult wound healing, the collagen fibers are arranged in dense parallel bundles [11].

1.8 Remodeling

The last phase in wound healing is the remodeling phase. During this phase, cellularity decreases by apoptosis, and the degradation of the excessive extracellular matrix takes place. In adult wound healing, the predominant type III collagen is replaced by type I collagen. However, in fetal recovered skin, type III collagen remains the main subtype.

The deposition of extracellular matrix is an interplay between synthesis and degradation of the components of the ECM. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) play an important role in this process. The MMP family consists of more than 20 members which are able to degrade most of the components of the ECM with different specific activities toward the different components. The process of ECM degradation is controlled by specific tissue inhibitors of metalloproteinases (TIMPs). Currently, four TIMPs have been identified which possess varying affinity to specific MMPs. An imbalance between MMPs and TIMPs affects the deposition of ECM. In scarring, reduced collagen degradation as a result of reduced MMP expression and increased TIMP expression causes accumulation of ECM components. Early gestational fetal skin and middle gestational fetal skin express lower MMP and TIMP levels than late gestational skin and adult skin. During fetal wound healing, several MMPs were increased in early gestational fetal wounds, whereas later during gestation, when wounds heal with scar formation, MMP levels were reduced, and TIMP levels were increased [12]. This later finding may explain the accumulation of ECM seen in scar formation.

1.9 Skin Appendix Formation

Early gestational wound healing results not only in restoration of the dermis and epidermis but also in the regeneration of skin appendages such as hair follicles and sebaceous and sweat glands.

Hair follicles contain several stem cell niches and play an important role in adult wound healing. In partial-thickness wounds in which part of the hair follicle is still intact, healing can occur without scar formation.

Hair follicle development during embryogenesis starts, depending on the anatomical location, between weeks 9 and 15. One could envision that early gestational skin contains stem cells and still has the mechanisms available to induce skin appendage development and create the stem niches but that these stem cells can also regenerate the skin. It was shown that allogeneic cells derived from fetal skin could enhance burn wound healing and reduce scar formation.

1.10 Conclusions

The fact that adult skin in an intrauterine environment still heal with scar formation despite the low inflammatory milieu, the presence of fetal growth factors, and even fetal cells able to migrate into the adult tissue shows that the processes leading to scarless healing or scar formation cannot be attributed to single individual mechanisms, cells, or other factors but that it is a result of complex of interconnected processes.

Take-Home Messages

- Early to midgestational skin wounds result in skin regeneration instead of scar formation.
- The exact mechanism behind scarless healing is still unknown.
- Several mechanisms have been indicated: reduced inflammation, altered cytokine profile, and different ECM composition.
- The process of scarless healing is a result of a complex of interconnected processes.
- Several characteristics of fetal skin are shared with oral mucosa which is also known for its reduced scar formation.

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Mechanobiology of Cutaneous Scarring

Rei Ogawa

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2

2.1 Background

The last phase of cutaneous wound healing produces the scar. Scars mainly consist of dermal-like collagens that are covered by the epidermis. The early stage of scarring is marked by inflammation, whose purpose is to close the wound gap. The source of the inflammation in the wound is the blood vessels, which exhibit vascular permeability after wounding. This allows the influx of inflammatory soluble factors and many types of immune cells from the circulation into the wound bed. Moreover, in the early stages of wound healing, resident cells, including collagen-secreting fibroblasts, accumulate in the damaged area. Finally, collagens, blood vessels, and nerve fibers are produced, resulting in an immature scar that is red, elevated, hard, and painful.

2.2 Role of Mechanobiology in Cutaneous Scarring

Under normal circumstances, the immature scar then undergoes the scar maturation process over several months. This process involves tissue remodeling, which associates with a natural decrease in the inflammation and the numbers of blood vessels, collagen fibers, and fibroblasts. However, sometimes the scar maturation process is not properly engaged because inflammation continues in the scar. Consequently, the immature scar stage is prolonged. This results in the pathological scars called hypertrophic scars and keloids. Many factors that prolong the inflammatory stage have been identified [1]. However, multiple lines of evidence acquired in recent years suggest that mechanical force can be an important cause of pathological scar development (some of these lines of evidence will be described in more detail below) [2]. This notion is also supported by the empirically acquired clinical understanding that noticeable scarring can be prevented by stabilizing surgical wounds with sutures and postsurgical dressings: the sutures help to approximate the wound edges with a small amount of intrinsic tension, while the dressings suppress the extrinsic mechanical forces on the wound/scar edges [3]. When the mechanical forces on and in the scar are imbalanced, a heavy scar can result.

2.3 Cellular and Tissue Responses to Mechanical Forces

The mechanical forces on scars/wounds include stretching tension, shear force, scratch, compression, hydrostatic pressure, and osmotic pressure. These forces are perceived by mechanosensors on and in the cells that reside in the extracellular matrix as well as by nerve fiber mechanoreceptors at the tissue level [4, 5].

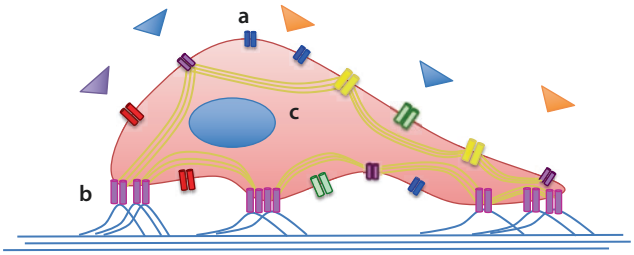


Fig. 2.1 Schematic depiction of the mechanosensors that allow cells to sense extrinsic mechanical forces. (**A**) Mechanosensitive ATP hemichannels and Ca^{2+} ion channels. (**B**) Mechanosensitive molecules on the cell membrane, including cell adhesion molecules. (**C**) Cytoskeletal elements, including the actin filaments. When the extracellular matrix is distorted by mechanical forces such as skin tension (purple, blue, and orange triangles indicate different mechanical forces), mechanosensors on and in the resident cells sense the forces and initiate mechanosignaling pathways that lead to a large variety of molecular biological changes, including gene expression. The mechanosensors include mechanosensitive cell membrane molecules such as ATP hemichannels and Ca^{2+} ion channels (**A**, blue, red, and green cylinder pairs). Others are cell adhesion molecules such as integrin (**B**, purple cylinder pairs). Cytoskeletal elements such as the actin filaments (**C**, the beige ropelike bundles within the cell) also play an important role in sensing and responding to extrinsic mechanical forces

The cellular mechanosensors include mechanosensitive cell membrane molecules such as ATP hemichannels, Ca^{2+} ion channels, and cell adhesion molecules such as integrin (Fig. 2.1). Cytoskeletal components such as actin filaments also sense mechanical force: when they do, actin polymerization and depolymerization occur [6]. Thus, when the extracellular matrix is distorted by mechanical forces such as skin tension, the cellular mechanosensors are triggered and initiate mechanosignaling pathways that lead to a variety of molecular biological changes [7], including gene expression, cell proliferation, angiogenesis, and epithelialization. The key mechanosignaling pathways [8] that are involved in scarring at the cellular level appear to be the integrin, MAPK/G protein, TNF-α/NF-κB, Wnt/β-catenin, interleukin, calcium ion, TGFβ/Smad, and FAK signaling pathways [9] (Fig. 2.2).

At the tissue level, sensory nerve fibers, namely, mechanosensitive nociceptors, in the skin act as mechanoreceptors and thereby produce the somatic sensation of mechanical force [5]. Thus, when mechanical stimuli are received by mechanosensitive nociceptors somewhere on the body, electrical signals are transmitted to the dorsal root ganglia, which contain the neuronal cell bodies of the afferent spinal nerves (Fig. 2.3). This causes the peripheral terminals of the primary afferent

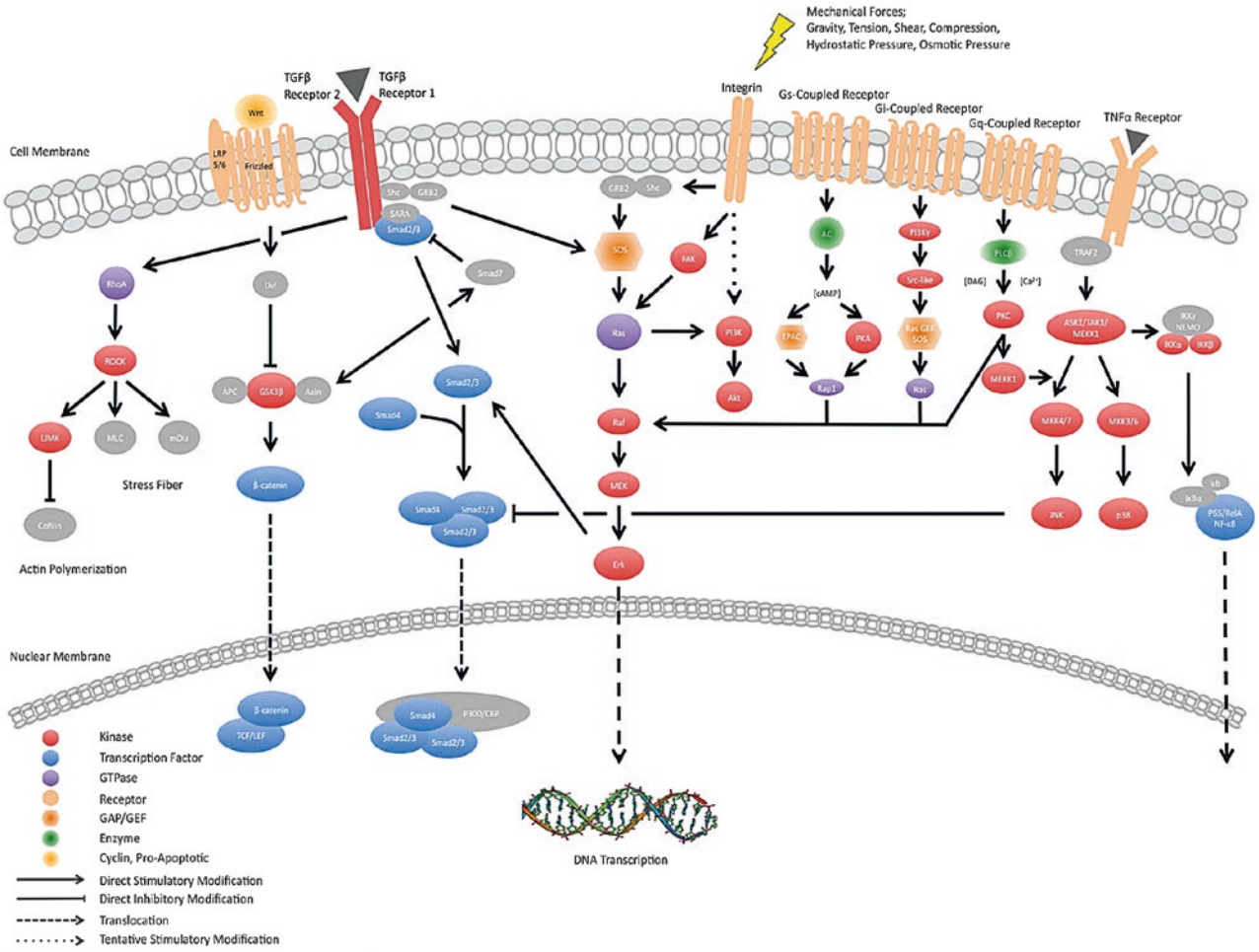


Fig. 2.2 Mechanosignaling pathways in cells subjected to mechanical forces. When the mechanosensors in or on the cells are triggered, they activate various mechanosignaling pathways that then regulate cell proliferation, angiogenesis, and epithelialization. (This figure is from reference [8] with copyright permission from the publisher. © All rights reserved)

sensory neurons that innervate the skin to release neuropeptides, including substance P, calcitonin gene-based peptide (CGRP), neurokinin A, vasoactive intestinal peptide, and somatostatin. Since the peripheral terminals of the neuropeptide-releasing neurons are often in physical contact with cells in the wound/scar, the neuropeptides can directly target keratinocytes, fibroblasts, Langerhans, mast, dermal microvascular endothelium, and infiltrating immune cells. This can alter cell proliferation, cytokine production, antigen presentation, sensory neurotransmission, mast cell degradation, and vasodilation. The triggering of mechanonociceptors is particularly known to increase vascular permeability under both physiological and pathophysiological conditions. All of these pro-inflammatory responses produce what is termed neurogenic inflammation [4, 5]. Notably, substance P and CGRP, which, respectively, act through the neurokinin 1 receptor and CGRP1 receptor, are synthesized during nerve growth factor regulation. It has been suggested that neurogenic inflammation/neuropeptide activity plays a role in the development of burn and abnormal scars such as keloids and hypertrophic scars [10].

2.4 Role of Mechanobiology in the Development of Pathological Scars

Traditionally, hypertrophic scars and keloids are diagnosed as separate clinical and pathological entities, even though both are characterized by prolonged and aberrant extracellular matrix accumulation. The so-called typical keloids grow beyond the confines of their original wounds and exhibit accumulation of dermal thick eosinophilic collagen bundles with dermal nodules under the microscope. By contrast, hypertrophic scars generally grow within the boundaries of wounds and are characterized histologically by dermal nodules alone.

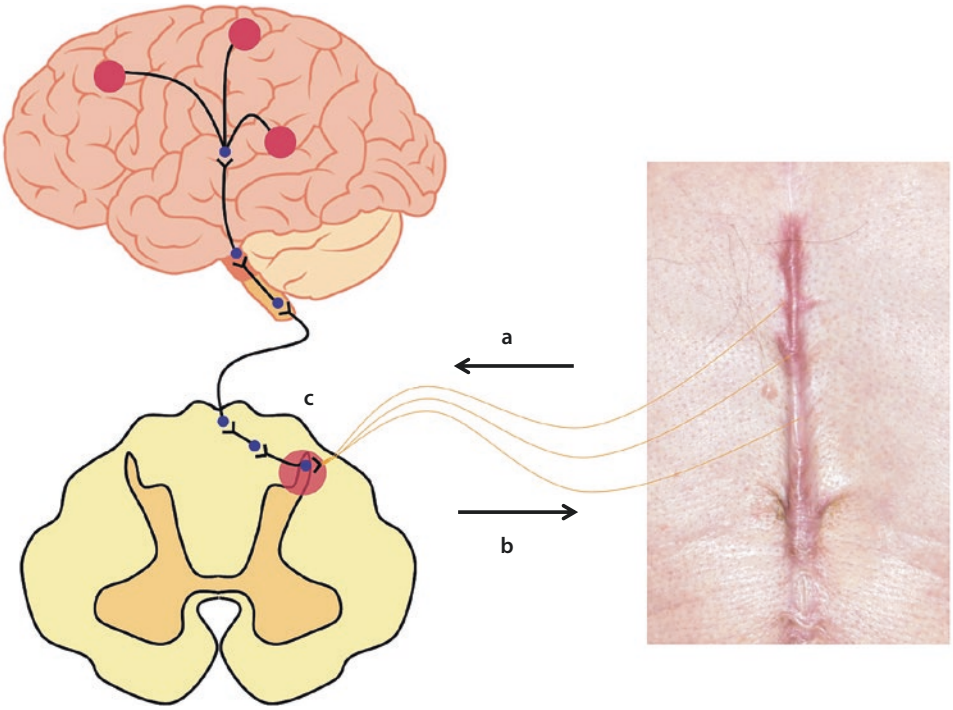


Fig. 2.3 Mechanosensitive nociceptors shape somatic sensations and tissue responses to mechanical forces. Tissues such as skin respond to external mechanical forces such as tension via mechanosensitive nociceptors, whose neuronal cell bodies are located in the dorsal root ganglia in the spinal cord **c**. Thus, when a mechanical force is placed on a scar, the mechanosensitive nociceptors in and around the scar convert the mechanical stimuli into electrical signals that travel to the dorsal root ganglia in the spinal cord and then to the brain **a**. This produces the somatic sensations to the mechanical force (e.g., pain and/or itch). Simultaneously, electrical signals return from the dorsal root ganglia to the skin mechanosensitive nociceptors **b**. This causes them to release neuropeptides from their peripheral terminals. Since these terminals are often in physical contact with cells in the scar, including epidermal and dermal cells, the neuropeptides can induce neurogenic inflammation, thereby promoting pathological scar formation and progression

One of the reasons why hypertrophic scars and keloids are considered to be separate clinical and pathological entities is that keloids are relatively rare in the Caucasian population, which may have limited clinical experience with these scars. However, even senior clinicians sometimes have difficulty in differentiating between the two conditions, particularly with the so-called atypical cases that bear characteristics of both scar types. This is particularly true in Asian countries, where keloids are very common. We currently believe that hypertrophic scars and keloids represent successive stages or alternative forms of the same underlying fibroproliferative pathological lesion and that their progression or development into one or the other classical form may be determined by a variety of pro-inflammatory risk factors (Fig. 2.4) [11, 12]. One of these is mechanical forces. The importance of this factor in pathological scarring is supported by a number of observations, including the fact that hypertrophic scars can be generated in experimental animal models by mechanical forces [13]. Moreover, an analysis of Asian patients showed that keloids tend to occur at specific sites (the anterior chest, shoulder, scapular, and lower abdomen-suprapubic regions) that are constantly or frequently subjected to mechanical forces, including skin stretching due to daily body movements [14]. Thus, the anterior chest skin is regularly stretched horizontally by the upper limb movements, the shoulder and scapula skin is constantly stretched by upper limb movements and body bending motions, and the lower abdomen and suprapubic skin regions are stretched hundreds of time a day by sitting and standing motions. Conversely, heavy scars rarely develop on the scalp, upper eyelid, and anterior lower leg, even in patients with extensive keloids or hypertrophic scars that cover much of the body. This pattern is likely to reflect the absence of tension on the skin in these regions. Thus, even in cases of deep wounding on the scalp and anterior lower leg, there is little tension on the wound because the skin on these regions is stabilized by the bones that lie directly below it. Moreover, there is little tension on the upper eyelid during the opening and closing of the eyes.

Another key piece of evidence that indicates the importance of mechanical forces in pathological scar formation and progression is the fact that keloids grow horizontally in the direction(s) of the predominant

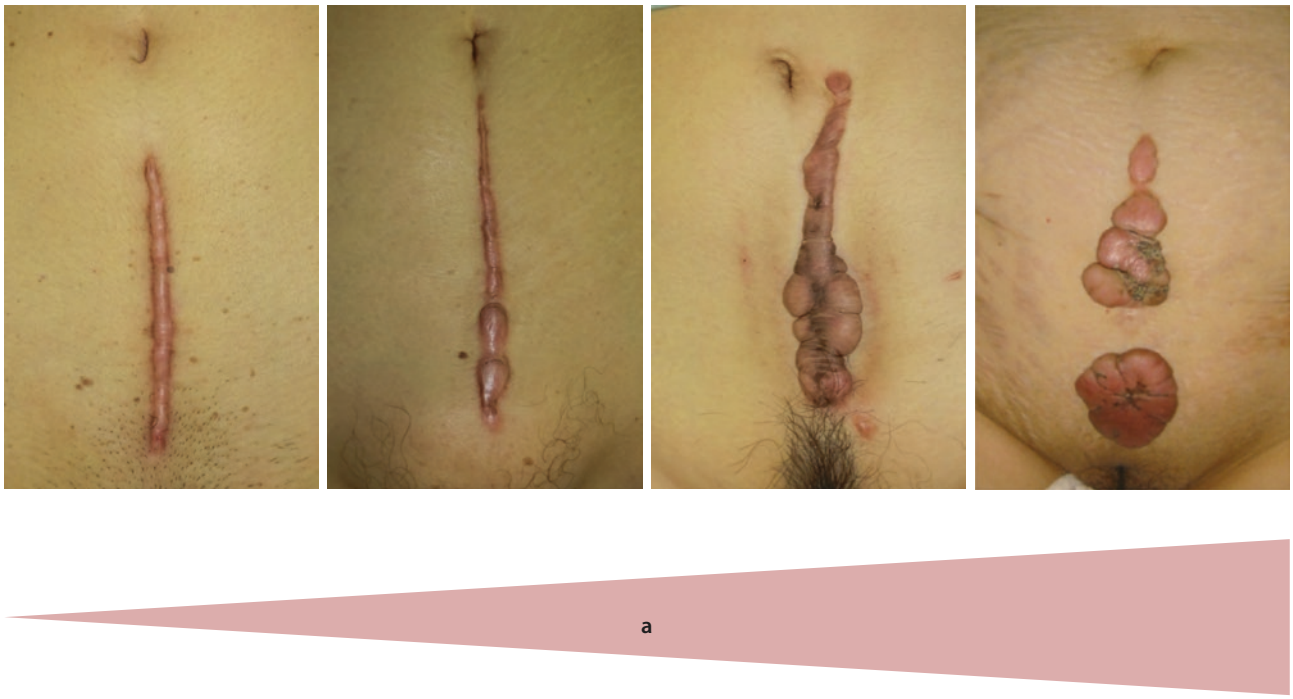
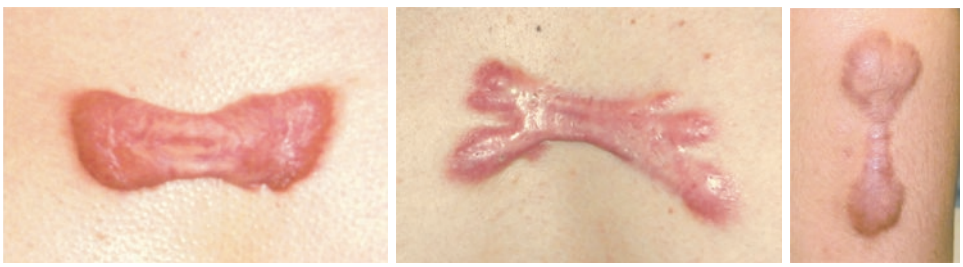


Fig. 2.4 Difference between hypertrophic scars and keloids. The main difference between keloids and hypertrophic scars is that keloids have stronger and more prolonged inflammation. **a** depicts the strength and/or duration of inflammation

Fig. 2.5 Typical shape of keloids on specific regions of the body. **a** The "butterfly" shape on the anterior chest. **b** The "crab's claw" shape on the anterior chest. **c** The "dumbbell" shape on the upper arm. These site-specific keloid shapes reflect the predominant directions of skin tension in these sites



forces on the wound/scar. This results in characteristic keloid shapes on specific locations. For example, keloids on the anterior chest grow in a "crab's claw" or "butterfly" shape, whereas upper arm keloids grow in a "dumbbell"-like shape along the long axis of the limb (Fig. 2.5).

Keloids exhibit stronger and more prolonged inflammation than hypertrophic scars. This together with all of the mechanobiological observations described above suggests that keloid and hypertrophic scars largely differ because of the degree of skin tension on the wound/scar, which in turn determines the degree of inflammation (Fig. 2.4). Thus, pronounced and highly repetitive skin tension on the wound may lead to greater inflammation and keloid formation, while less strong or different mechanical forces lead to a weaker or qualitatively different inflammation that leads to hypertrophic scar formation. This is supported by our previous finite element analysis of the mechanical force distribution around keloids [15], which showed that both the skin tension on the keloid and the inflammation within the keloid are particularly high at the leading keloid edges (Fig. 2.6). Thus, the mechanical forces coming from the predominant direction(s) drive high inflammation at the leading keloid edges: this provokes local collagen production, which in turn causes the keloid to invade further in the direction of the skin tension.

It should be noted, however, it is highly likely that the inflammatory status in heavy scars is also shaped by many other risk factors, including local, genetic, and systemic factors such as hypertension (high blood pressure) [16].

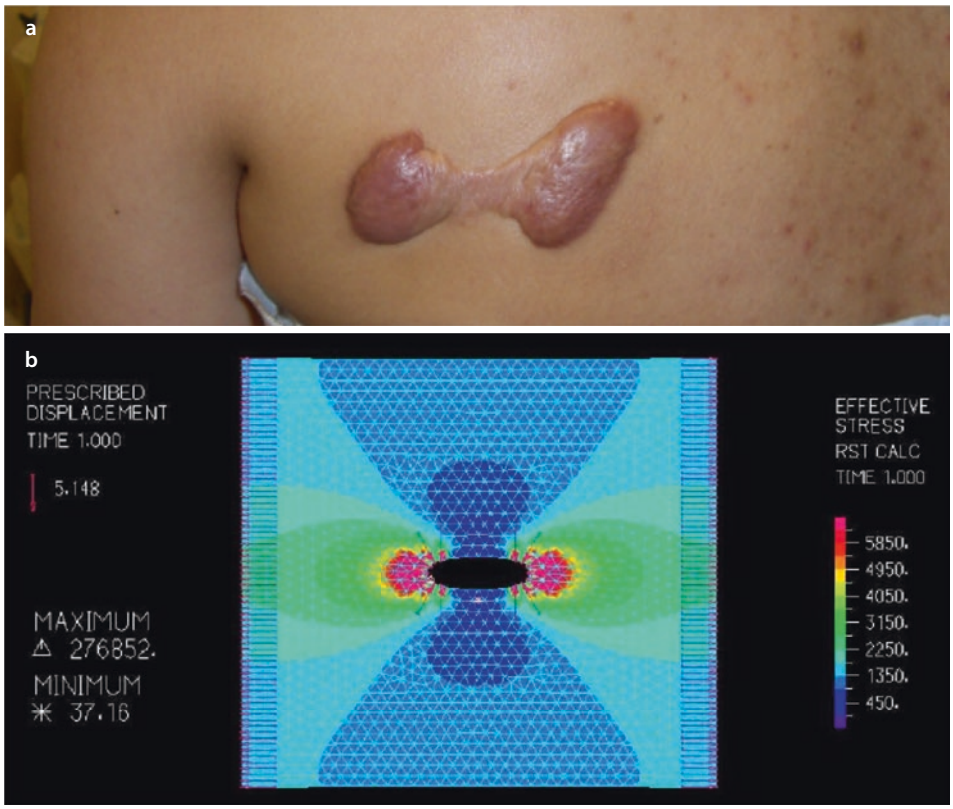


Fig. 2.6 Distribution of the mechanical forces around keloids. **a** A scapular keloid. **b** Finite element analysis of the mechanical force on the scapular keloid. The inflamed and elevated portions of the keloid **a** match with the areas of high tension in the keloid (red color in **b**). This suggests that high skin tension prolongs and amplifies the inflammation in the periphery of keloids. (The figure is from reference [15] with copyright permission from the publisher. © All rights reserved)

2.5 A Pathological Scar Animal Model that Is Based on Mechanotransduction

Many researchers have sought to develop animal models of heavy scars by using mice, rats, and rabbits. It should be noted that the scars of all of these models, especially the keloid models, seem to be driven more by an acute inflammatory response than by chronic inflammation: consequently, the resulting scars are largely immature. Nevertheless, an interesting model is the hypertrophic scar mouse model in which heavy scars are induced by placing a mechanical force on the edges of a cutaneous incision. Analysis of this model shows that when scars are subjected to tension, they exhibit less apoptosis and that inflammatory cells and mechanical forces promote fibrosis [13]. In addition, studies with this model show that during pathological scar development, cellular mechanosignaling pathways interact actively with the extracellular matrix and crosstalk extensively with the hypoxia, inflammation, and angiogenesis pathways.

2.6 Mechanotherapy for Scar Prevention and Treatment

2.6.1 Stabilization Materials

To limit skin stretching and external mechanical stimuli during wound healing/scarring, wounds and scars should be covered by fixable materials such as tape, bandages, garments, and silicone gel sheets. Several randomized controlled trials have shown that such wound stabilization reduces the incidence of hypertrophic scars or keloids. Our computer analysis of the mechanical forces around scars also showed that silicone gel sheeting reduces the tension at the scar edges [17].

2.6.2 Sutures

The fact that mechanical tension promotes keloid and hypertrophic scar development together with the fact that these scars arise from the dermis (especially the reticular dermis) suggests that closing surgical

wounds with sutures that place little tension on the wound dermis may reduce the risk of pathological scar formation after surgery. Therefore, we use subcutaneous/fascial tensile reduction sutures that place the tension on the deep fascia and superficial fascia layer rather than the dermis (see ▶ Chap. 21). This minimizes the use of dermal sutures; in fact, dermal sutures can be avoided altogether if the wound edges approximate each other closely after the fascial sutures are placed.

2.6.3 Z-Plasty, Skin Grafting, and Local Flaps

In scar revision surgery, it is important to choose the surgical approach that most effectively reduces tension on the scar. An excellent choice is the Z-plasty, which disrupts the line of tension on linear scars (see ▶ Chap. 21). Another choice is to use skin grafts. Full-thickness skin grafts (FTSG) are a better choice than split-thickness skin grafts (STSG) because the latter associate with a greater risk of secondary contracture. However, if adjacent normal skin is available, it is better to use local flaps rather than FTSG because they have a much lower risk of contracture and better esthetic outcomes. Once the decision to use a local flap has been made, one then has to decide between an island flap and a skin-pedicled flap. While this choice depends somewhat on the scar geometry and other patient-specific variables, skin-pedicled flaps are generally the better choice because they have greater extensibility than island flaps and are therefore good for releasing the tension of a scar (see ▶ Chap. 21). This greater extensibility probably reflects the fact that the entire perimeter of the island flap is surrounded by new scar whereas the skin-pedicled flap maintains a connection with normal skin, which is much more elastic than scar tissue.

2.7 Conclusion

It is suggested that mechanical forces on the skin strongly influence the cellular behavior that leads to scarring. These observations led us to focus on the importance of reducing skin tension when keloids and hypertrophic scars are surgically removed to prevent their recurrence. Clinical studies revealed that subcutaneous/fascial tensile reduction sutures, which apply minimal tension on the dermis, are effective in reducing recurrence. Moreover, we have found that by using Z-plasty and skin flaps, which release tension on the wound, huge scars can be successfully treated.

Take-Home Messages

- Mechanical force can be an important cause of pathological scar development.
- The mechanical forces on scars/wounds include stretching tension, shear force, scratch, compression, hydrostatic pressure, and osmotic pressure.
- An evidence that indicates the importance of mechanical forces in pathological scar formation and progression is the fact that keloids grow horizontally in the direction(s) of the predominant forces on the wound/scar.
- There is the hypertrophic scar mouse model in which heavy scars are induced by placing a mechanical force on the edges of a cutaneous incision.

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Scar Formation: Cellular Mechanisms

Ian A. Darby and Alexis Desmoulière

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3.1 Background

Tissue repair after injury is a complex phenomenon involving intricate and coordinated mechanisms. Even though during the last decade, many studies have increased our knowledge on the different cellular players involved in this process [16], many gray areas remain, particularly concerning the dialogue between different cell populations acting during wound healing and scar formation. Interestingly, an abnormal course of the inflammatory phase at the beginning of the healing process appears to have effects long after scar formation. In addition, the relationships between cells and the extracellular matrix remain a key aspect in understanding the normal development and remodeling of scars.

3.2 Introduction

The skin provides the primary protection against external injuries for the body and is also essential in the maintenance of general homeostasis. Located beneath the epidermis, the dermis represents the thickest compartment of the skin and is composed mainly of a dense extracellular matrix network of collagen fibers supporting the specific dermal appendages, including hair follicles, sebaceous glands, and sweat glands. Dermal (myo)fibroblasts play a major role in the synthesis and maintenance of the extracellular matrix as well as in the wound-healing process [4]. During healing, fibroblasts proliferate and migrate into the wound space, though the origin of these cells remains to be clearly elucidated. Moreover, research on progenitor cells present in the skin, which can differentiate into many different cell types, represents an interesting source of cells that may be able to promote (when correctly stimulated) wound healing, improve the repair process in impaired or difficult-to-heal wounds or be able to modify the process of excessive scarring. In this chapter, these different aspects will be expanded on, including the biochemical, cellular, and physical factors that are involved in regulating healing and scarring in skin wounds (e.g., cytokines, mechanical tension, and innervation).

3.3 General Mechanisms of Scar Formation

Immediately after wounding, the healing process commences leading to (partial) restoration of the injured tissue. Wound healing passes through three dynamic and interrelated phases which temporally overlap [3]. Based on morphological changes seen in the wound tissue during the course of the healing process, these phases are defined as the inflammatory phase, the proliferative phase (with the development of the granulation tissue) and reepithelialization phase, and the remodeling phase which includes maturation and scar formation. The inflammatory phase begins with capillary damage, where blood loss results in a clot forming, which consists of fibrin and fibronectin and stops further blood loss. The wound space is thus filled with a provisional matrix that provides a scaffold into which various cells can migrate. The initial source of chemokines in the wound is platelets that are present in the clot, and these degranulate and provide multiple factors that stimulate the recruitment of inflammatory cells, neutrophils, and macrophages. At the same time, fibroblasts and endothelial cells are attracted by growth factors that are chemotactic for these cells. The proliferative phase of healing which follows includes angiogenesis, the growth of new vessels into the wound. Angiogenesis is vital for tissue repair since it provides vascular perfusion of the wound, delivering oxygen and nutrients and thus contributing to cell proliferation, including the proliferation of fibroblasts. The wound is initially hypoxic, as it lacks normal perfusion, and hypoxia itself is an important stimulus for the release of growth factors, including those that regulate angiogenesis. During the proliferative phase, angiogenesis proceeds and eventually reestablishes a more normal level of perfusion. The regulation of angiogenesis may represent a target for improving wound repair, particularly in those cases where delayed or abnormal angiogenesis has been suggested to play a role in healing impairment. Fibroblasts present in the granulation tissue become activated and are then termed myofibroblasts. These myofibroblasts are responsible for the synthesis and deposition of extracellular matrix components which progressively replace the provisional matrix [6]. Myofibroblasts also show contractile properties, playing a major role in the contraction and maturation of the granulation tissue. Scar formation, which is the third phase of healing, involves progressive remodeling of the granulation tissue (Fig. 3.1). A major role in this process is played by proteolytic enzymes, particularly the family of matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitor of metalloproteinases [TIMPs]). Synthesis of extracellular matrix is then reduced, though not completely stopped, and the components that make up the matrix are modified as the matrix is remodeled. Collagen type III, the major collagen present in granulation tissue, is progressively replaced by collagen type I, the main structural protein in normal unwounded dermis. Finally, elastin which is largely responsible for the elasticity of the skin and which is absent in granulation tissue also reappears. In deep human wounds, elastin fibers do not show complete regeneration after wound healing being both deficient and not showing normal structural

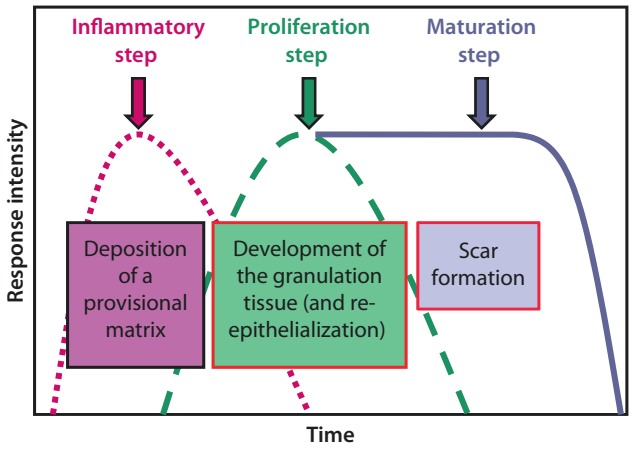

Fig. 3.1 The various phases of the healing process. After damage, inflammation leads to the formation of granulation tissue during which myofibroblasts appear. A significant neoangiogenesis is also observed. A new epidermis can then develop over this granulation tissue. Subsequently, remodeling of this granulation tissue occurs via apoptosis of the cells present in the granulation tissue (myofibroblasts and vascular cells), and the extracellular matrix is gradually reorganized

organization. During the resolution phase of wound healing, apoptosis of both vascular cells and myofibroblasts results in a significant reduction in cell number in the granulation tissue. Whether myofibroblasts can reacquire a quiescent phenotype thus returning to a "normal" dermal fibroblast phenotype is still open to question.

3.4 Morphological and Biochemical Characteristics of Myofibroblast Phenotype

The earliest descriptions of myofibroblasts, based on their electron microscopic morphology, identified ultrastructural specializations showing some similarity to those of smooth muscle cells, in particular prominent bundles of cytoplasmic microfilaments. Further ultrastructural and molecular markers that define myofibroblasts have since been identified, including cell-cell and cell-matrix adhesions, stress fibers, and expression of α-smooth muscle actin [9]. Both in vivo and in vitro, the presence of fibroblasts exhibiting prominent microfilament bundles in their cytoplasm (known as stress fibers) can be observed; however, these cells do not necessarily contain α-smooth muscle actin-positive microfilaments. In vitro, these fibroblasts can also be shown to secrete a splice-variant form of fibronectin, ED-A fibronectin. These cells have been termed proto-myofibroblasts, and their stress fibers contain only β- and γ-cytoplasmic actin. Proto-myofibroblasts can exert tractional forces in connective tissue, and they may be induced by mechanical stress; however, to undergo full differentiation into myofibroblasts, they require stimulation with transforming growth factor (TGF)-β1 (see below). Fully differentiated myofibroblasts are then capable of exerting increased force due to contraction. The expression pattern of myofibroblasts and smooth muscle cells shows several differences. Smooth muscle cells express smooth muscle myosin heavy chain, smoothelin, and h-caldesmon, while myofibroblasts are generally negative for these markers. Desmin, an intermediate filament protein which is normally expressed in muscle cells, has also been used as a negative marker of myofibroblasts, since during normal wound healing myofibroblasts have been found to be desmin-negative. In some conditions of pathological scarring, myofibroblasts have been observed to be desmin-positive. Overall though α-smooth muscle actin is also expressed in smooth muscle cells and pericytes, it still represents the most reliable phenotypic marker of myofibroblast phenotype.

Given the important roles of myofibroblasts in tissue repair and scarring, in particular their role in contraction, the exact mechanisms regulating contraction in such tissues need to be clearly identified. Examination of spontaneous intracellular Ca^{2+} oscillations has shown that intracellular Ca^{2+} oscillations are coordinated between contracting myofibroblasts via adherens junctions but occur randomly between fibroblasts and non-contacting cells. Therefore the following model of mechanical coupling for myofibroblasts can be proposed: individual cell contraction is transmitted via adherens junctions leading to the opening of mechanosensitive ion channels in adjacent cells. The resulting Ca^{2+} influx induces a contraction that can feed back on the first cell and/or stimulate other contacting cells allowing the cells to work like a syncytium. This mechanism of coordination of myofibroblast activity may improve the remodeling of cell-dense tissue [8].

3.5 Cellular Origins of Myofibroblasts

Recruitment of fibroblasts from the local connective tissue is generally accepted to be the major source of myofibroblasts in the wound. Dermal fibroblasts that are located at the wound margins can acquire a myofibroblastic phenotype and then play a role in tissue repair. However, there is considerable heterogeneity in fibroblastic cell subpopulations. These fibroblast subpopulations are present in different locations within the skin and have specific activation and deactivation properties. At least three subpopulations have been

identified in the dermis: superficial (or papillary) fibroblasts (the papillary dermis is approximately 300–400 μm in depth and is arranged as a ridgelike structure), reticular fibroblasts which are present in the deep dermis (which consists of thick collagen and elastin fibers that are arranged parallel to the surface of the skin), and fibroblasts which are associated with hair follicles. These cell subpopulations can be isolated for cell culture and then, depending on the age and nature of the skin sample, show distinct differences in phenotype in vitro.

It has been recently suggested that local mesenchymal stem cells may also be involved in the tissue repair process. These progenitor cells have been identified in the dermal sheath that surrounds the exterior of hair follicles, facing the epithelial stem cells. These cells are involved in regeneration of the dermal papilla and can also differentiate into wound-healing myofibroblasts after damage or injury.

Recent data has also suggested a role for circulating cells, termed fibrocytes, in the tissue repair process. Fibrocytes may enter damaged skin together at the same time as inflammatory cells and may then acquire a myofibroblastic phenotype. In burn wound, fibrocytes may infiltrate the wound where they both stimulate a local inflammatory response and additionally secrete extracellular matrix proteins, thus contributing to the pathological (hypertrophic) scarring that can be seen postburn injury.

Another bone marrow-derived circulating cell has also been suggested to play a role in tissue repair. Mesenchymal stem cells are bone marrow-derived nonhematopoietic precursor cells that may be present in both normal and damaged connective tissue, where they infiltrate the tissue and then contribute to the maintenance and repair of the tissue. Indeed, these cells have the capacity to seed into several organs and then differentiate into myofibroblasts, similar to those seen during wound healing. The degree to which damaged tissues or organs are infiltrated by these cells is dependent on the severity of tissue injury.

Lastly, epithelial- or endothelial-to-mesenchymal transition of either differentiated or malignant epithelium (or endothelium) can result in a phenotypic change to fibroblasts or myofibroblasts that are then responsible for extracellular matrix production. Although this mechanism is now accepted as playing an important role in fibrogenesis after tissue injury, it appears to play a less prominent role in normal tissue repair. Overall, myofibroblasts derived from circulating fibrocytes, mesenchymal stem cells, epithelial- or endothelial-to-mesenchymal transition, or bone marrow-derived cells may supplement local fibroblast recruitment and differentiation where their numbers are insufficient for the repair and remodeling process [14].

3.6 Regulation of Myofibroblast Phenotype

Wound healing and skin homeostasis are regulated by a number of cytokines and growth factors. Some growth factors act directly on granulation tissue formation and fibroblasts activity, while others have effects on vascular and epithelial cells. Of the factors with direct effects on fibroblasts, TGF-β1 is notable as it is a potent inducer of myofibroblast differentiation [18]. In addition to its role in inducing expression of α-smooth muscle actin, TGF-β1 also powerfully stimulates the synthesis of extracellular matrix proteins. TGF-β1 also favors the deposition of matrix by an effect on the balance between MMPs and their inhibitors, TIMPs, by reducing MMP activity while stimulating TIMP expression. The action of TGF-β1 on fibroblast to myofibroblast differentiation requires the presence of ED-A fibronectin, underlining the close relationship between growth factor activation, the extracellular matrix, and regulation of cellular function (◘ Fig. 3.2). It is interesting to note that granulocyte macrophage colony stimulating factor can also increase the number of myofibroblasts in vivo; however, this is most likely due to its activation and recruitment of macrophages which in turn increases the levels and availability of TGF-β1 [15]. Finally, microRNAs (miRNAs) have also been implicated in the induction of myofibroblasts in both fibrotic conditions and in cancer. Specifically, expression of miR-21 appears to be correlated with high levels of TGF-β1 stimulation of the myofibroblast phenotype. A recent study has suggested that the mechanism underlying this may be through effects on TGF-β1 inhibitory pathways. Improvements in our understanding of the effects of miRNAs in regulating fibrosis, potentially through actions on myofibroblast differentiation and activity, may allow miRNAs to be targeted in therapies aimed at inhibition of fibrosis and scarring.

3.7 Role of Myofibroblasts in Pathological Scarring and Fibrosis

In some cases, wound healing proceeds in a pathological course resulting in pathological scarring [17]. Such abnormal repair processes may be the result of impaired remodeling of the granulation tissue resulting in, for example, abnormal repair of the skin in the form of hypertrophic or keloid scars and to fibrosis in internal organs. In the case of excessive scarring in the skin such as hypertrophic scars, normal healing fails and the granulation tissue continues to expand, likely due to abnormal and excessive secretion of growth factors and/or to a lack of molecules that in normal healing are responsible for induction of apoptosis or remodeling of the

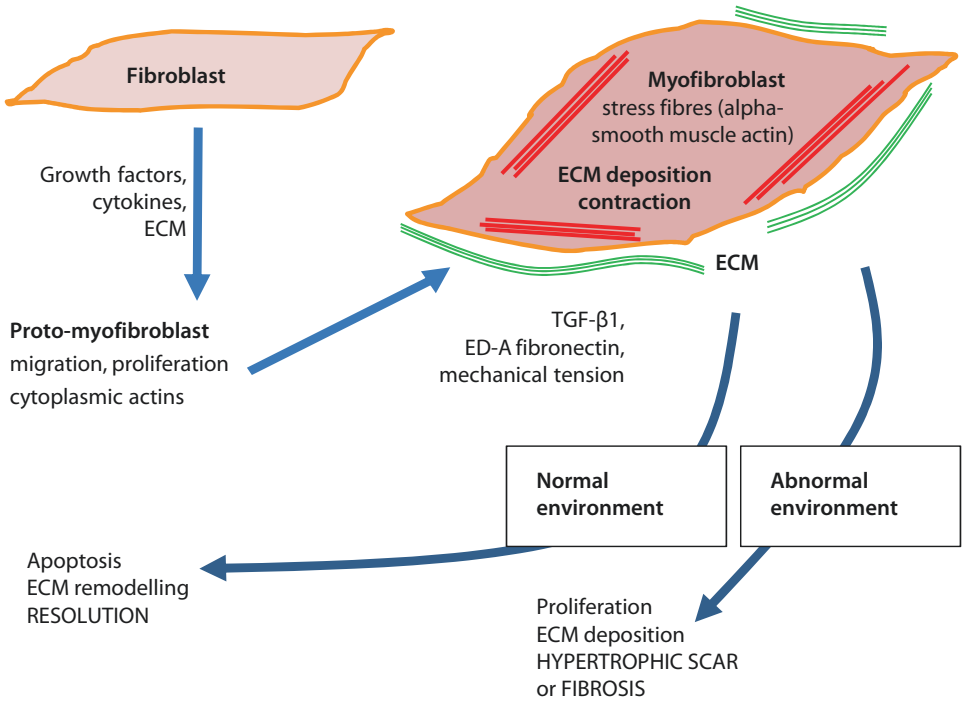

Fig. 3.2 Illustration showing the evolution of the fibroblast phenotype during normal and pathological conditions. Changes observed in fibroblast phenotype as cells differentiate towards a myofibroblast phenotype begin with the appearance of proto-myofibroblasts. These cells possess stress fibers composed of β- and γ-cytoplasmic actins. These then evolve, at least in some cases, into fully differentiated myofibroblasts. These cells possess stress fibers containing α-smooth muscle actin. Soluble factors such as transforming growth factor-β1 (TGF-β1), extracellular matrix (ECM) components such as ED-A fibronectin, and/or the mechanical microenvironment are all involved in myofibroblastic differentiation. The myofibroblast may then disappear by apoptosis, while deactivation, leading to a quiescent phenotype, has not been clearly demonstrated at least in vivo. If the remodeling phase of the granulation tissue does not occur (with no apoptosis of the myofibroblasts and vascular cells present in the granulation tissue nor reorganization of the extracellular matrix), myofibroblasts may then persist, leading to pathological conditions characterized by excessive scarring

extracellular matrix. When the stimulus driving the response to injury persists in internal organs, excessive deposition of extracellular matrix then leads to organ fibrosis. As is observed in pathological healing in the skin, the occurrence of fibrosis and its chronic nature may be a consequence of an imbalance between matrix deposition and matrix degradation. The mechanism underlying this is most likely an imbalance in the levels of MMPs and their inhibitors, TIMPs.

Hypertrophic scars and keloids are both characterized by an abnormal accumulation of extracellular matrix; however, they represent two very different cutaneous pathologies. In the case of hypertrophic scars, these do not extend beyond the periphery of the lesion, while keloids do extend beyond the margins of the original lesion. α-Smooth muscle-positive myofibroblasts are abundant in hypertrophic scars, and these cells contract, inducing retraction of the scar, particularly when the scar tissue is located in a region that is subjected to mechanical tension. This is particularly the case when the scar is adjacent to joints including the shoulders, elbows, wrists, knees, and ankles. Conversely, retraction does not occur in keloids. The development of hypertrophic scars is frequently observed after severe burns, and it appears that prolonged inflammation contributes to the increased risk of hypertrophic scarring. Conversely chronic wounds, such as venous leg ulcers, can also show prolonged inflammation with the mixture of pro-inflammatory cytokines and MMPs leading to a failure of matrix deposition and repair. It is therefore suggested that after cleansing of the wound, treatment should be aimed at producing the most rapid recovery possible with the aim of limiting the time spent in the inflammatory stage of healing.

3.8 The Role of Mechanical Tension

Due to both their contractile nature and their intimate relationship with the extracellular matrix, myofibroblasts are sensitive to their mechanical environment, and mechanical signaling has been shown to play important roles in regulating the activity of myofibroblasts [10]. Differentiation markers of myofibroblasts, including stress fibers, ED-A fibronectin, and α-smooth muscle actin expression, appear earlier in granulation tissue

that is subjected to increased mechanical tension. This has been shown in experiments using splinting of a full-thickness wound with a plastic frame and comparing this to unsplinted, normally healing granulation tissue. Additionally, mechanical forces can be altered by culturing fibroblasts on substrates of varying stiffness, and these experiments have shown alterations in fibroblast phenotype dependent on substrate compliance. In culture, fibroblasts grown on soft, compliant substrates do not show stress fiber expression, while increasing the stiffness of the substrate induces a rapid change in morphology and the appearance of stress fibers. In cultured fibroblasts, shear forces, from movement of fluid, are also able to increase TGF-β1 synthesis and thus stimulate fibroblast differentiation to a myofibroblast phenotype. Shear forces are able to affect fibroblast differentiation in the absence of other stimuli that are normally involved in their differentiation, for example, exposure to cytokines or pre-straining of the extracellular matrix which regulates TGF-β1 bioavailability. As mentioned above, the role of mechanical stress in stimulating myofibroblast activity has also been shown in experiments using mechanically stressed skin wounds in mice. These wounds are stretched or splinted, resulting in an increased mechanical load that in turn increases myofibroblast activity and results in increased scar formation. These models to some extent mimic hypertrophic scarring that is sometimes observed in humans. The mechanical environment of the wound and the tension present are thus essential factors that need to be taken into account and managed in order to reduce scarring. To this end controlled immobilization of the wound should be employed. Interestingly, devices that manage the mechanical environment and tension of the wound are now appearing on the market (e.g., Embrace® from Neodyne Biosciences, Inc. or Zip® from ZipLine Medical, Inc.).

3.9 Role of Innervation in Skin Healing

Recently it has been shown that innervation of the skin plays an important role in both normal and pathological wound healing. However, the precise roles of sensory and autonomic innervation during wound healing remain to be clearly established [12]. Keratinocytes, melanocytes, fibroblasts, and myofibroblasts have all been shown to express a variety of neurotrophins including nerve growth factor, neurotophin-3, brain-derived neurotrophic factor, as well as their receptors, and these promote cellular proliferation and differentiation. Neuropeptides including calcitonin gene-related peptide, substance P, and vasoactive intestinal peptide are able to modulate the activity of MMP-2 and MMP-9, both of which play important roles in granulation tissue remodeling and scar formation. Additionally, these neuropeptides also act on collagen type I and type III synthesis during skin wound healing, promoting dermal fibroblast adhesion and their differentiation into myofibroblasts. The effects of these neuropeptides on the composition of the extracellular matrix and its organization are certainly essential since it is well-established that the mechanical microenvironment, which is dependent on the organization of the extracellular matrix, can affect fibroblast to myofibroblast differentiation. Lastly, regulation of MMPs can also affect the subsequent activation of latent TGF-β1 which involves MMPs.

Injury to the skin induces the release of a number of inflammatory mediators, from both immune cells and sensory nerve endings. These include interleukin-1β, tumor necrosis factor-α, bradykinin, substance P, calcitonin gene-related peptide, nerve growth factor, and prostaglandins, and their release by these cells contributes to the "inflammatory soup" present in the wound. It has been suggested that changes in substance P levels may be involved in the aberrant wound-healing response seen in hypertrophic scarring. Furthermore, it has been observed that in cocultures of fibroblasts and neurites, the direct contact of these cells is able to induce myofibroblast differentiation leading to increased retraction of collagen lattices, mimicking the contraction seen in wound repair.

In keloids, nerve fiber density is significantly higher than in normal skin samples, and symptoms including itch, pain, abnormal thermal sensory thresholds to heat as well as cold, and pain associated with heat sensation are all reported suggesting the involvement of small nerve fibers in the pathogenesis of this disease. In hypertrophic scars, published data are inconsistent with either a decrease or an increase of the number nerve fibers having been reported. Nevertheless, in burn patients with chronic pain, abnormal cutaneous innervation has been reported. A recent pilot study has been published which compared healthy skin versus postburn scars from the same patient [2]. These authors examined the expression of genes involved in regulation of innervation and additionally looked at the intraepidermal density of nerve endings. Significant differences in the patterns of expression were observed when comparing healthy skin and postburn scars. Based on studies of a mouse model of hypertrophic scarring induced by mechanical loading, it has been suggested that innervation of the skin and the level of inflammation present may both play roles in the development of hypertrophic scars.

The role of the sensory nervous system in wound healing in the skin has been examined using several ani-

mal models of denervation. Surgical denervation has been employed, as has chemical denervation, and mice with genetic modifications resulting in denervation have also been used. Studies using surgical denervation have shown that wound healing is retarded in these animals, with a reduction observed in the number of inflammatory cells infiltrating the wound, delayed contraction of the wound, and a delay in reepithelialization. Another skin denervation model, which used chemical sympathectomy induced by intraperitoneal administration of 6-hydroxydopamine, also showed that denervation interfered with wound healing. 6-Hydroxydopamine-induced sympathectomy has also been shown to modify wound healing with an increase in wound contraction, a reduction in mast cell migration and delayed reepithelialization. These alterations in healing are associated with a decrease in neurogenic inflammation. Lastly, these studies have definitively shown that neuropeptides released by sensory fibers play an important role during wound healing, affecting the granulation tissue in particular.

3.10 Therapeutic Options

It has been recently shown, in human pulmonary fibrosis, that mechanical stretching of tissue can contribute to the development of fibrosis via mechanical activation of TGF-β1 [5]. Stretching of the extracellular matrix in the lungs, due either to breathing or to mechanical ventilation that is employed to support breathing in cases of lung injury or lung disease, may contribute to TGF-β1-driven disease progression. Since it is not possible to stop breathing to avoid mechanical TGF-β1 activation from established fibrotic tissue, therapeutic intervention might however be possible aimed at the cellular side of mechanical TGF-β1 activation. Thus, in organs that are subjected to mechanical stress, such as the lungs and skin, the role of TGF-β1 in excessive scarring and fibrosis is clearly crucial, and the mechanisms involved in activation of TGF-β1 represent an important therapeutic target.

The presence and activity of fibroblasts is vital for normal skin homeostasis, while the presence of myofibroblasts is crucial for tissue repair and has evolved to speed the process of normal tissue repair [1]. The importance of fibroblast activity in normal repair has been very well documented using in vitro models of dermal substitutes. For example, a living dermal equivalent (containing fibroblasts) that has been applied to skin graft beds was found to reduce pain, improve hemostasis, and also improve the mechanical and cosmetic properties of the graft, in particular, producing a normal undulating dermal-epidermal junction by 3–4 months after grafting and also leading to the presence of elastic fibers, which were detectable 6–9 months after grafting. Therefore, it seems apparent that tissue engineering approaches to normal repair require fibroblasts and myofibroblasts to be effective [7]. It is, however, very important to keep in mind that many different populations of fibroblasts exist and that these have different properties. These recent observations thus offer new perspectives for skin repair and for tissue engineering. In addition, promotion of normal reinnervation and adequate levels of neuropeptides during the healing process certainly appear to be crucial for improving skin healing and to avoid the occurrence of pathological repair processes and scarring [13]. Despite the existence of many areas that still require elucidation in myofibroblast biology, it seems clear that myofibroblasts are pivotal cells for the control of extracellular matrix deposition and remodeling during normal repair and are also important in pathological conditions such as excessive scarring. Myofibroblasts thus definitively represent an essential target to be considered when developing new therapeutic strategies.

3.11 Conclusion

Myofibroblasts are key cells during wound healing. It has become increasingly evident that a lack of myofibroblast apoptosis is a major mechanism leading to excessive scarring [11]. Blocking pro-survival mechanisms, particularly those linked to the mechanical environment, and modifying the myofibroblast phenotype to obtain cells able to remodel the excessive deposition of extracellular matrix certainly represent new ways to develop therapeutic options that could positively modulate scar formation.

Take-Home Messages

- Myofibroblasts play a major role during granulation tissue formation with transforming growth factor-β1 being the main soluble factor involved in myofibroblastic differentiation.
- Myofibroblasts, through mechanotransduction pathways, are very sensitive to their mechanical environment.
- Myofibroblast apoptosis and extracellular matrix remodeling are necessary for normal scar formation.
- Abnormal mechanical tension facilitates the development of hypertrophic scars.
- Normal innervation and neuropeptide secretion are necessary to maintain skin homeostasis and normal wound healing.

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Epidemiology of Scars and Their Consequences

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The Epidemiology of Keloids

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Take-Home Messages

- Despite the fact that keloids are common throughout the world, their epidemiology has not been adequately investigated.
- The demographic distribution of keloids, mainly on the geographical regions and ethnic racies.
- Genetic risk factors can shape keloid rates, in particular certain diseases appear to amplify or suppress keloid formations.
- Environmental factors also contribute to keloid development and progression and therefore shape keloid rates, such as local mechanical stimuli.

4.1 Background

Keloids are pathological scars that are characterized histologically by an overwhelming aggregation of fibroblasts and collagen type I within the inflammatory reticular dermis [1]. Their clinical characteristics include continuous growth and invasion into the neighboring healthy skin beyond the original wound boundary via an erythematous and pruritic leading edge. They also show a strong tendency to recur when they are surgically excised in the absence of adjuvant therapies. Despite the fact that keloids are common throughout the world, their epidemiology has not been adequately investigated.

In this chapter, we will summarize the limited epidemiological data on keloids that exists to date. Most of these data are from English language papers that are listed in PubMed. Below, we will describe what is known about (1) the demographic distribution of keloids, mainly on the geographical regions and ethnic races; (2) the internal genetic factors that shape keloid rates; and (3) the external environmental factors that influence keloid epidemiology. The aim of the chapter is to facilitate a greater understanding of the complexity and diversity of keloids from an epidemiological perspective, thereby potentiating further and deeper explorations into individualized strategies that prevent and treat keloids.

4.2 Demographic Risk Factors That Shape Keloid Rates

The studies on the demographic distribution of keloids in the world are sparse and occasionally contradictory. However, keloid rates can be affected by geography and ethnicity.

In terms of geographical distribution, it has long been cited that the incidence of keloids ranges widely from 0.09% in England to 16% in Zaire [2, 3]. While these reviews did not indicate how these incidences were determined, they are somewhat supported by the few large-scale studies on geographical incidence that have been performed. One of these was a review of the 5735 patients who underwent surgery in the 33 surgical facilities in Zambia between 1993 and 2008: the study showed that of the 5774 surgical diagnoses, 514 are related to keloids. Thus, keloids accounted for nearly 9% of all those surgical cases in Zambia during the study period [4]. Moreover in Kenya, the keloid prevalence is 8.5% among people with normally pigmented skins [5]. By contrast, the keloid incidence in Japan is around 0.1% [6] (Table 4.1). Considering that the keloid incidence data is limited and scattered, which can hardly be comparable in a strictly defined background covering key factors such as statistical period/cycle, population size/composition, and diagnostic criteria on scar type/severity, it is still difficult to depict an accurate keloid distribution map at this time. And the average keloid incidence can only be estimated as 5–10% in African, 0–0.1% in Asian, and <0.1% in other countries, as seen in Fig. 4.1.

Table 4.1 The incidences of keloid reported in different countries

Country	Keloid incidence (%)	Reference
England	0.09%	[2, 3]
Japan	0.10%	[6]
Kenya	8.50%	[5]
Zambia	9%	[4]
Zaire	16%	[2, 3]

It is suspected that this large geographical variation in keloid rate may reflect racial differences in skin pigmentation (Fig. 4.2). However, the data on keloid prevalence in various races is conflicting. First, Louw states that both Blacks and Asians are more susceptible to keloid formation than Caucasians [3]. Indeed, the Black/Caucasian ratio was reported varying from 14:1 to 2:1 [7]. However, the above reports may suggest that Asians could have similarly low incidences of keloid as Caucasians (0.1% in Japan versus 0.09% in England) [2, 3, 6]. Two studies also suggest that at least one specific type of keloid, acne keloidalis nuchae (AKN), is much more common in Blacks than in Asians. Na et al. showed that of 254,785 patients who attended the dermatology department of a Korean hospital in 2005–2017, 17 had AKN (0.007%) [8]. By contrast, another study showed that of 13,422 new patients who visited a large university hospital in Benin in 1993–2002, 0.7% (90 cases) had AKN, and the prevalence was reported as 0.37% (90

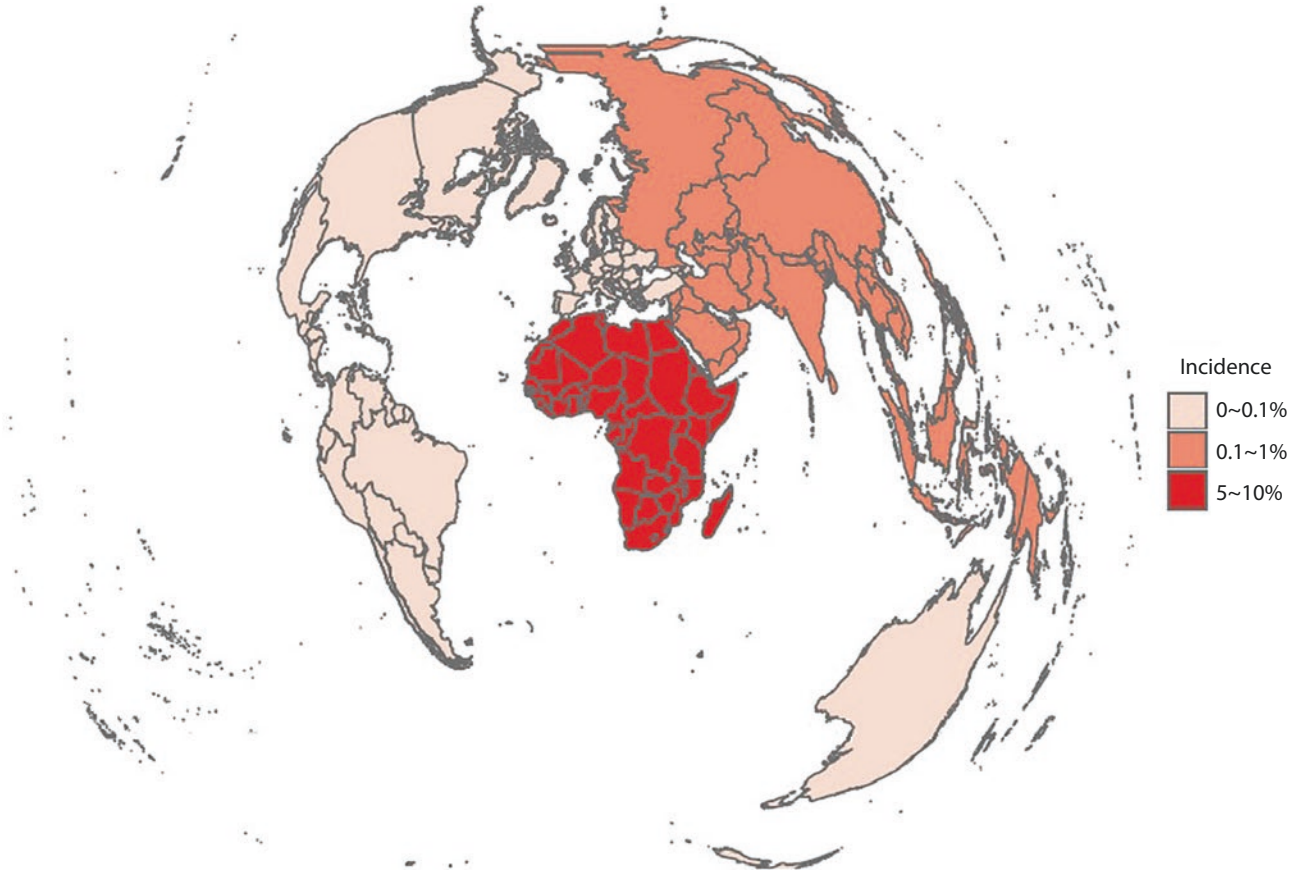

Fig. 4.1 Heatmap of keloid epidemiology in the world. The average keloid incidence can only be estimated as 5–10% in African, 0–0.1% in Asian, and <0.1% in other countries

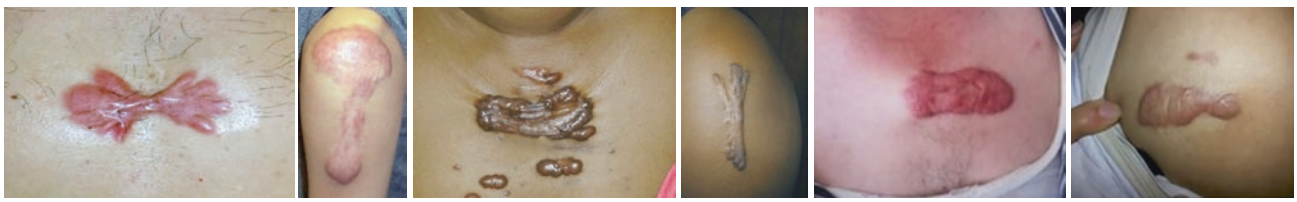

Fig. 4.2 Chest and shoulder keloids in different racial groups of Asians, Africans, and Caucasians. 4.2.1 The images are from Huang et al. with permission (Huang et al. [11]). 4. 2.2 The images are from Bayat et al. with permission (Bayat et al. [12]). 4. 2.3 The images are from Shaheen et al. with permission (Shaheen et al. [13]. © All rights reserved)

cases out of 26,522 patients overall) [9]. The latter study is supported by several other studies that show that AKN is common in Blacks. For example, as high as 4.7% of Black boys in the last year of high school in South Africa can develop AKN [10]. Moreover, the postulated relationship between high skin pigmentation and greater susceptibility to keloid formation is not borne out by two studies. One is a cross-sectional study on randomly selected villages in Kenya and people with albinism who were recruited via an albino association in Kenya and dermatology training center clinics and special schools in Tanzania. Of the 1416 African people who were recruited, 1185 had normally pigmented skin, and 231 had albinism. And 954 among the 1416 people have scars on their body. For them, the total prevalence of keloid was 8.3%. The subjects with normal pigmentation did not differ significantly from the subjects with albinism in terms of keloid prevalence (8.5% versus 7.8%; $P = 0.599$) [5]. The second study described the 175 keloid patients who visited the General Hospital in Kuala Lumpur in West Malaysia in 1959–1967. West Malaysia has a multiracial population. An analysis of

the ethnicities of the keloid patient cohort showed that keloid was more common in the relatively fair-skinned Chinese: while 56% of the keloid patients were Chinese, this ethnicity accounted for only 47.47% of the population. By contrast, 22.86% and 17.14% of the keloid patients were darker-skinned Indians and Malays, respectively; these ethnicities accounted for 19.52% and 29.58% of the population, respectively [7].

4.3 Genetic Risk Factors That Shape Keloid Rates

The effect of ethnicity on keloidogenesis suggests that keloid formation is somewhat underpinned by genetic variation. This is borne out by multiple genetic studies that show that keloidogenesis associates with certain gene mutations or polymorphism [14]. Keloids also show a familial tendency [15]. Here, we will discuss less well-known genetic associations with keloids, namely, certain diseases that appear to amplify or, conversely, suppress keloid rates.

The diseases that associate with an increased risk of keloid include the Rubinstein-Taybi syndrome (RSTS), the Ehlers-Danlos syndrome, the Lowe syndrome, and the novel X-linked syndrome, and others (Table 4.2). RSTS is also called broad thumb-hallux syndrome. It is characterized by broad thumbs and toes, facial abnormalities, and short stature [16]. The etiological mutation lies in gene encoding the cyclic AMP response element-binding protein (CBP) on chromosome 16p13.3 [17] and E1A-binding protein (EP300) gene which encodes p300 protein (a cAMP response element-binding protein homologue) [18]. Keloid is reported to occur in 24% (15/62) of RSTS patients, either spontaneously or secondary to minor trauma [19]. The Ehlers-Danlos syndrome type IV (the vascular subtype) is an inherited disorder of connective tissue that is characterized by acrogeria, translucent skin, propensity to bruising, and significant arterial, digestive, and uterine complications [20]. The causative mutation is in COL3A1 gene, which encodes the pro-α1(III) chain of collagen type III [21]. Several case reports show that this syndrome can paradoxically associate with extensive keloid formation [22]. The Lowe syndrome (also called the oculocerebrorenal syndrome of Lowe [OCRL]) affects the eyes, nervous system, and kidneys [23]. It is caused by a mutation in the OCRL gene that reduces the amount of the OCRL-1 protein [24]. The formation of corneal keloids in patients with Lowe syndrome is relatively common. It is generally provoked by corneal contact lens use or after intraocular lens implantation [25]. Novel X-linked syndrome is characterized by symptoms of cardiac valvular disease, spontaneous keloid scarring, and reduced joint mobility. The causal mutation is filamin A (FLNA) substitution G1576R [26]. Other syndromes that may associate with spontaneous keloid formation include the Dubowitz syndrome [27], the Noonan syndrome [28], and the Goeminne syndrome [29], which are inherited in autosomal recessive, autosomal dominant, and sex-linked incomplete dominant ways, respectively, though the actual gene mutation remained unclear.

The diseases that associate with protection from severe pathological scarring are Hansen's disease and von Recklinghausen's disease. Hansen's disease (also known as leprosy) is a chronic disease that arises after infection with *Mycobacterium leprae* and *Mycobacterium lepromatosis*. It is characterized by granulomas of the nerves, respiratory tract, skin, and eyes and the gradual destruction of the intraepidermal innervation. Extensive scarring is extremely rare in patients with Hansen's disease [30, 31]. von Recklinghausen's disease is also known as neurofibromatosis type I (NF-I). It is characterized by the growth of tumors on the nerves. A study of 30 Nigerian patients with neurofibromatosis who underwent surgery showed that none of them developed keloid or hypertrophic scars after surgery, even though their wound healing was poor and some of their wounds were closed under tension [32]. Similarly, a worldwide multicenter study on 57 patients with von Recklinghausen's disease showed that none of the patients developed hypertrophic scar or keloid after surgery: in general, their wounds healed remarkably well. The main complications were the development of hematoma and wide white scar in six patients. By contrast, two of the 35 patients with a solitary neurofibroma who were included in the study developed hypertrophic scars after surgery [33].

4.4 Environmental Risk Factors That Shape Keloid Rates

Environmental factors also contribute to keloid development and progression and therefore shape keloid rates. One such factor is local mechanical stimulus. An interesting feature of keloids is that they show a distinct site specificity. When we analyzed 1500 keloids in 483 Japanese patients (the keloids generated from artificially created wounds, namely, those created by surgery and piercing, were excluded), we found they tended to occur on the anterior chest region (48.9%), scapular regions (26.9%), lower jaw/neck region (12.1%), upper arm (4.8%), dorsal regions (2.5%), lower abdomen (1.9%), femoral regions (1.7%), knee (0.5%) and upper abdomen (0.5%) [34]. All of these regions are characterized by high skin tension/friction. That skin tension promotes keloid development is also shown by the fact

Table 4.2 The syndromes associated with keloidogenesis

Syndrome	Other names	Characteristic features	Keloid lesions	Genes or inheritance concerned	Reference
Rubinstein-Taybi syndrome (RSTS)	Broad thumb-hallux syndrome	Broad thumbs and toes, facial abnormalities, short stature	24%	CBP on chromosome 16p13.3; EP300	[16–19]
Ehlers-Danlos syndrome type IV (vascular type)		Acrogeria, translucent skin, propensity to bruising, and significant arterial, digestive, and uterine complications	Extensive keloid formation	COL3A1 gene that encodes the pro-α1(III) chain of collagen type III	[20–22]
Lowe syndrome	Oculocerebrorenal syndrome of Lowe (OCRL)	Affects the eyes, nervous system, and kidneys	Corneal keloids	OCRL gene that reduces the amount of the OCRL-1 protein	[23–25]
Novel X-linked syndrome		Cardiac valvular disease, spontaneous keloid scarring, and reduced joint mobility	Spontaneous keloid scarring	A G1576R mutation in filamin A (FLNA)	[26]
Dubowitz syndrome		Intrauterine growth retardation, low neonatal weight, short stature, characteristic facies, atopic dermatitis, and mental retardation	Spontaneous keloidal lesions	Autosomal recessive transmission	[27]
Noonan syndrome		Craniofacial appearance, congenital cardiac defects, orthopedic abnormalities, psychomotor and growth retardation, and some skin changes including keloidal tissue formation	Keloidal tissue formation	Autosomal dominant inheritance	[28]
Goeminne syndrome		Congenital muscular torticollis, multiple keloids, cryptorchidism, and renal dysplasia	Multiple spontaneous keloids	Sex-linked incomplete dominant inheritance	[29]

that the keloids on certain regions grow into specific shapes. Thus, anterior chest keloids form symmetrical butterfly shapes that reflect the predominant stretching directions of the chest skin that are caused by the upper arm movements. By contrast, keloids on the scapula form dumbbell shapes that run down the long axis of the arm and are caused by the skin stretching caused by the hanging upper arm. Moreover, earlobe keloids often grow into balls that reflect the circular nocturnal friction on the earlobe from the head moving on the pillow [34]. This role of mechanical tension in keloid growth is further supported by the recent case of a patient in our center whose symmetrically distributed butterfly keloid on the chest was accidentally split in half at the midline. The patient was right-handed. In the subsequent 2 years, the right half butterfly of the keloid continued to progress as usual. By contrast, the left half butterfly grew much less strongly and indeed exhibited signs of amelioration [11].

4.5 Conclusion

Regardless of whether keloids occur spontaneously or after trauma, these lesions are clearly the result of both internal genetic and external environmental factors. These factors underlie the association between keloids and various demographic risk factors, namely, geographical region and ethnicity. However, our understanding of these demographic factors is limited by the paucity of and inconsistencies in the epidemiological research on keloids. To identify the respective contributions of genetic and environment factors to keloid formation, it will be necessary to conduct large-scale investigations with specific study designs, such as studies on twin cohorts or cross-sectional studies on the members of families that show a predilection toward keloidogenesis. Such explorations will help to orient further keloid research, thereby aiding the development of effective therapeutic approaches.

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Epidemiology of Scars and Their Consequences: Burn Scars

Margriet E. van Baar

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_5

Background

This chapter focuses on the epidemiology of burn scars and their consequences. Burn scars are the result of a pathological healing process in specific burn injuries.

The occurrence of burn injuries and resulting scars and their consequences will be discussed. This includes scar contractures and reconstructive surgery. Next, the predisposing factors for the occurrence of burn scars will be addresses. The chapter ends with the clinical implications.

5.1 Burn Injuries and Their Treatment

Burn injuries are a global public health problem. According to estimates of the WHO, burn injuries cause 180,000 deaths every year. The majority of these deaths occur in low- and middle-income countries. Two-third of these deaths occur in the WHO regions of Africa and Southeast Asia.

The nonfatal burns are a leading cause of morbidity, including long hospitalizations, disability and problems in returning to normal life. In the United States annually, 486,000 burn injuries receive medical treatment. In addition, 40,000 hospitalizations are related to burn injuries.

National burn injury incidence data are scarce. In Europe, incidence rates of hospitalized burn injuries are reported between 2 and 29 per 100,000 inhabitants; in Australia, 36 per 100,000 has been reported.

Reviews on burn injury incidence data describe a decline in the incidence rates of burn-related hospital admissions in both low- and middle-income countries. In high-income countries, a similar trend is observed.

5.1.1 Burn Care

In the past decades, there has been a shift in focus from mortality to morbidity in burn care in high-income countries. Recently, the European Burns Association stated in its guidelines that "the main goal of burn care is to ensure optimum resuscitation in the emergency period and then to reach re-epithelialization of injured or destroyed skin either by support of spontaneous healing or by surgical necrectomy and grafting with split thickness skin graft. Subsequent treatment is to ensure the optimum post burn quality of life". This goal only includes the minimum surgical procedure. In nowadays burn care, other surgical techniques including skin substitutes, full skin transplantations and ReCell are also applied.

In high-income countries, a trend is described towards a growing specialized burn care. In the Netherlands, the majority of these hospital admissions are seen in specialized burn centres. This is in line with the trend towards further specialization of health care in general and also because of limited travel distances in our country. In addition, it has been suggested that many patients are transferred towards tertiary care facilities because of a lack of basic skills in the assessment and care of burn wounds at community and rural hospitals.

5.1.2 Acute Phase

The acute treatment of burn injuries is guided by their severity, indicated by the burn size and the burn depth. Burn size is represented by the percentage of the total body surface area burned (TBSA). The burn depth is related to the dermal layers which are affected by the burn injury. Accurate diagnosis of both burn size and burn depth is crucial to start appropriate treatment at the correct level of care required. It guides the initiation of fluid resuscitation, acute escharotomy in case of circumferential deep burns and the decision for conservative or surgical wound treatment. Burn size also has an important prognostic value in predicting burn-related mortality. Both burn size and burn depth are of prognostic value for eventual burn scar pathology.

The most widely used classification for burn injuries divides burns into three categories of increasing depth: superficial partial-thickness, deep partial-thickness and full-thickness burns. Superficial partial-thickness burns involve only the epidermal layer and the superficial part of the dermis. In deep partial-thickness burns, the epidermis and the majority of the dermis are destroyed, with damage to deeper skin structures such as blood vessels, nerves and hair follicles. In full-thickness burns, all layers of the skin are destroyed, and there may also be damage to subdermal structures, such as the muscle, cartilage or bone. In these wounds, no viable epidermal appendages remain in the bottom of the wound, which makes spontaneous healing from the wound bed impossible.

In superficial partial-thickness burns, conservative treatment will be chosen to support spontaneous wound healing, which is expected within 10–14 days. In deep partial-thickness burns, surgical treatment is sometimes necessary to reach wound closure. In full-thickness burns, surgical wound closure will be necessary in the majority of wounds, except in the very small-sized ones.

Other important parts of burn care include oedema management, early mobilization and scar management.

Treatment protocols vary between burn centres, including wound dressings, early mobilization and timing of surgery. According to Dokter et al., in the Netherlands, 45% of all burn injury patients admitted to burn centres receive surgery approximately 15 days post burn. In burn centres in Australia and New Zealand, a similar proportion is operated upon (47.2%) in general within 1 week post burn (mean 6 days post burn).

5.2 Prevalence of Burn Scars and Their Consequences

5.2.1 Definition of Scars

The consequences of burns can be severe, affecting multiple domains. The focus in this chapter is on the prevalence of pathological physical scar formation and its consequences.

Burn scars can cause aesthetic and functional problems, resulting in limitations in activities of daily living, the return to normal social roles and impacted quality of life. The psychological consequences will be further elucidated elsewhere in this book.

Early studies on pathological scarring in burn wounds have distinguished between hypertrophic scars and contractures (Magliacani (1997) in [1]).

Hypertrophic scars are a dominant type of pathological scar formation after burns. Nowadays, hypertrophic scarring is described as "the greatest unmet challenge after burn injury."

Hypertrophic scars are generally elevated, firm and erythematous. They can also tend to be pruritic and tender. By definition, they are limited to the site of the original wound and grow in size by pushing out the scar margins. Hypertrophic scarring is known to decrease with time.

Next to hypertrophic scars, contractures are another important type of pathological scar formation after burns. A contracture is defined as the pathological result of excessive scarring and ongoing scar contraction that results in loss of range of motion (ROM) over joint areas. Scar contractures may limit daily functioning and as a result affect health-related quality of life after burns.

Modern scar assessment addresses a broader range of scar features from both the patients' perspective and the perspective of the health-care professional. Scar quality from a patient perspective depends on the presence or absence of several visual, tactile and sensational features [2]. For research purposes, an ideal scar evaluation protocol should include both subjective and objective measurements. These different perspectives will result in different scar assessment tools and different scar outcomes. Results indicate the level of scar morbidity and not the mere presence or absence of scar pathology.

Examples of frequently used scar assessment scales are the Vancouver Scar Scale and the Patient and Observer Scar Assessment Scale (POSAS; see ► www.posas.org).

A final approximation of burn scarring is the occurrence of reconstructive surgery after burns. The need for reconstructive surgery after burn injuries can be viewed upon as an indicator for problematic scar development, requiring a surgical intervention to relieve scar morbidity.

5.2.2 Prevalence of Hypertrophic Scarring

The estimates of prevalence of scarring vary widely. Prevalences of hypertrophic scarring between 8% and 67% are reported [3]. These data are all related to burn centre populations in high-income countries.

One of the first reports was written by Deitch et al. in 1983, based on a combined retrospective and prospective study in a mixed population of children and adults. They reported hypertrophic scars after conservative wound healing in 30% of their patients with a dark skin and in 15% of their Caucasian/White patients at 9 to 18 months post burn. Hypertrophic scars were documented in case of increased thickness or elevation of the burn wound; changes in colour or pigmentation alone were not classified as hypertrophy.

Two decades later, Bombardo reported a prevalence of 67% of hypertrophic scars in a dominantly Caucasian sample of patients after major burns. Again, data were based on retrospective chart analysis in patients after major burns, examining the mentioning of the word hypertrophic in the charts. No description was provided on the timing of the scar assessments.

More recently, estimates of prevalence of hypertrophic scars are derived on assessments using validated instruments. The Vancouver Scar Scale is traditionally a well-known scale to evaluate burn scars. In 2017, Wallace et al. assessed the prevalence of hypertrophic scars, using the Modified Vancouver Scar Scale. Raised hypertrophic scarring over 1 mm was reported in 7.8% of the patients treated in a Western Australian burns unit up to 1 year post burn [4].

5.2.3 Prevalence of Contractures

Although contractures are a dominant feature after burn injuries, data on prevalence of burn scar contractures are scarce. In a recent review by Oosterwijk [5] et al., only 10 relevant studies were available for inclusion. The prevalence at discharge was 38–54% and decreased with an increasing time post burns.

The included studies indicated an elevated risk for contractures in deep or surgically treated burn injuries, in females and children. In addition, contractures seemed to occur more frequently in the upper extremity joints, specifically in the shoulder and elbows.

Assessment of scar contractures was based on range of motion measurement in six studies; in four studies, the method of scar contracture assessment was not described. In addition, study design, study period, study population and timing of scar contracture assessment varied largely. Consequently, the authors concluded that "prevalence of scar contractures after burn is insufficiently reported and varies considerably between studies." This impedes the analysis of determinants of scar contractures and possible interventions [5].

Recently, Schouten et al. assessed scar contractures in a prospective cohort study using passive ROM assessments up to 12 months. Scar contractures one year post burn were only found in operated burned joints. Scar contractures at discharge in non-operated joints all returned back to normal in 6 to 9 months. Again, scar contractures were more often seen in the upper part of the body, especially in the shoulder [6].

5.2.4 Scar Quality Assessment

In contrast to the assessment of scar hypertrophy or scar contractures, scar quality assessment addresses a broader assessment of scar-related characteristics, including colour, thickness, relief, pliability, pain and pruritus. The Patient Scar Assessment Scale and the Patient and Observer Scar Assessment Scale (POSAS), for example, consist of the two six-item numeric scales reflecting the patient's perspective and the observer's perspective. This is in contrast to another frequently used scale, the Vancouver Scar Scale, which reflects the observer perspective only and has some methodological difficulties, especially concerning the item "pigmentation."

The POSAS was introduced in 2004. Both the self-reported mean patient POSAS and the observer POSAS are based on scores on six individual scar characteristics. These scar characteristics are scored on a numerical 10-point scale, in which 1 represents a scar comparable with "normal skin" whereas 10 represents the "worst scar imaginable."

Using the POSAS, substantial scar morbidity is reported, even several years after the burn injury. In patients after mild to intermediate burn injuries, mean self-reported patient POSAS scores varied between 1.8 and 2.9 more than 2 years post [7]. In a similar sample 5 years post burn, these patient POSAS scores were even higher, reflecting more scar morbidity. The mean patient POSAS was 3.0, and 7% had a POSAS score above 4 (on a scale from 1 to 10) on all six scar characteristics.

In patients after severe burns (with a mean TBSA of 24.0%), scar morbidity was higher, with a patient POSAS of 4.5 (SD 2.0) [8].

5.2.5 Prevalence of Reconstructive Surgery

The need for reconstructive surgery after burn injuries can be viewed upon as an indicator for problematic scar development, requiring a surgical intervention to relieve scar morbidity. Of course, the possibilities to perform reconstructive surgery will influence the occurrence of reconstructive surgery.

Recent studies in patients after a burn centre admission in the Netherlands showed that 13.0% of these patients received reconstructive surgery in a ten-year follow-up period after burn injuries. In patients with head and neck burns, the prevalence of reconstructive surgery was 8.9% [9]. Vlies et al. reported a prevalence of 15% in patients after hand burns. These prevalences are lower than the one reported in the early 1990s by Prasad et al. (19.9%). This can probably be related not only to improvements in acute burn care between the 1970–1985 and 1990 but also to the more frequent use of non-surgical therapies in the rehabilitation phase, like silicones and laser therapy. Another explanation for these differences may be the higher burn size in the study of Prasad with a mean TBSA of 16.4% and 5.8% full-thickness burns, compared to our sample (9.8 and 3.4%). Also follow-up time differed; patients in the study of Prasad were followed for a variable period of 5 to 20 years.

Another Dutch study by Hoogewerf et al. in patients after head and neck burns described a prevalence of 5.3% reconstructive surgery. This prevalence is lower than the one found in the 10-year follow-up period, probably because of the shorter follow-up period of 2–7 years post burn.

5.2.6 Maturation Pattern

In general, hypertrophic scars develop in the first months after the burn injury. Then, scar hypertrophy is described

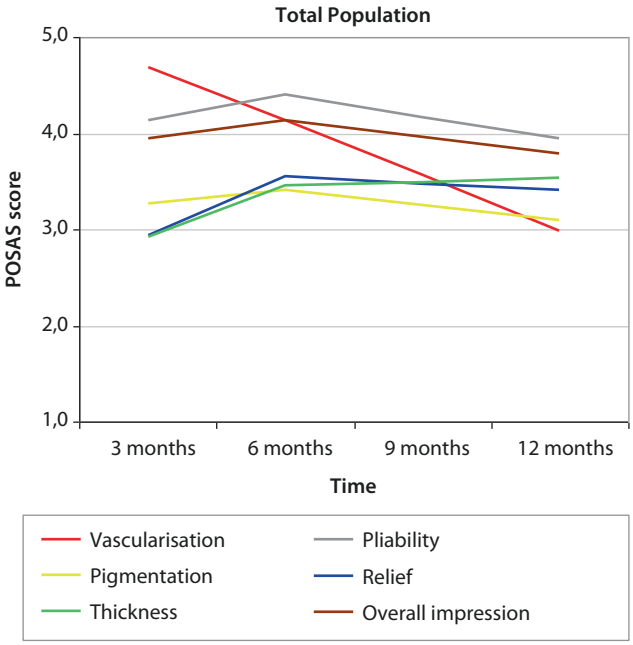

Fig. 5.1 Maturation pattern after burn injuries, assessed with observer scales of POSAS (Van der Wal et al., personal communication; see also Wound Repair Regen. 2012;20:676–87)

to increase up to 6 months. At 12 months, there is a tendency to regress, according to several studies [2].

Individual scar characteristics have an individual maturation pattern. Vascularization shows a continuous decrease from 3 months post burn onwards, and relief and thickness show increased scar morbidity during at least the first year post injury (Fig. 5.1).

5.3 Factors Predicting Scar Outcome After Burns

Several studies investigated the predictors of pathological scar formation after burn injuries.

Some groups of predictors can be distinguished, including patient, injury and treatment characteristics.

5.3.1 Patient Characteristics

A few patient characteristics are recognized for their predictive value in pathological scar formation.

Sex: The relation between sex and scar quality is ambiguous.

There are several studies reporting a poorer scar quality in females. In Dutch studies using the Patient and Observer Scar Assessment Scale (POSAS), a poorer scar quality was reported in females two and five years after burns. Observers reported a poorer scar quality in female participants two years post burn, but the females themselves reported similar scar quality, compared to their male counterparts. However, after taking skin type and surgical treatment into account, scar quality was similar [7].

In patients five years after burns, female participants reported a similar overall patient POSAS score but a poorer overall scar opinion, compared to men. This sex differences remained, also after controlling for other relevant factors including length of hospital stay [8].

In an Australian study predicting raised scars (<1 mm) in adults, based on the Modified Vancouver Scar Scale, females had an increased risk of raised scars, also after taking into account other relevant factors [4]. In a similar study in children, no gender differences were found.

However, in earlier studies, using a variety of scar assessments, this gender difference was not observed [1].

Age: An older age has been shown to reduce the risk for pathological scarring in several studies. The risk for raised scars was reduced in patients over 45 years of age, compared to patients 30 years of age and under [2]. In a paediatric study, the youngest children (0–5 years) were at higher risk to develop raised scars [10].

Skin type: Skin type is a well-known factor influencing the scar formation and scar quality. In one of the first studies on prediction of scar quality from Deitch in 1983, scar hypertrophy was more often reported in patients with a darker skin. In recent studies, skin type is often classified using the Fitzpatrick skin type test. This score classifies skin types in six categories, from type I (palest) to type VI (deeply pigmented dark brown to darkest brown). Having skin types V or VI was associated with a poorer scar quality, based on both the patient and observer POSAS [7]. In addition, darker skin (skin types IV–VI) has an increased risk on raised scars [4]. In children, this association was not reported [10].

5.3.2 Injury and Treatment Characteristics

Several injury and treatment characteristics have been documented to influence scar formation and scar quality.

These include several burn severity indicators, including increased burn size (percentage of total body surface area burned (TBSA)), high %TBSA full thickness, wound complications and a longer time to wound healing.

In addition, several treatment characteristics have been described to be related to poor scar quality, including a prolonged hospital stay, type of surgery (none, ReCell, skin grafting, dermal substitute), multi-

ple surgeries, repeated surgery in the same wound, reconstructive surgery and artificial ventilation [4, 10]. Again, all these treatment features are related to the severity of the burn injuries, complexity of wound healing and possible complications. Length of stay in these analyses is the representation or proxy for the severity of the burn injuries and the complexity of the burn care process including wound healing and possible complications.

5.3.3 Patient, Injury and Treatment Characteristics Combined

To identify the independent predictors of poor scar outcome, the potential predictors have to be taken into account together in one analysis, which requires adequate numbers to reach significant power of the analysis. Some examples of such studies are summarized here.

Raised scars in children up to 16 years of age, one year post burn, could be predicted by greater burn size (%TBSA), a prolonged healing time (over 14 days) and multiple surgical procedures. Patient characteristics did not contribute to this prediction of scars after burn injuries in children [10].

Raised scars in adults one year post burn could be predicted again by increasing burn size (%TBSA) and by the type of surgical intervention (as a proxy for burn depth), wound complications and prolonged hospital stay. In addition, patient predictors were found, being a young age (<30), the female gender and darker skin were for raised scars in adults [4].

Reported scar quality 2 years post burn could be predicted by one patient-related and one injury/treatment-related characteristic: a dark skin type and more than one operation in the same wound were independently related to lower long-term scar quality, 2 years after the injury [7]. Self-reported scar quality 5 years post burn was predicted by length of hospital stay. In addition, the female gender predicted the overall scar opinion. Thus, all other patient-, injury- or treatment-related potential risk factor predictors did no longer predict scar quality, after taking these predictors into account [8].

Some general remarks can be made based on these findings. Firstly, injury- and treatment-related characteristics are the main predictors of scar outcomes after burn injury. These characteristics are related to burn size (total body surface area burned) and burn depth (number or type of surgery) or the overall healing process in general (length of stay, wound healing complications). Intrinsic patient-related risk factors seem to play a role as well but are less consistent predictors of scar outcome. This includes the risk factors the female gender and also a younger age and darker skin.

An important limitation of three of the aforementioned studies is the sample size. In sample sizes up to 251 patients, only a limited number of predictors can be revealed in multivariate analysis. This was illustrated by the results of the adult study from Wallace et al.; their analyses on 616 people after burns revealed seven significant predictors [4, 10], compared to the maximum of three predictors in the other smaller-sized studies.

5.4 Clinical Relevance

Knowledge on risk factors for poor scar outcome can be used to tailor treatment, aftercare and scar prevention to these patients with a high-risk profile.

Current evidence shows that injury- and treatment-related characteristics are the main predictors of scar outcomes after burn injury. These characteristics are related to burn size (%TBSA) and burn depth (number or type of surgery) or the overall healing process in general (length of stay, wound healing complications). Intrinsic patient-related risk factors seem to play a role as well but are less consistent predictors of scar outcome. This includes the risk factors the female gender and also a younger age and darker skin.

Future studies, with greater sample sizes, will probably reveal additional predictors for scar outcome. Especially, paediatric scar outcome is not yet well studied.

5.5 Conclusion

Early studies on pathological scarring in burn wounds have distinguished between hypertrophic scars and contractures. Prevalences of hypertrophic scarring after burn injuries are reported between 8% and 67%; a recent prospective study revealed a prevalence of 8%. Data on prevalence of burn scar contractures are limited; reported prevalence at discharge varied between 38 and 54% and decreased with an increasing time post burn. Prevalence of reconstructive surgery after burn varied between 5 and 20%, up to 10 years post injury.

Factors predicting pathological scar formation after burn injuries include patient, injury and treatment characteristics. Injury- and treatment-related characteristics are the main predictors of scar outcomes after burn injury. These characteristics are related to burn size (total body surface area burned) and burn depth (number or type of surgery) or the overall healing process in general (length of stay, wound healing complications). Intrinsic patient-related risk factors seem to play a role

as well but are less consistent predictors of scar outcome. This includes the risk factors the female gender and also a younger age and darker skin.

Knowledge on risk factors for poor scar outcome can be used to tailor treatment, aftercare and scar prevention to these patients with a high-risk profile.

Take-Home Messages

- Pathological scarring in burn wounds can result in hypertrophic scars and/or contractures.
- Reported prevalence of hypertrophic scarring after burn injuries varied between 8% and 67%.
- Reported prevalence of burn scar contractures varied between 38 and 54%.
- About 5 to 20% of patient after burn injuries receive reconstructive surgery, reflecting scar pathology.
- Factors predicting pathological scar formation after burn injuries include patient, injury and treatment characteristics.
- Injury- and treatment-related characteristics are the main predictors of scar outcomes after burn injury, including burn size (TBSA burned), burn depth (number of type of surgery) or the overall healing process in general (length of stay, wound healing complications).
- Intrinsic patient-related risk factors, including the female gender and also a younger age and darker skin, are less consistent predictors of scar outcome.
- Knowledge on risk factors for poor scar outcome should be used to tailor treatment, aftercare and scar prevention to these patients with a high-risk profile.

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Scar Epidemiology and Consequences

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_6

6.1 Introduction and Background

Cutaneous scarring is a dynamic process following a physical alteration of the cutaneous barrier. It is a slow process, taking place in three phases: debridement, granulation and epidermization, each of these phases bringing into play different cellular mediators. Then comes the maturation phase of the scar, which reaches its final appearance usually after two years of evolution.

It is important to distinguish between defective scars, which may result out of poor surgical technique, issuing to a dermal separation, keeping the epidermal layer in continuity. These scars are stable over time and do not belong to the same category than pathological scars, which are true evolutionary abnormalities of cutaneous scarring, linked to abnormal cell proliferation of myofibroblasts, with different scenarios depending on the degree of anarchy of the collagenic bundles.

6.2 Reminder of the Spectrum of Scars

6.2.1 Contractures

Located generally opposite the joints or when a wound is perpendicular to the lines of Langer, they can alter considerably the function according to their importance and their localization. They are particularly common in burned patients or after a thin or semi-thick skin graft.

6.2.2 Extended Scar

They are mainly observed from the first postoperative weeks. Most often pale, asymptomatic, they pose mostly aesthetic problems without functional discomfort. Stretch marks (often abdominal) are a type of enlarged scar and a consequence of a rupture of the dermis, without epidermal alteration. The absence of elevation or thickening differentiates them from hypertrophic scars.

6.2.3 Atrophic Scar

The plan of these scars lies under the plan of healthy peripheral skin. They are usually small. Frequent on the face, they are mostly consequences of acne or chicken pox.

6.2.4 Hypertrophic Scar

They are characterized clinically by an elevation of the plane of the scar which is thickened, inflammatory, but which remains limited to the cicatricial banks. They never invade the healthy peripheral skin. They are also distinguished from keloid scars by their spontaneous regression within two years of the onset of the wound. They are often itchy and even painful.

6.2.5 Keloid Scar

Unlike hypertrophic scars, keloid scars extend beyond the margins and also affect healthy skin around the scar. Functional symptoms (itching and pain) are very common and hinder quality of life. They have no tendency to regress. After excision, the rate of recurrence is major, making the management of these scars, which must be multimodal, complex.

Pathological (hypertrophic or keloid) healing is a complex process, resulting from many factors. During normal healing, the myofibroblasts participating in the cutaneous contraction enter apoptosis. A lack of apoptosis of these myofibroblasts, and consequently their excessive accumulation, explains the occurrence of raised and inflammatory scars [1]. Another factor contributing to the pathogenesis of these scars is an accumulation of immature collagen [2].

6.3 Hypertrophic Scars

Hypertrophic scars are the result of excessive proliferation of myofibroblasts and increased deposition of collagen within the scar [1, 2]. The scar then exceeds to the surface of the healthy peripheral skin, can be inflammatory and itchy, and even painful. They differ from keloid scars due to their tendency to regress within two years and because they never exceed the scarred margins [3, 4, 5]. However, diagnostic errors are still common in practice.

6.4 Basic Epidemiology

The frequent confusion between hypertrophic scars and keloids (despite the above definitions) means that there is little data on their epidemiology. The studies found are often of low level of evidence, centered on a given geographic population. Mahdavian Belavary et al [5] studied the rate of hypertrophic scars after breast reduction or median sternotomy. At three months, 60% of patients developed hypertrophic scars. At one year, there was persistent hypertrophy in 32% of patients included. These figures are consistent with previous studies, found between 38% and 68% postoperative hypertrophic scars [6]. An analysis of data over time would be interesting, in order to evaluate the average duration of evolution of these scars. No sex ratio was found in the literature, as men and women were similarly affected by the occurrence of hypertrophic scars.

6.4.1 Risk Factors

Many risk factors for the occurrence of scarring hypertrophy are admitted. There are many studies in the literature but many are of a low level of proof (levels IV–V). Butzelaar et al. [7] found as major risk factors the age, the existence of allergic terrain, the existence of bacterial colonization (with or without infection) within the wound, and cutaneous tension. Most of the hypertrophic scars are found between the ages of 11 and 30 years. This can be explained by the presence of sagging skin with age and a decrease in the inflammatory response [8]. It is often accepted that a dark phototype (African skin) is a risk factor for hypertrophic scars. Nevertheless, in the literature, the studies are of a low level of proof and the opinion of the authors is partaged, not allowing to bring a valid and reliable conclusion to this idea. Unlike keloid scars, there does not appear to be a genetic cause for the occurrence of hypertrophic scars [9]. Butzelaar et al [7] found a protective trend of smoking for the development of hypertrophic scars. Cancer chemotherapy also seems to be a protective factor; however, there are many confounding factors to consider in the studies in question (role of cancer itself, possible undernutrition).

6.5 Keloid Scars

The keloid scar is an abnormality of cutaneous healing specific to humans. The main problems, apart from their unattractive and annoying appearance, are their non-improvement in the time and frequency of recurrence despite the medical and surgical treatments undertaken. They can even be aggravated by surgical resection if it is not strictly intra-lesional.

6.5.1 Basic Epidemiology

Again, few studies have investigated the prevalence or incidence of keloid scars. Yet each year, it is estimated that about 100 million scars are developed, and among them 11 million would become keloids [10].

In the literature, the prevalence varies widely according to the population studied [3, 11].The estimations are as follows:

- 4.5 to 16% in black and Hispanic populations of American origin
- 16% in Zaire
- only 0.09% in England

They are responsible for pruritus or pain in 20–40% of cases [3].

6.5.2 Risk Factors

Keloid scars may be found on all localizations, but are more frequent in some areas [11, 12]:

- Ear lobe
- Pre-stern and deltoid region
- Under umbilical area (pubic area)

These are areas where skin tension is important, thus joining the frequent locations of hypertrophic scars. By definition, they do not touch the mucous membranes.

They can be observed at any age but peak frequency is between 10 and 30 years [13, 18]. Some authors explain this by the role of cutaneous tension which is more important in young subjects [3]. There also appears to be a hormonal factor, keloid scars being more frequent in the pubertal period [3]. The hormonal role is still discussed: if they are actually more common in pubertal period, keloids that appear at these ages also have a tendency to hyperpigmentation. During pregnancy, some authors have observed a more frequent appearance or enlargement of keloid scars [14].

It is also accepted that subjects with a dark phototype are more frequently affected, although we may experience keloid scars in all phototypes [15, 16].

The hypothesis of a genetic predisposition is beginning to be well anchored. It is estimated that 5 to 10% of cases have family keloids [17]. Marneros et al. [18] found that transmission is autosomal-dominant mode, the clinical penetrance is incomplete, and the expression is highly variable. There appears to be susceptibility to the development of keloids in Japanese and African-American families in relation to chromosomes 2 and 7 [19].

There are cases of spontaneous keloids in the literature, but these would ultimately be due to undetected microtrauma [20]

6.6 Specific Situation: The Burnt Patient Healing

Hypertrophic scarring after a burn (whether it has healed spontaneously or required skin grafting) is a common problem in clinical practice. In addition to being dysgraculous, these scars are generally itchy and even painful and can significantly alter function and quality of life, especially if they are responsible for skin retraction. Since this type of healing is quite specific to the burned patient, we chose to treat it in a separate chapter.

6.6.1 Scarred Hypertrophy in Burned Patients: Epidemiology

The data of the literature are very variable on this subject. In the majority of cases, the studies are small, and few distinctions are made between the different populations (adults vs. children, light phototype vs. dark phototype, spontaneously scarred burn vs. transplanted).

Deitch et al [21] found a prevalence of 15% (white patients) to 30% (black patients) in burn patients who healed spontaneously.

Mc Donald and Deitch [22] analyzed the prevalence of scar hypertrophy in patients treated with thin skin grafts. Of the children included, 75% had cicatricial hypertrophy. In adults, the prevalence was 50% in patients with black skin, compared to 7% in patients with fair skin.

Spurr and Shakespeare [23] followed 82 children and found 65% hypertrophic scars. Bombaro et al. [24] reported an average of 67% cicatricial hypertrophy (up to 100% in children with non-white skin). Finally, Delavary et al. [25] found a rate of 60% hypertrophic scars in burn patients, mainly in the first three months after the onset of the burn. According to them, young and non-smoking subjects are more likely to develop hypertrophic scars. In each of these studies, the number of patients remains low and the population monocentric. Further and larger studies would be needed to better identify populations at risk. The risk factors identified to date are young age, location of the upper limbs or neck, dark phototype, repetition of surgical procedures, initial severity of burn, and time to heal [25]. Lawrence et al [26] also find these risk factors in the literature, in addition to the female sex and skin grafts that required expansion (mesh-graft). Their review of the literature found a prevalence of hypertrophic scars ranging between 32 and 72%.

6.6.2 Retracted Scars

Retraction or contraction of the skin following a burn results from an excessive, hypertrophic scarring, of which we have just spoken. Functional consequences can be major and threaten the socio-professional future of patients. They are frequent and particularly disabling in the articular areas. The prevalence is very variable according to the studies, one finds on average between 38 and 54% of contraction in the years following the occurrence of the burn [27]. According to the authors, these would be more common in severely burned patients, children, women, and upper limb. Gangemi et al. [28] analyzed 703 burned patients and found on average 77% of pathological scars (44% hypertrophy, 5% contractures, 28% combining both). They also found as risk factors the female sex, the young age, localization of the burning of the upper limb or the neck, the repetition of the surgical procedures, and the expansion of the skin grafts when these are realized.

6.7 Impact of Scars

Although many studies concern the epidemiology and management of scars, very few have been interested in the consequences of these scars. However, it is estimated that more than one in two patients are not satisfied with the appearance of their scars, 20% of patients suffer from anxiety, and more than 50% feel that their privacy is affected by the presence of their scars [29].

6.8 Conclusion

Few studies have really focused on the epidemiology of scars and their consequences. When studies are conducted, they often concentrate around a given geographic population and report only a small number of patients. There are probably many lost sight, since many patients live surely with their scars (hypertrophic, keloids) without consulting. Larger scale studies should be carried out to determine the frequency of occurrence of these scarring abnormalities, in order to better identify them and, consequently, to better treat them.

Take Home Message

The epidemiology of pathologic scars is diverse. Sixty percent of scars located on the thorax may become hypertrophic, and a patient from Zaire has 100% more risks to develop a keloid than a patient native from England. Burns may issue up to 77% of pathologic scars, combining hypertrophic, retractile, and keloid scars. The role of hormonal status, nutrition, and many other factors has been suspected in keloids.

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Other Scar Types: Optimal Functional and Aesthetic Outcome of Scarring in Cleft Patients

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_7

7.1 Background

Cleft lip and palate are facial and oral malformation due to failures in the embryologic craniofacial development during early pregnancy. They occur in approximately 1 in 750/1000 births in Europe, which makes it the most common congenital craniofacial abnormality. Different variations in phenotype of this malformation exist. It can occur unilateral (left or right) or bilateral, with involvement of lip and/or alveolus and/or palate and can be microform, incomplete, or complete. Unilateral cleft lip and palate are the most common type, whereby the upper lip, the orbicularis muscle, the alveolar bone, the floor of the nose, and the hard and soft palate are interrupted, creating an open communication between nasopharynx and oropharynx.

Patients with a cleft lip and palate are treated in specialized cleft centers by a multidisciplinary team, consisting of geneticists; (plastic) surgeons; orthodontists; dentists; ear, nose, and throat (ENT) doctors; speech and language therapists; and psychologists. All surgical interventions aimed at closure of the cleft lip and palate induce restriction of maxillary growth. Surgical timing, staging, and techniques differ between treatment centers. The lip is usually closed at 3–6 months after birth and the soft palate at 6–12 months. In some cleft centers, the hard palate is closed before 12 months after birth in either a one-stage or two-stage procedure. Other cleft centers prefer to close the hard palate later in life, at 18 months to 3 years, or during the closure of the alveolar gap at the age of 8–11 years.

Having cleft lip and/or palate has a noteworthy impact on quality of life and psychosocial functioning. Postoperative scarring is a common cause of patient dissatisfaction. The degree of postoperative scarring in cleft patients is associated with symptoms of anxiety, depression, and a lower self-esteem. For cleft surgeons, every possible measure to optimize functional and aesthetic outcome is important.

7.2 Objectives of Cleft Lip Surgery

The goal of cleft lip surgery is to close the lip separation, provide optimal function in terms of speech, mastication, dental protection, breathing and feeding, and provide an aesthetically pleasing facial scar and optimal shape of nose and nostril. The visible facial scar and its effect on nose and lip aesthetics are a daily reminder to the patient of its underlying cause. Over the years, different surgical techniques have been described regarding surgical closure of the cleft lip. The ideal technique should create a balanced lip, allow for easy adjustments, and produce a favorable scar pattern combined with a symmetrical shape of the nose. Closure of a cleft lip, also called "cheilorrhaphy," is a functional and aesthetic reconstruction of the upper lip, orbicularis muscle, nasal floor, and ala.

Table 7.1 Short overview of the "surgical treatment of cleft patients" protocol of the Amsterdam University Medical Center

Unilateral cleft lip and palate	Bilateral cleft lip and palate	Cleft palate
3 months: Lip closure	3 months: Lip closure	
9 months: Palatography	9 months: Palatography	9 months: Palatography
7–9 years: If necessary, hard palate closure If necessary, orthognathic surgery	7–9 years: If necessary, hard palate closure if necessary, orthognathic surgery	7–9 years: Hard palate closure
>15 years If necessary, secondary corrections	>15 years If necessary, secondary corrections	>15 years If necessary, secondary corrections
>17 years If necessary, rhinoplasty	>17 years If necessary, rhinoplasty	

7.3 Treatment Protocol

As stated above, surgical timing, staging, and techniques differ between treatment centers. In Table 7.1, a short overview of the "surgical treatment of cleft patients" protocol of the Amsterdam University Medical Center is provided.

7.4 Cleft Lip Reconstruction: Surgical Techniques

Precise surgical technique and adequate aligning of anatomical structures is important for the postoperative aesthetic result and scar formation. Patients with a cleft lip have, besides the obvious interrupted upper lip, a typical flared nostril and a septum deviation. As stated above, different surgical techniques are used to reconstruct this defect, each with its pros and cons. Though many approaches exist, the Millard (rotation advancement) and Fisher (anatomic subunit) approaches are historically most frequently performed.

7.4.1 Unilateral Cleft Lip

7.4.1.1 Millard Lip Closure

Since the 1950s, the Millard rotation advancement technique for surgical lip closure was the most popular among cleft surgeons. It consists of downward rotation of the medial cleft component and a lateral lip advancement flap. The majority of the scar can be placed at the philtral column. A disadvantage of this approach is that the superior part of the scar crosses the philtrum perpendicularly at the columellar base. Various modifications of the traditional Millard technique have been developed to overcome this disadvantage.

7.4.1.2 Fisher Lip Closure

In 2005, Fisher published his lip closure technique, in which the anatomical subunit principles guide lip repair. In this technique, a circumferential incision at the cleft side of the columella is continued to the Cupid's bow top in a straight manner. This mirrors the unaffected philtral ridge. To lengthen the medial flap, small inlet incisions are frequently necessary. To prevent upper lip shortening, a triangular flap above the cutaneous roll can be incorporated (◘ Figs. 7.1, 7.2, and 7.3).

7.4.2 Bilateral Cleft Lip

"Bilateral cleft lip" can manifest in different ways, in which symmetrical complete bilateral

cleft lip–cleft palate is the most prevalent. When looking at the lip alone, the bilateral symmetrical complete variant accounts for 50% of cases, bilateral incomplete for 25%, and asymmetrical bilateral (complete/incomplete) for 25%. A one-stage surgical approach is advocated in most centers.

The Millard–Mulliken technique is frequently employed. A cranially based philtrum flap is created, the gap is closed, and orbicularis oris continuity and lip continuity are restored. Ideally, both scars are positioned symmetrically at the philtral ridge.

In several cleft centers these surgical techniques are combined with preoperative nasoalveolar molding (NAM). The aim of NAM is to improve the shape and form of the alveolar wall and nose and to bring the divided lip together with an orthodontic plate, nasal spring, and tape (Plaatje). In our center NAM is only used in cases with bilateral cleft lips. Furthermore, a nasal conformer is used in unilateral cases to improve the shape of the affected nostril postoperative.

7.4.3 Additional Measures to Improve Scarring

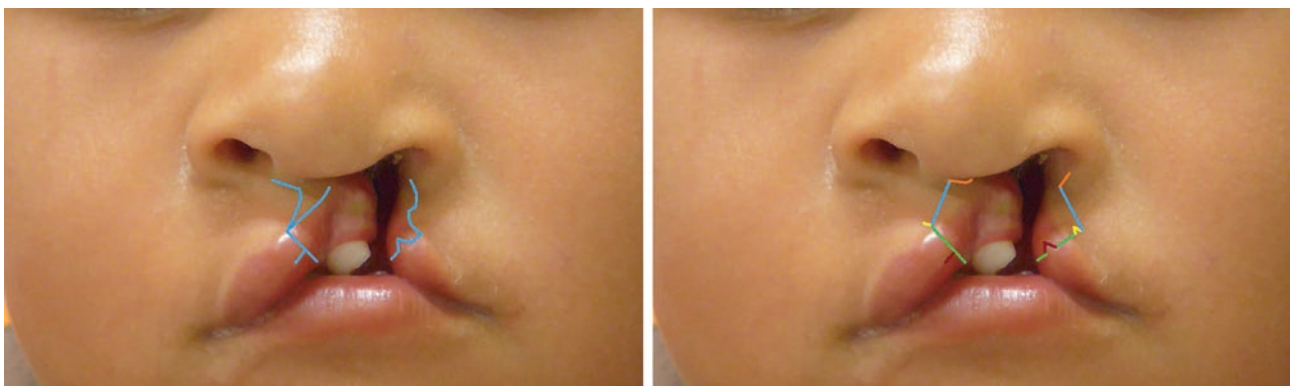
Visible facial scarring after cleft lip repair is inevitable. There are however some perioperative measures that can be taken to minimize scar morbidity in terms of hypertrophy and contraction.

7.4.3.1 Perioperative Botulinum Toxin

After surgical correction of the lip and philtrum, the underlying orbicularis oris muscle contracts in a direction perpendicular to the cutaneous scar. This results in accentuation of dynamic rhytides, which may slowly result in widening of the surgical scar. Some surgical teams temporarily paralyze the orbicularis oris muscle, by intraoperatively injecting it with botulinum toxin. Several studies showed a beneficial effect on postoperative scar width; however, the sample size is relatively small in most studies, and objective assessment tools are scarcely employed.

7.4.3.2 Sutureless Skin Closure

Using (too many) cutaneous sutures in a facial wound may cause a foreign body reaction and subsequent suboptimal scarring. The possibility of visible cross-hatching of sutures is unappealing.



◘ **Fig. 7.1** Preoperative planning for Millard (left) and Fisher (right) lip closure

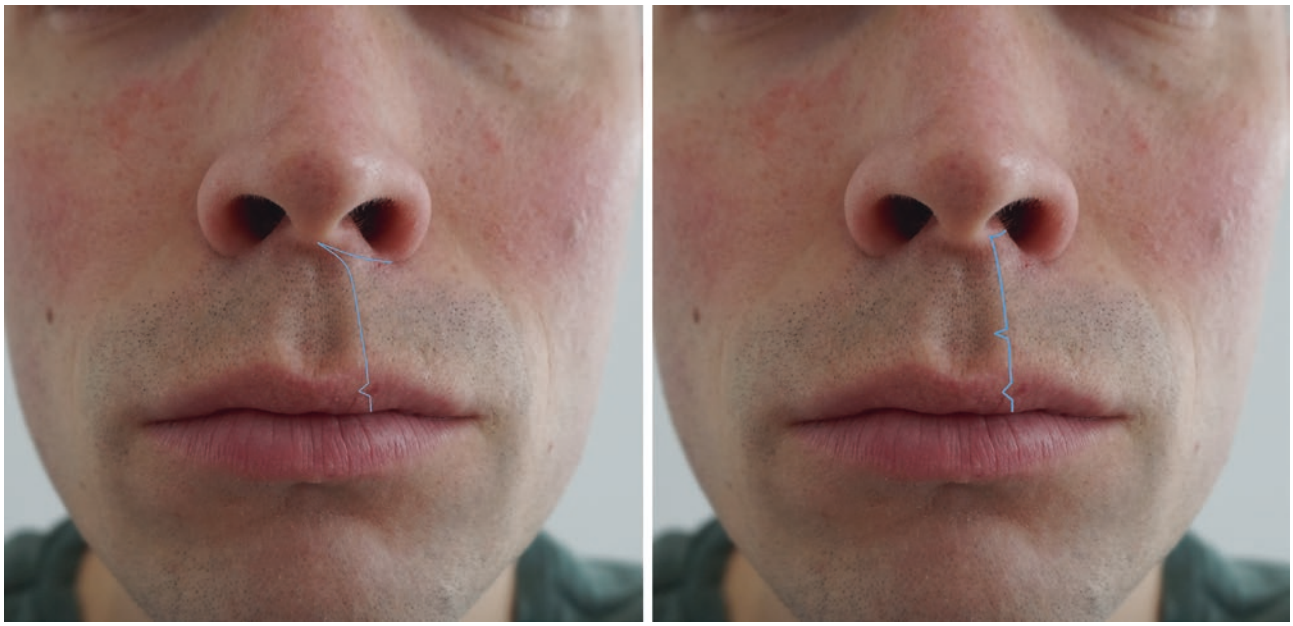


Fig. 7.2 Postoperative scar pattern after Millard (left) and Fisher (right) lip closure. Note, different surgeons use different modifications of both techniques

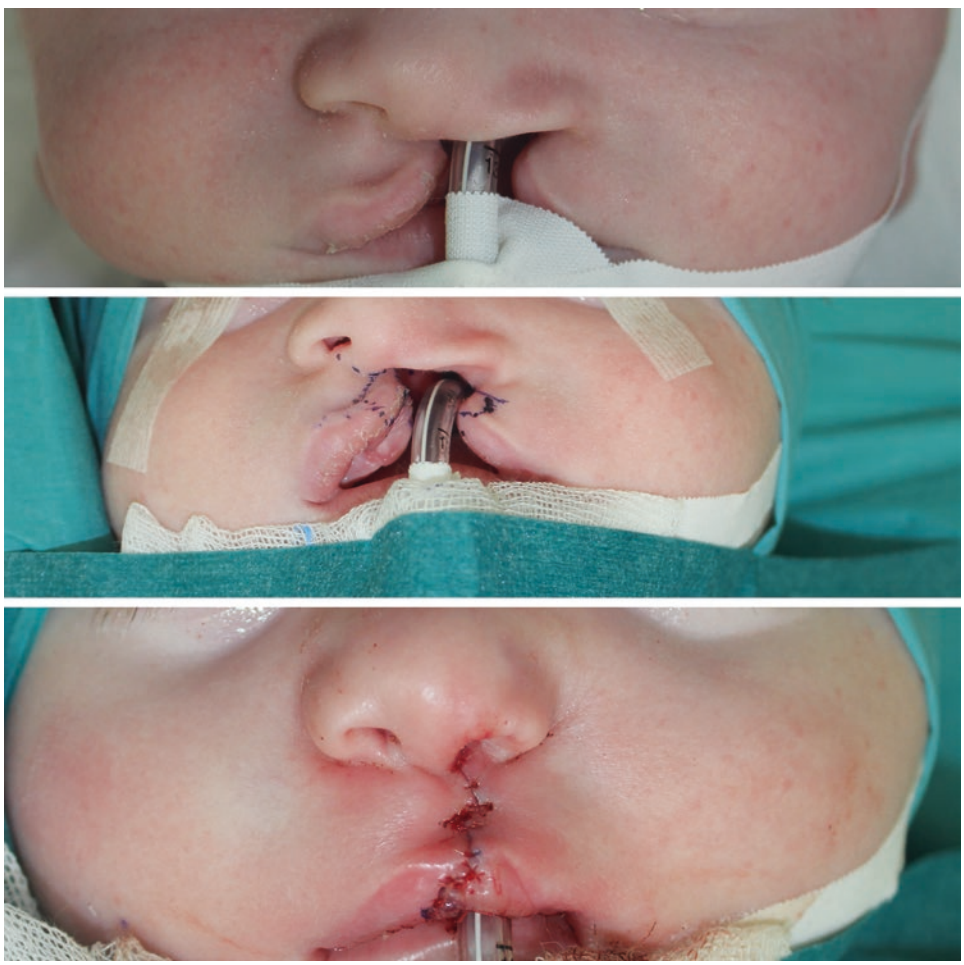


Fig. 7.3 Preoperative (upper), planning (middle), and direct postoperative (lower) result of the Fisher lip closing technique in a patient with complete unilateral cleft lip and palate

Some advocate the use of sutureless skin closure, in which the cutaneous layer approximation is performed using surgical glue, such as butyl cyanoacrylate or amcrylate. An additional advantage is that is generally faster to perform, which reduces intraoperative time. No large, prospective comparative studies are performed on this subject.

7.4.3.3 Silicone Application

Topical silicone application is used for treating/preventing hypertrophic scars in different body locations. This is also the case for cheiloplasty scars. To which extent hypertrophic cheiloplasty scars can be treated/prevented with this application is unknown. Side effects of this treatment comprise skin rash and fusibility problems, such as loss of adhesiveness. Using silicone gel seems to be non-inferior to silicone sheeting.

7.4.3.4 Postoperative Laser Therapy

Use of carbon dioxide fractional laser, sometimes combined with intense pulsed light treatment, in the direct postoperative phase is shown to improve scars in terms of pliability and color. Though proven safe, pain during the session and crust formation are frequently reported.

7.4.3.5 Hair Transplantation

In male cleft patients, limited or missing moustache growth may be noticeable in the scarred area, especially in men with dark hair and ample hair growth. Hair graft transplantation can be performed; however, the poor vascularization of scar tissue poses a problem, because this is not a good bed for graft survival. Some use fat grafting of the scar before hair transplantation to optimize graft survival.

7.5 Secondary Cleft Lip Reconstruction

Secondary cleft lip reconstruction is frequently performed due to scar contracture, which has a negative impact on lip, philtrum, and nose aesthetics. The exact incidence of secondary lip correction is unknown and dependent on many factors, for example, patient factors, treatment protocol, access to health care services, etc. In the Western world, the estimated incidence is 40–60%. Conservative management of these cases is seldom successful. Surgical correction typically employs use of the Rose–Thompson effect (in which a scar is lengthened by using concave excisions of the scar, which is subsequently closed in a straight line), one or multiple Z-plasties, or a combination of these strategies. Some perform fat grafting of the scar to loosen it and provide more length. Remaining volume deficiencies, for example, volume deficiencies of the lip, can be restored in the same procedure with lipofilling or dermal fat grafts.

7.6 Evaluation of Aesthetic Outcome

One of the goals in the treatment of cleft lip (and palate) repair is improving nasolabial aesthetics by restoring symmetry and proportion of the nose and lip. Traditionally, aesthetic assessment is performed by symmetry measurements with a caliper. The last two decades, several scoring systems have been proposed for a simpler and quicker assessment. Most of these scoring systems use two-dimensional (2D) photographs in combination with Likert or visual analog (VAS) scales. The most frequently used method is the Asher–McDade (AMD) system, which utilizes a five-point Likert scale ranging from "excellent" to "very poor" to grade four anatomical nasal and lip structures. In 2016, the Cleft Aesthetic Rating Scale (CARS) was developed as a new tool to allow rapid assessment of the nose and lip separately.

The majority of assessment methods are focusing on symmetry and on the shape of the nose and lip, whereas the scar appears to be of secondary importance. In 2010, the Patient and Observer Scar Assessment Scale (POSAS) was proposed to assess the scar after cleft lip repair. Nevertheless, it remains unknown to which extend visible scarring plays a role in facial aesthetics after cleft surgery.

To determine the aesthetic outcome in a more objective way, measurements using three-dimensional (3D) photographs seem to be promising nowadays. These methods show a high reliability, but these techniques require expertise and costly equipment and are therefore not readily available worldwide. To compromise, computer-based programs, like SymNose, have been developed. These programs allow symmetry measurements on 2D images of the nose and lip by tracing the outline of the upper lip and the lower border of the nose. By reflecting the left side of the midline over the right, the percentage mismatch of the nonoverlapping area is calculated.

However, an internationally accepted assessment method for the aesthetic evaluation of cleft lips is still not available.

7.6.1 Palatal Scarring

7.6.1.1 Palatal Closure

Both the hard palate and soft palate can be involved in palatal clefts, resulting in a gap from anterior to posterior, affecting the maxilla, the mucosa, the levator veli

palatini muscle, the tensor veli palatini muscle, and uvula muscle. An open communication between the nasopharynx and oropharynx prevents the infant to create an intraoral negative pressure, which is mandatory for productive suckling during (breast)feeding. A positive oropharyngeal pressure and elevation of the palate allows for the normal articulation of the oral consonants, most notably the oral stop-plosives, [p, t, k, b, d, g] in English. This can only be achieved by partitioning the oropharynx from the nasopharynx. Therefore, the aim of palatal closure, also called "palatography" or "palatoplasty," is functional reconstruction of structures that are necessary for feeding and speech development early in life. Different types of palatoplasties have been described to close the soft and the hard palate whereby several surgical considerations must be addressed. The most important anatomical structure, which should not be harmed during surgery is the greater palatine neurovascular bundle, proceeding through the greater palatine foramen through the lateral posterior hard palate. It is essential to obtain a tension-free closure of the palatal flaps, preventing compression or stretching of the neurovascular bundle. Releasing incisions may be necessary to achieve complete closure from anterior to posterior.

7.6.1.2 Timing of Palatal Closure

Impaired maxillary growth and an abnormal speech development are common findings in

patients after repaired cleft lip and palate. Delayed closure of the palate beyond 12 years or no closure at all minimizes abnormal facial growth, yet early closure of the palate, that is, before 12 months after birth, is necessary for normal speech development. Studies on speech development, maxillary growth, and timing of palatal closure show different results due to confounding variables as surgical technique, surgeon's experience level, and lack of standardized speech outcome or standardized indications for secondary maxillary surgery. Therefore, consensus on the optimal timing of palatal closure has not yet been reached.

7.6.1.3 Maxillary Growth

Impaired maxillary growth in cleft patients often results in typical features as crowding, lateral crossbite, and open bite. The exact pathophysiology of abnormal facial growth after cleft lip and palate repair remains unclear. It is a widely accepted hypothesis that abnormal maxillary growth has an iatrogenic cause and is secondary to surgical intervention due to scarring. However, other studies suggest that intrinsic maxillary underdevelopment contribute to impaired facial growth as well. It is most likely that a combination of intrinsic and iatrogenic factors is responsible, making it mandatory for a surgeon to minimize scarring in the oral cavity.

7.6.1.4 Speech Development

Due to a congenital short palate, hypernasal speech, and nasal air emission during speech are common findings in children after a cleft palate repair. Hypernasality and nasal air leakage are often the result of velopharyngeal insufficiency, which means that the velopharyngeal valve does not close completely and consistently during the production of oral sounds. As scarring tissue tends to contract in longitudinal direction, the palate frequently becomes even shorter or movement of the soft palate becomes inadequate, preventing the soft palate to make contact with the pharyngeal wall. Several techniques have been described to create more length of the palate, such as the V–Y pushback repair (Veau–Wardill–Kilner), the buccal mucosal flap, the double opposing Z-plasty (Furlow), or the lengthening of the soft palate with a pharyngoplasty.

7.7 Conclusion

Cleft lip and palate scars influence lip, philtrum, and nose aesthetics, as well as speech and growth of the maxilla. Optimal scar management can be divided in surgical (precise surgical technique, planning, and adequate aligning of anatomical structures) and nonsurgical methods (botulinum toxin, silicone application, carbon dioxide fractional laser).

Take-Home Message

- Cleft lip and palate are facial and oral malformation due to failures in the embryologic craniofacial development during early pregnancy.
- The goal of cleft lip surgery is to close the lip separation; provide optimal function in terms of speech, mastication, dental protection, breathing and feeding; and provide an aesthetically pleasing facial scar.
- Cleft lip scars influence lip, philtrum, and nose aesthetics.
- Optimal scar management can be divided in surgical (precise surgical technique, planning, and adequate aligning of anatomical structures).
- And nonsurgical methods (botulinum toxin, silicone application, carbon dioxide fractional laser).
- In secondary lip correction, cleft surgeons typically make use of the Rose–Thompson effect, one or multiple Z-plasties, or a combination of these strategies.

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Hypertrophic and Keloid Scar: Genetics and Proteomic Studies

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Genetics of Keloid Scarring

Alia Sadiq, Nonhlanhla P. Khumalo, and Ardeshir Bayat

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8.1 Background

Overview Keloid disease (KD) is an aesthetically and physically distressing skin disorder [74]. KD is considered a benign tumor of the dermis that develops as a result of a dysregulated healing response to cutaneous wounding [88]. Phenotypically, it is an exophytic proliferative fibrous growth of ill-defined etiopathogenesis [15, 17]. Keloid scarring is an enigma and a challenge to clinicians especially dermatologists and surgeons [87], due to its poor response to clinical management [88].

Keloids are reported to have a high incidence in darker skin races and certain ethnicities of Afro-Caribbean origin [4]. The incidence of keloid cases is 16% in black Africans [15] and keloid predominance in females as compared to the males might be due to more piercing trends in females [82].

This benign skin disease can either occur sporadically, or can exhibit a familial pattern. Keloid disease is considered a genetic disease due to a strong genetic susceptibility to keloid formation as it occurs predominantly in people of African and Asian descent, runs in families, and has been found in twins. However, a well-defined comprehensive mode of inheritance still remains unknown due to insufficient studies to uncover the genetic basis of keloid formation. Nevertheless, inheritance patterns for X-Linked or autosomal dominant trait have been found in families with keloids [71]. Although no specific genes have been identified, that is directly linked to the development of keloids, a few genetic loci have been reported to have a potential role in disease susceptibility. A study conducted in a Japanese population revealed four potential SNPs (single-nucleotide polymorphisms) in three chromosomal regions [76]. Anatomical sites affected with KD also vary in different keloid-prone families [9]. Keloid scarring may comprise of multiple genes, and affected individuals could possess variable genetic susceptibility for a set of genes or gene mutations associated with keloid phenotype [4]. Association studies for keloids such as gene polymorphisms and mutations have been conducted for some genes including SMAD3, SMAD7, and SMAD6, TGF-β1–3, and TGF-βRI-III to investigate the respective genetic basis of disease pathology. Some genetic networks such as cellular apoptosis, MAPKs, TGF-β, IL-6 and PAI-1 have also been studied in keloid pathology [8, 10–13, 15, 99] and also found associated with immunogenic processes as well as other biological pathways (PAI-1, Bcl-2, p53, and collagen deposition) [88]. Complexity and differences in the inheritance modes and familial keloid scarring reflect the variability and heterogeneity in genetic susceptibility, family history, twin genetic makeup, inheritance patterns, linkage, genetic associations, variation in gene expression and respective gene pathways, HLA (human leukocyte antigen) polymorphism, epigenetics, and ethnic populations [88]. Currently, none of hypothesized mechanisms can directly explain the disease pathology. Moreover, the lack of effective treatment options underlines the lack of understanding about disease process and complex and multivariable pathogenesis [74].

Objectives The objectives of this review are to investigate the evidence related to the genetic basis and its association with keloid disease. A comprehensive literature search was performed using PubMed, Google Scholar, CNKI and Embase databases, by applying combinations of relevant MeSH (Medical Subject Headings) words as title. The key search terms included "Keloid, HLA immunogenetics, Linkage, and Large scale population SNP analysis." The appropriate keywords included "Keloid, RNA Sequence analysis, Microarray, Micro RNA, Methylation, Mutation, Epigenetics, and FISH." All retrieved records were compiled in the study for comprehensive review and evaluated based on significance, methodology, evidence, and reproducibility (Fig. 8.1).

8.2 HLA Immunogenetics

Human leukocyte antigen (HLA) is the only complex genetic polymorphic system present on the 6th chromosome (short arm) and is involved in presentation and processing of peptide antigens via HLA class I and II [23]. The association or involvement of HLA in keloid etiology remains elusive as the pathology of dermal fibrosis and poor wound-healing remain ill understood [74].

A study conducted in Caucasians and Chinese Hans populations demonstrated the involvement of immunogenetics (HLA alleles) in keloid etiology. Generally, environmental exposure during the wound-healing process alters the antigen presentation and expression levels of HLA molecules that trigger respective immune response including prolonged inflammation and subsequent release of profibrotic cytokine/chemokines contributing to the excessive extracellular matrix (ECM) deposition, leading to the development of the keloid phenotype. The presence of (altered) immune cells in keloids, provides the insight into the disease pathology. Variable/altered gene and protein expression in keloids supports the contribution of a dysregulated immune system for disease progression or development [4]. The association of immunogenic molecules with the keloid phenotype, has been shown by a study, in which peripheral blood mononuclear cells of keloid patient exhibited increased expression levels of HLA-DR, -DQ, -DP and CD1a molecules in keloid patients [57].

The association of keloids with HLA-I alleles, has been studied in Chinese Han population (192 patients and 252 healthy individuals) to find out the HLA status

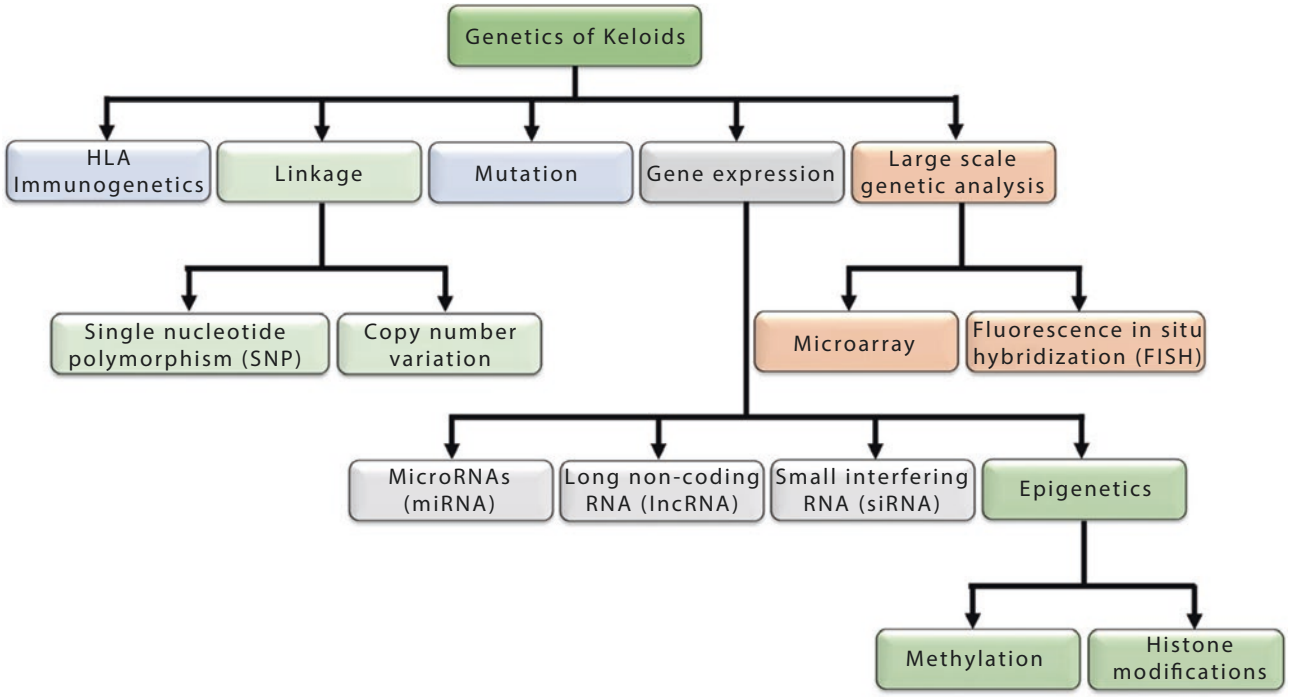

Fig. 8.1 Association of various genetic elements with keloid development

as a potential contributor to the keloids formation. The frequencies of HLA-A*03, A*25, Cw*0802, and B*07 were significantly high in keloid group but, the frequency of HLA-A*01 was highly decreased in comparison with healthy individuals. This study described high risk haplotypes (A*03-B*07, A*25-B*07, A*03-Cw*0802, A*25-Cw*0802, and B*07-Cw*0802) as contributing components in keloid formation. Interestingly, keloid site specificities, number, severity and details of family inheritance were also associated with specific alleles of HLA class. It shows that maybe these alleles are linked (linkage) with genes, which are responsible for keloid susceptibility [65]. Of note, HLA-I alleles (A*01, A*03, A*25, B*07 and Cw*08:02, HLA-DQA1 and DQB1) previously associated with KD in participants of Chinese ethnicity were shown to have no significant differences in allele frequencies in keloid cases from Jamaican Afro-Caribbean ethnic group [4].

Keloid patients were also found to have an association with blood type A and human leukocyte antigens HLA-B14, HLA-B21, HLA-BW35, HLA−DR5, HLA-DRB1, HLA−DQA1, HLA-DQB1, and HLA-DQW3 [78, 88, 110]. The association of HLA-I histocompatibility antigens, patient's family history with earlobe keloids pathology, has been studied in females of Black ethnic group. This study revealed some factors that appear in high frequency and acts as a risk factor when associated with: (i) HLA-A 9, (ii) HLA-A 23, (iii) HLA-Aw 34, (iv) HLA-Cw 2 antigens, history of (v) hypertension and (vi) post-ear piercing infection [29].

Association between HLA-DRB1 phenotype and keloid etiology has been studied in Caucasians populations of Northern European origin (keloid cases n = 67, control n = 537). It was revealed that frequency of HLA-DRB1*15 was high (38.8%) in Caucasians keloid cases, which appeared as a risk factor of developing KD following injury [17]. Frequencies of serologically detectable HLA antigens, i.e., HLA-B14 and HLA-Bw16, were subsequently found to be more (25%) common as compared to the control, which further suggests that, the individuals having HLA-B14 or HLABwl6 phenotype may be at risk for keloid formation [51].

It seems that most likely there is an association between alleles of HLA class and/or shield against dermal fibrosis, because allele loci (DQ and DR) from class II is a promising genetic marker owing significance contribution in poor wound healing and fibrosis [74]. All of these investigations deliver a strong statement about significant involvement of immunogenic component in keloid pathogenesis [19, 23].

8.3 Linkage

The prevalence of KD in identical twins, in families, in certain ethnicities, and at multiple sites strongly supports a genetic predisposition in the development of keloid phenotype [9, 71]. Certainly, the risk of KD occurrence is higher in genetically susceptible individuals (Bayat et al. [8, 12, 16]). In addition to that, recur-

rence rate (50%) is also higher in the African population with family history having positive keloid cases [9]. The linkage loci of KD were initially found to be on chromosomes 2q23 and 7p11 by Marneros et al. [72], but no putative gene target was further identified.

Single-nucleotide polymorphisms (commonly found to be useful genetic markers in various association studies) may also confer a risk for keloid disease development, such as PTEN (The phosphatase and tensin homolog) gene polymorphisms at rs2299939, rs17431184, rs555895, and rs701848) were found significantly related with high risk of keloid development in Chinese Han population. In addition, it was found that CC genotype from rs2299939 appeared as a risk factor in keloid patients as compared to ACTC haplotype prevalence in population, which seems protective factor against keloid formation [55, 56].

The GWAS (genome-wide association study) identified three keloid susceptibility loci (rs873549 at 1q41, rs8032158 at 15p21.3 and rs940187 and rs1511412 at 3q22.3) in a Japanese population. Furthermore, an association study of these susceptibility loci was also investigated in keloid patients from Chinese Han population. The SNPs 1q41 (rs873549, and rs1442440,) and 15q21.3 (rs2271289 present in NEDD4) revealed significant association with keloid in the Chinese Han population. In addition, AG haplotype was identified as risk factor whereas, GA and AA haplotypes appeared as protective factors from rs1442440 and rs873549 SNPs. It is also suggested that 15q21.3 and 1q41 loci shows genetic association and predisposition for keloid formation in Japanese and Chinese Han populations [116].

Predisposing genes also showed linkage association with keloid susceptibility genes. A study conducted in a selected Han Chinese keloid pedigree, mapped to the region about 1 Mbp on chromosomes 10q23.31, between Fas gene marker D10S1765 and D10S1735, provides the first genetic evidence of a predisposing Fas gene linkage association with keloid susceptibility genes [22].

Another genome-wide association research study (keloid cases =824, Healthy cases= 3205) found strong association of keloid cases with four more SNP loci present at three chromosomal locations (3q22.3–23, 1q41, and 15q21.3) in a Japanese population. It was found that SNP rs873549 at chromosome 1 showed the most significant association with keloid cases [76].

The linkage between the susceptibility locus (18q21.1, SMAD, and PIAS2) to keloid and two loci, 18q21.1and 15q22.31-q23, was also investigated through pedigree linkage analysis in a five-generation Han Chinese keloid family. Seven critical regions of microsatellite markers on chromosomes 18q21.1 and 15q22.31-q23 and were included in analysis. Out of the seven markers, only two (D18S460, D18S467) showed linkage to the disease locus [108]. SMAD genes 3, 6, and 7 are known to be involved in fibrotic disorders, and their association with keloid disease susceptibility was also studied in Jamaican keloid patients. Thirty-five SNPs across these genes were genotyped using time-of-flight mass spectrometry (MALDI-TOF MS) and iPLEX assay. Linkage disequilibrium (LD) was established between several of the SNPs investigated. These findings indicated that the SMAD SNPs were not significantly associated with high risk of keloid formation in the Jamaican population. This study also highlighted the importance of identification of genetic bio-markers as a candidate such as SMAD, which can be helpful diagnostic, prognostic tool and can provide hope for development of new therapeutics for keloid scar management [15].

Keloid predisposition loci at chromosome 7p11 was studied in a Chinese population pedigree [21] consisting of 5 affected generations and a total of 32 members. Four microsatellites on chromosome 7p11 were selected as the genetic markers. This study provided the first genetic indication that keloid predisposition loci did not locate on chromosome 7p11 in Chinese population, furthermore, it suggested that familial keloid predisposition loci are heterogeneous.

Recently in another research study, analysis was conducted through whole genome sequence data, and identified "Leu401Pro variant" in ASAH1 (N-acylsphingosine amidohydrolase) gene, that revealed co-segregation pattern with keloid phenotype in a large population of Yoruba family. This genetic variant is known to play a role in tumor formation, inflammation and cell proliferation, which suggested that it may be involve in keloid development through various other mechanisms. This study also found some rare coding variants but their susceptibility for non-syndromic development of keloid is not known [85].

8.4 Large-Scale Population Single-Nucleotide Polymorphism (SNP)

Researchers have started to investigate deeper into the human genome by using high-throughput microarray genotyping technologies with an objective to develop high-density SNPs map arrays in families with keloid history. Previously genome-wide case-control association study described three susceptibility loci (i) 1q41, (ii) 3q22.3-23, and (iii) 15q21.3 in association with keloid disease, in a Japanese population [76]. NEDD4 gene present in 15q21.3 chromosomal locus, is involve in up regulation of collagen type 1 and fibronectin, that result in extracellular matrix formation [24].

An independent case-control study was conducted to find correlation between SNPS i: e rs2118610, rs873549, rs2271289, rs1511412) and phenotypes of keloid cases in Chinese Han population. This study revealed that inheritance patterns of four SNPs (particularly SNP rs2271289)

were dominant in severe keloid cases, in comparison with mild cases and control groups. Similar pattern of association of SNP rs2271289 with keloid cases, appeared in family with no case history of keloids as well as in groups having multiple keloid sites. These associations revealed that SNP rs2271289 is a strong contributing factor and a likely candidate in keloid pathology [114].

Association of FOXL2 gene, keloid and SNP rs1511412 have also been identified in Japanese population [76], but this association wasn't significant in the Chinese Han population [116] may be due to low frequency of this variant. Another SNP rs1511412 showed significant association with FOXL2 gene and keloid cases, which appeared as genetic risk factor for keloid development in various ethnic groups of Asian population [64].

A comprehensive study of familial keloids, based on genetic and clinical parameters, was conducted in mostly African Americans, White, Japanese, and African Caribbean families. Individuals affected with keloids exhibited a variable pattern of expression within the families, for example some family members had minor keloids on earlobes and other had large body areas highly affected with severe keloids. In same family, seven members were identified as unaffected but obligate carriers for keloid phenotype. The genetic analysis revealed an autosomal dominant inheritance pattern along with variable phenotypic expression [71].

8.5 Gene Expression

Gene regulation and unique genetic components have also been studied in keloid dermal fibroblasts (KDF). Studies revealed up-/downregulated expression of various genes (Table 8.1). The specific genes and their differentially regulated expression may have direct implications toward understanding the keloid development [25].

8.6 MicroRNAs (miRNA)

MicroRNAs are 21–23 nucleotide molecules, targeting the 3'UTR of mRNA and microRNA deregulation may indicate a potential need for clinical intervention [2]. Role of various miRNAs has been established for activation of fibroblasts. A study reported 32 microRNAs differentially expressed in keloid tissues [63], in which total 23 miRNAs (e.g. miR-4269, miR-21, miR-382) were up-regulated and 9 miRNAs (e.g. miR-205, miR-203, miR-200b/c) were down-regulated. These miRNAs are involved in various cellular signaling networks particularly wound- healing, development of scar and collagen synthesis [39]. Various studies revealed that microRNAs play a key regulatory role in keloid fibroblasts, for instance, miR200b was found associated with abnormal proliferation in fibroblasts and miR200c was involved in radiation-induced cell apoptosis pathway [50, 55, 56, 61, 117]. These microRNAs may be considered potential candidates for therapeutic targets for keloids [33]. Three common miRNAs, has-miR-21, has-miR-199a-5p and has-miR-214 were found in some studies [69, 104, 105] among them, has-miRNA-21 exhibited variable expression [40]. Comparative expression profiles study of miRNA was further extended and found that, keloid derived fibroblasts have total nine different miRNAs as compared to the normal skin fibroblasts. Out of nine, six were up-regulated (hsv1-miR- H7, miR-320c, miR-31- 5p, miR-23b-3p, miR-152, miR-30a-5p) and three (miR-143-3p, miR-4328 and miR-145-5p) were down-regulated [54, 66]. Some of the key miRNAs that appear differentially expressed in keloid cells have been assessed in more detail the table below (Table 8.2).

8.7 Long noncoding RNA (lncRNA)

Long noncoding RNA, remains uncovered with respect to their association with keloid pathology. The advanced microarray technology was used first time to investigate the keloids in 2015 by Liang et al. group that demonstrated constantly up-regulated (total 1,731) and down-regulated (782) lncRNAs in keloids. In this study, a total of 55 pathways were highlighted: out of which 11 pathways were related to the upregulated transcripts and 44 with downregulated transcripts in keloids. In addition to that, it has been found that the CACNA1G-AS1, as one of the selected lncRNA, may have a potential role in keloid development [58]. The lncRNAs regulating encoding transcripts/genes are considered to participate in Wnt signaling pathway in keloids [95]. The lncRNA H19 stimulate cell proliferation in keloid fibroblasts which reversed by H19 siRNA treatment on keloid fibroblasts [113].

8.8 Small Interfering RNA (siRNA)

RNA interference is an evolutionally conserved genetic regulatory mechanism involving inhibition of target gene expression at transcriptional, or translational level, or by degrading the mRNA [101]. Advances in gene silencing [102] provide the opportunity to apply RNA interference technology to uncover the details of molecular mechanisms maintain keloid tissue growth [6]. It is found that β-catenin expression significantly increased in keloid tissue [18] and has been shown to have a role in the regulation of keloid scarring. Knockdown of

Table 8.1 Differential gene/protein expression markers in keloid-derived primary fibroblasts

S. No	Cellular genetic marker	Expression studies	Level	Role in keloid fibroblasts	Sample source	Role in normal dermal fibroblasts	Reference
1	TGF-β1	mRNA Site-specific gene expression by qRT-PCR	Slightly more	Fibrosis-inducing factors Fibronectin biosynthesis Leads to overproduction of ECM	Primary keloid-derived fibro P2–P4	Proliferation, collagen Deposition and transdifferentiation	[14, 46, 60]
2	TGF-β3	mRNA	Low	Fibrosis-inducing factors	Primary keloid-derived fibro P2–P4	reduces connective tissue (collagen) deposition	[14]
3	TGF-βRII	mRNA	Low	Fibrosis-inducing factors	Primary keloid-derived fibro P2–P4	TGF-β downstream signaling	[14]
4	TGF-βRI/TGF-βRII	mRNA by real-time PCR Immunohistochemistry	High	Enhanced collagen synthesis	Primary keloid-derived fibro P2–P4	TGF-β downstream signaling	[14]
5	Versican (CS/DS–proteoglycan (PG) (VCAN)	mRNA by real-time PCR protein by dot blot, Western blot, and immunostaining	High	Excessive deposition contributes significantly to keloid volume	Keloid tissue and primary keloid-derived fibroblast	Cell adhesion, migration, proliferation, differentiation	[107]
6	Lumican (LUM)	Microarray analysis (mRNA KL Fb/mRNA normal Fb)	High	//	Primary keloid-derived Fb, passage 2 and 4	//	//
7	Aggrecan	//	//	//	//	//	//
8	Collagen a1 (X)	//	//	ECM component	//	//	//
9	Collagen a1 (II)	//	//	//	//	//	//
10	Collagen a2 (IX)	//	//	//	//	//	//
11	Collagen a1 (XI)	//	//	//	//	//	//
12	Collagen a1 (VIII)	//	//	//	//	//	//
13	Thrombospondin 1	//	//		//		//
14	Collagen a1 (XVII)	//	//	//	//	//	//
15	Collagen a3 (IX)	//	//	//	//	//	//

16	HIF1A (Hypoxia-inducible factor1, alpha)	mRNA by real-time PCR Protein by immunohistochemistry, immunofluorescence staining, Western blot	//	Transcriptional regulator, which helps the cells to adapt in the hypoxic microenvironment. Indicators are ECM accumulation and cell proliferation, invasion, and differentiation/ transformation (transition of human dermal fibroblasts to a myofibroblast-like phenotype via the TGF-β1/Smad3 pathway)	Keloid tissue and primary keloid-derived fibroblast		[68, 115]
17	Vimentin	//	//	Mesenchymal marker	//	EMT marker	//
18	Fibronectin	//	//	Mesenchymal marker	//	EMT marker	//
19	Connective tissue growth factor (CTGF)	qRT-PCR Protein by Western blot Immunohistochemistry	//	Fibrosis	// Keratinocyte-fibroblast coculture	Cell adhesion, migration, proliferation, angiogenesis	[46, 115, 49]
20	Atypical chemokine receptor 3 (ACKR3)	qRT-PCR	//	Cholesterol biosynthesis I/ II, Vasculo-/angiogenesis cancer tissue morphology	Keloid tissue and primary keloid-derived fibroblast		[46]
21	Tumor necrosis factor (TNF)	//	//	//	//		//
22	Ephrin receptor B4 (EPHB4)	//	//	//	//		//
23	Forkhead box F2 (FOXF2)	//	//	//	//		//
24	Insulin-like growth factor (IGF) binding protein 3 (IGFBP3)	//	//	Activating collagen synthesis and cell proliferation, decreasing apoptosis	//		[86]
25	Transgelin	//	//	Early detecting cell transformation marker	//	Proteins responsible for changes in cell shape and structure	//
26	Annexin A2 (ANXA2)	//	//	Marker of apoptosis	//	Apoptosis	//
27	Ribosomal protein S18	//	//	Protein synthesis	//	Protein synthesis	//

(continued)

Table 8.1

S. No	Cellular genetic marker	Expression studies	Level	Role in keloid fibroblasts	Sample source	Role in normal dermal fibroblasts	Reference
28	60 S ribosomal protein (L36a)	Clontech's Atlas™ Human cDNA Expression Array	Low	Protein synthesis	//	Protein synthesis	[25]
29	Nuclease-sensitive element DNA binding protein (NSEP)	Clontech's Atlas™ Human cDNA Expression Array	Low	Transcription	//	Transcription and regulation of essential growth control genes	[25]
30	Interleukin-6 (IL-6)	Translational study for IL-6, Pro-hybridization and ELISA	//	IL-6-induced cell proliferation	Primary keloid-derived fibroblast, passages 4 to 8	Immunoregulatory cytokine known for role in fibrotic autoimmune diseases	[106, 38]
31	Vascular endothelial growth factor (VEGF)	VEGF-ELISA kit	//	Increases granulation-tissue formation	Primary keloid-derived fibroblast passages 2	Angiogenesis	[93, 38]

Abbreviations: *KL* keloid; *Fb* fibroblasts. Symbols: //, same as above

Table 8.2 Differential expression of miRNAs and their effects on keloid fibroblasts

S. No	Type of microRNA	Expression level in keloid fibroblasts	Role in keloid phenotype	Reference
1.	miR-7	Low	Induce excessive collagen expression	[31]
2.	miR-29a	Low	Collagen I and III expression regulation, TGF-β/Smad signaling pathway, fibrosis	[73, 41, 112]
3.	miR-199a	Low	Influence proliferation of keloid fibroblasts via cell cycle regulation	[104, 105, 109]
4.	miR-21	High	Stimulate fibroblast proliferation and apoptosis via P13K/AKT pathway and synthesis of extracellular matrix	[62, 75, 100]
5.	miR-196a	High	Regulates the stabilized elevated expression of COL1A1 and COL3A1 genes	[1, 48, 54]
6.	miR-152	High	It promotes keloid fibroblast proliferation and collagen synthesis	[54, 63]

β-catenin/siRNA inhibits cell proliferation and induces arrest in G0/G1 phase of cell cycle. It also induces apoptosis in fibroblasts via down-regulation of cyclin D1 and Wnt2 pathways. Keloid fibroblasts (KFs) overexpress AMF (autocrine motility factor), which acts through RhoA/ROCK1 signaling network, to enhance their cell migration and proliferation. Knocking down AMF/siRNA significantly reduces the migration as well as proliferation potential of KFs that ultimately reduces keloid size [98].

TIMP-1 and small interfering RNA regulation has an important role in keloid pathology. Generally, it is known that keloid phenotype appears as a result of disproportion between synthesis and degradation of extracellular matrix. There are two main vital components (i) Matrix metalloproteinase (ii) Tissue inhibitors of metalloproteinase, which regulate the process of synthesis degradation and remodeling of ECM. Knockdown of TIMPs (siTIMP-1 or siTIMP-2)/siRNA resulted in suppression of MMP-1/TIMP-1 and MMP-1/TIMP-2 complex molecules but upregulation of MMP-2 and increased collagen type I degradation. KFs also showed increased apoptosis and reduced cell viability [3].

The role of siRNA during TGF-β-induced regulation of of PTB (Polypyrimidine Tract-Binding Protein) in keloid pathophysiology has been demonstrated recently [43]. It is a splicing regulator and known to play an important role in tumor cell proliferation, invasion and metastasis. TGF-β1 stimulation caused over expression of PTB along with its upstream regulatory component (C-MYC) in keloid derived fibroblasts, resulting in dysregulation of alternative splicing events, leads to enhanced fibroblast proliferation and deposition of fibronectin in keloid. PTB/siRNA knockdown shift the alternative splicing of RTN4 and USP, and caused significant reduction in fibroblasts proliferation and deposition of COL3A1 and FN1, that resulting in the fast regression of keloid tissues.

Silencing the Smad2 (Sma and *Drosophila* mothers against decapentaplegic homolog 2) downregulate the TGF-β-induced synthesis of procollagen, in keloid derived fibroblasts [35]. The role of siRNA during Smad3 (Sma and *Drosophila* mothers against decapentaplegic homolog 3)-induced TGF-β signaling in keloid pathogenesis has been studied. Smad3 is recently characterized as an intracellular effector of TGF-β signaling pathway. TGF-β participate as key component in fibrotic pathology by stimulating keloid fibroblasts to synthesize extracellular matrix excessively, including collagen I and III. The knockdown of Smad3/siRNA expression caused significantly and uniquely decrease in types I and III procollagen level. Thus Smad3 is thought to play a significant role in the TGF-β-induced keloid fibrosis [101].

Keloid derived fibroblasts over expressed NLRC5 (NOD-like receptor family CARD domain containing 5) belongs to the family of nucleotide-binding domain and leucine-rich repeat. It has been shown that silencing of NLRC5 results inhibition of proliferation and expression of ECM in keloid derived fibroblasts via inhibition of TGF-β1/Smad signaling network, suggesting potential therapeutic target keloids [67]. Increased expression of Stat3 (signal transducer and activator of transcription 3) was also found in keloid tissue. Stat3 is a latent transcription factor activated under the stimulation of various growth factors and cytokines during wound-

healing process. Short interfering RNA inhibited its expression and subsequent phosphorylation and resulted in reduction of collagen synthesis, cell proliferation and migration in keloid derived fibroblasts, hence suggesting another therapeutic candidate for the treatment of keloids [59].

Keloid fibroblasts characteristically showed overexpression of collagen and PAI-1. Short interfering RNA targeted treatment results in reduction the collagen deposition, which showed that PAI-1-targeted siRNA interference may offer therapeutic alternative in keloid formation [99]. Another study showed that silencing of PAI-1 caused significant reduction in keloid volume up to 28% in fourth week. It also decreased the synthesis of collagen I and III and resulted in shrinkage of keloid tissue mass [96].

VEGF (vascular endothelial growth factor) plays vital roles in the regulation of inflammation and angiogenesis during wound-healing process. The role of vector-based RNAi (shRNA) for inhibition of VEGF expression in keloid fibroblasts has been studied. siRNA sequences (clone of three potential short interfering RNA sequences) were used to silence the VEGF gene in keloid fibroblasts that resulted in significantly inhibited VEGF gene expression and fibroblasts growth. In addition, the expression of plasminogen activator inhibitor-1 (PAI-1) was also downregulated. This study provides the insight about the modulation of VEGF production as a potential therapeutic strategy for keloid [111].

Silencing by HIF-1α siRNA in keratinocytes resulted in decreased expression levels of fibronectin and vimentin, whereas ZO-1 and E-cadherin expression levels were restored. This indicated that HIF-1α stimulation can regulate the respective mesenchymal changes, caused by hypoxia in the keloid derived keratinocytes during keloid development [68].

Knockdown of PAI-2, Hsp27, α2β1-integrin/siRNA also cause significant reduction in ECM deposition, cell anchorage, and mobility in keloid derived fibroblasts [94]. Hsp70/siRNA and Hsp47-shRNA knockdown decreased collagen synthesis in keloid derived fibroblasts [20, 90]. hTERT gene regulates telomere length homeostasis and influences cell cycle of fibroblasts. Knockdown of hTERT-siRNA in keloid fibroblasts was shown to reduce telomere length and fibroblast growth [87].

The role of siRNA in apoptosis of keloid fibroblasts has also been investigated. Keloids exhibited increased reactive oxygen species (ROS) production and disrupted apoptosis mechanisms. ROS plays an important role in the induction of apoptosis under pathological conditions. Cellular defense mechanisms against oxidative stress and apoptosis are regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) through activation of B-cell lymphoma 2 (Bcl-2) protein. Transfection of fibroblasts with the Nrf2-specific siRNA resulted in increased apoptosis and decreased cell viability [53]. NRG1/ErbB2/Src/PTK2 signaling pathway in fibroblast migration and the role of siRNA have been investigated in keloid development. Keloid fibroblasts exhibit upregulation of the polypeptide growth factor neuregulin-1 (NRG1) and receptor tyrosine-protein kinase erbB-2 (ErbB2) oncogene that contributes to altered cytokine expression profiles, increased Src and protein tyrosine kinase 2 (PTK2/FAK) gene expression, and migration in keloid fibroblast. siRNA knockdown of ErbB2 gene resulted in reduced migration and Src/PTK2 expression but didn't affect the NRG/ErbB2/Src/PTK2 network, revealing the possibility that this network may affect migrating potential of keloid fibroblasts indirectly [47]. Therefore, siRNA silencing on various targeted mechanisms such as Smad2,3-TGF-β, HIF-1α-EMT, PAI-1-VEGF production, and NRG1/ErbB2/Src/PTK2 signaling pathway in keloid pathogenesis, proposes that their production can be modulated by using siRNA based regulation, and this strategy seems promising candidate for keloid therapeutics.

8.9 Microarray Analysis

Various advanced molecular biology techniques such as PCR, cDNA approaches, cloning, whole genome sequencing provides the huge platform to investigate the differentially regulated genes in term of microarray analysis from variety of biological samples [70]. Functional genomic provides a tool to probe and monitor the genetic interactions [27]. Complex pattern of genotypic differences and respective multiple fibrosis-related pathways in keloid fibroblasts have been studied by microarray approach. Comparative Affymetrix-based microarray analysis was carried out on keloid fibroblast RNA. Approximately 500 genes were found differentially regulated out of total the total 38,000 genes observed. Interestingly, study also revealed that increase in expression of various IGF-binding protein and related protein in comparison with set of protein related to Wnt signaling pathway, who exhibited decrease in expression [91]. Total 2,215 differentially expressed genes (DEGs) have been found in comparative analysis of after and before normal wound, and surprisingly total 3,161 DEGs have been identified in keloid-prone individuals. Among those genes, only 513 genes were related to normal individuals, total set of 1,449 genes were found specifically related to keloid phenotype. Moreover, hierarchical distribution of differentially expressed keloid-specific genes resulted into two distinct clusters. Further probing into keloid-specific pathways revealed 24 pathways linked with differentially activated genes. Most importantly, some other vital signaling pathways like NOTCH, MAPKs, TLRs and insulin regulation, have also been found altered during post-wounding analysis in keloid prone individuals. Furthermore, Genetic association network analysis

revealed, divergent gene expression profile of key genes that contribute in cytokines signaling pathways [79, 83].

8.10 Epigenetics

Study of inheritable characteristics of genome that doesn't affect the genetic sequences but only gene function, comes under the term of epigenetics. It is also known to contribute significantly in regulation of various gene expressions. Recently, there is further extension to this terminology that is epigenetic modification, which is currently being applied to get comprehension of molecular aspects of keloid pathology. This study revealed that there are some evidences pointing the involvement of epigenetic changes/modifications triggering the constant activation of fibroblasts in keloid [30]. These epigenetic alterations include changes in microRNAs, DNA methylation as well as histone modifications. These three event are well known crucial events that involve in early cellular growth, differentiation and development, hence these aspects of molecular features have also been included as an important candidate for investigations to understand their role/associations in keloid pathology [28]. Recent studies are coming up with findings about the epigenetic mechanisms that may contribute in keloid formation [42].

8.10.1 Methylation

DNA methylation is the well-known aspect of epigenetic modification [103]. It has been hypothesized that DNA methylation is responsible to maintain the myofibroblats transformation of fibroblasts during the process of fibrosis in wound healing events, this modification set the basis for deviation from normal wound-healing mechanism. Gene expression profile acquired by myofibroblasts is significantly differ from fibroblasts [81, 97]. Therefore it is crucial to understand respective epigenetic modifications that resulted in acquiring highly differentiated gene expression profile in my myofibroblasts that will help to trace the respective network leading to fibrotic phenotype in keloids [77]. Previous research study found that keloid fibroblasts showed alternations in DNA methylation [84]. Involvement and significance of epigenetic modification in keloid pathology has been revealed in recent study, that showed reversal of expression profile in TGF-β1, phosphor-smad2, 3 (down-regulation) and smad7 (up-regulation) by the treatment of 5-aza-dC (5-aza-2 deoxycytidine), which is an inhibitor of DNA methyltransferase [118].

Expression of DNA methyltransferase 1 (DNMT1) was found 100% elevated in keloid as compared to the fibroblast (8%) from normal skin samples [32], suggesting its involvement in keloid scar formation. Furthermore, different DNA methylation patterns have also been studied in keloid vs normal cells and tissue and analyzed via large scale genome profiling using advanced approach (Infinium Human Methylation 450 BeadChip), results explained that 152 unique genes showed total 192 different methylation patterns in promoter region CpGs. Moreover respective gene network analysis, revealed four common hierarchical regulatory networks, consisting of four key regulators, (i) PENK (ii) PRKG2, (iii) pryoxamide (iv) tributyrin, and total 19 intermediate regulatory molecules. This analysis highlighted the involvement of regulatory networks in keloid phenotype development [36, 45] and with the development of this study approach in recent research since last five years, methylome of keloid have been characterized as most hypo-methylated rather than hyper-methylated [45].

List of hyper-methylated genes includes CACNB2, ACTR3C, PAQR4, SLCO2B1, C1orf109, LRRC61, AHDC1, FYCO1, CMKLR1 and CCDC34 as compared to hypo-methylated group of genes, which are GHDC, DENND1C, MX2, ANKRD11, SCML4, GALNT3, IFFO1, WIPF1, PPP1R13L and CFH. Recently, further analysis was carried out using bioinformatics approach by applying Ingenuity Pathway Analysis (IPA) software on data set, obtained from keloid samples, revealed some key pathways shows significant association with keloids. These pathways include (i) histidine degradation VI (ii) metastasis signaling pathway of colorectal cancer (iii) phospholipase C signaling (iv) P2Y purinergic receptor signaling and (v) Gai signaling pathway [44]. Keloid fibroblasts having multiple genes with differential methylation, exhibited significant difference in expression profile of genes related to fibrosis such as IGFBP5 (IGF/IGF-binding protein 5), JAG1 (Jagged 1), SFRP1 (secreted frizzled-related protein1), MMP3 (matrix mettallopeptidase 3), CTGF (connective tissue growth factor) and DPT (dermatopontin) [84]. These finding support the statement about the involvement of DNA methylation in keloid formation, but needs further extension of research studies to explore respective key changes/modification that leads subsequent stages of development resulted in keloid pathogenesis [36, 44, 45].

8.10.2 Histone Modifications

Histone modifications include changes in distal N-amino acids specifically, phosphorylation at Threonine or Serine, ubiquitination at Arginine or Lysine and acetylation at Lysine amino acid. There are some enzyme such as histone deacetylases (HDACs) and acetyltransferases (HATs), which are involve in these modifications, and result in altered gene expression profile [7]. Interestingly, it has been noted that histone deacetylases over expressed

in keloid tissue. This over expression pattern has also been observed under TGF-β1 induced stimulation in normal fibroblasts and murine Swiss 3T3 fibroblasts [34]. *In vitro* research study showed that treating the keloid fibroblasts with HDAC inhibitor resulted in decreased production of collagen [92]. Inhibition of histone acetyltransferases caused anti-fibrotic affects, increased expression of p300 (which is a cofactor, essential for acetylase activity) in fibroblasts (isolated from scleroderma patients samples) [37].

These studies suggest that both DNA methylation and histone modification are crucial to cause differential gene expression profile, exhibited by keloid fibroblasts, furthermore, as such, any sustainable modification responsible to deliver epigenetic changes, can leads towards phenotypic alteration of keloid fibroblasts. This scenario recommending that inhibitors of histone modification can be an important candidate to consider with therapeutic point of view for management of keloid pathology [5, 80, 84].

8.11 Mutations

Role of mutations was investigated in a study conducted in keloid cases from a Caucasian population (95 cases). Large scale genome wide analysis in the exon (1–7) and promoter regions showed presence of some novel mutations in Caucasian population [13]. But up till now, none of the gene mutations have been found associated with keloid cases [88]. One *in vitro* study reported a p53 mutation that was found in keloid fibroblasts from cultured cells [26], that may suggest the role of acquired inheritable gene changes in keloid cells [88].

8.12 Copy Number Variation

Copy number variations (CNVs) are known to be associated with various human disorders including skin diseases. Research study conducted in keloid cases from Caucasian population revealed that CNVs found at 11q11, 8p23.1, 19p13.1, 22q13.1, 17q12, and 2q14.3, specifically 6p21.32 (that contain HLA-DRB5 region) are associated with keloid pathology [89].

8.13 FISH (Fluorescence In Situ Hybridization)

Keloid derived fibroblasts exhibited differential phenotypic and genotypic expression as compared to neighboring normal skin fibroblasts. Real-time RT-PCR and proteomics tools (2-DAGE, immunoblot analysis, and immunohistochemistry) have been used to investigate these differentially expressed specific set of genes and proteins in keloid derived fibroblasts. Proteomic analysis revealed that there are sixteen different spots which differentiate keloid fibroblasts from normal fibroblasts, among all, Hsp70 was most up-regulated protein in keloid derived fibroblasts. These results were also validated by immunohistochemical and western blot analysis conducted on keloid vs normal skin tissue. This study indicated that Hsp70 overexpression may be associated with keloid pathology and its inhibition can be studied for therapeutic purpose [52].

8.14 Conclusions

Keloids are benign dermal tumors that develop as a result of a dysregulated cutaneous wound-healing process. Several research findings support the idea that there is an association between various genetic elements such as linkage, autosomal-dominant, oligo-genic or additive inheritance in families and keloid development, predominantly in people of African and Asian descent. In addition to that, differential gene expression studies in families and keloid fibroblasts indicate heterogeneous genetic events, revealing complexity of underlying genetic basis of keloids. Therefore, it's quite obvious that single gene phenomena is not a possible causative factor for keloid formation. To address this complexity, a likely scenario may involve the understanding of genetic pathway interactions including environmental factors, healing mechanisms, wound matrix degradation, and immunologic response.

Take-Home Messages

1. Keloid is a complex skin pathology with varied susceptibilities and ethnicities. This disease is a clinical challenge because it lacks effective treatment and often recurs after excision.
2. Well-defined comprehensive mode of inheritance is still not known because of insufficient genetic investigations.
3. HLA system represents the highest level of diversity of any functional genetic association with keloid disease.
4. Recent advanced approaches like high-throughput microarray facilitating the genetics and epigenetic investigations may be helpful in understanding the underlying complex basis of keloid formation.
5. There could be a possibility to identifying potential candidate set of genetic markers for diagnostic or prognostic purpose.
6. There is need to uncover the specific biological mechanism and respective signaling networks of keloid fibroblasts.

Acknowledgments This study was supported by the National Research Foundation and the South African Medical Research Council grants.

Further Readings/Additional Resources

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International Scar Classifications

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_9

There has been a wide variety of therapies proposed for the treatment of scars, most of them with a lack of firm randomized controlled clinical trials to support their efficacy, and among other deficiencies, there has been often a lack of appropriate labeling or classification of scars to allow optimal evaluation of existing literature. There is a real benefit to a consistent classification of different types of scars so that different clinicians use a consistent vocabulary allowing a systematic evaluation of treatments and outcomes. One problem has always been the changes in scars over time so that improvements may not necessarily be due to the treatment intervention but simply scar maturation.

Scar classifications have previously been published including notably the 2002 publication in PRS which gained widespread acceptance because it represented the consensus of 12 experts from an international group incorporating Europe, North America, and Australia. In subsequent publications, this classification has been found to sound and not needing further modification. We will use this classification again in this updated textbook.

Scarring is the inevitable consequence of tissue injury as opposed to tissue regeneration which is the true restoration of the normal architecture of the skin. True tissue regeneration after injury occurs only in the fetus during the first two trimesters and in amphibians who can even regenerate amputated limbs. In the optimal outcome of a thin flat thin linear scar, the sequence of tissue repair after injury is tightly regulated. After initial platelet aggegation, provisional matrix is deposited, followed by influx of inflammatory cells and subsequent cell proliferation including fibroplasia and angiogenesis. Wound healing overlap, and are followed by cellular apoptosis with resolution of inflammation. Permanent matrix deposition (collagen) begins within 3 days. Maximal collagen deposition occurs in the first few weeks with a combination of type 1 and type 3, followed by many months of collagen breakdown and synthesis with increasing type 1 collagen with increased organization and scar strength. These phases of inflammation, cell proliferation and collagen remodeling result in a fine line scar in the scenario of an incison ("normal" scar), and a wider flat scar in the scenario of an injury over a broader area.

9.1 Immature Scar

Even a normal scar goes through a period when it is immature, meaning it is pink, often with a healing ridge (edema plus collagen synthesis). Collagen accumulation typically peaks about 3 weeks after surgery and then goes through about 6 months of remodeling with steadily increasing collagen organization, conversion from a mix of type 1 and type 3 collagen to almost entirely type 1 collagen with increased cross-linking, and continued increase in tensile strength. The gains in scar strength are due to improvement in collagen organization and cross-linking rather than an increase in collagen. A useful analogy is to compare the difference between raw wool from a sheared sheep, versus the fine knit of a woolen coat. The amount of wool is the same, but the woven wool is far stronger. However, although the strength of a scar is maximal in approximately 6 months, complete scar maturation as measured by resolution of erythema typically takes a year or even longer. In a human volunteer study conducted by Renovo, superficial scars took longer than a year for the erythema to fully resolve in one-third of patients. In scars in thicker skin with more depth, or in a group of patients with more active scarring process, it probably takes even longer. In my own clinical practice with approximately 20,000 patients of all ages and ethnic backgrounds, my experience mirrors the study by Renovo (◘ Table 9.1).

The resolution of erythema is a useful marker of scar maturity (◘ Fig. 9.1). In all scars, erythema eventually resolves, but in a few percent of patients, I have seen it take longer than 2 years and in a rare hypertrophic scar as long as 10 years. In a study we conducted on burn patients, we found that the average scar elasticity (a measure of collagen remodeling), as measured by a device that applied a constant force to the skin and measured how much it stretched, continued to increase over 5 years (Bartell et al). Although the patients were not followed longitudinally, we simply correlated elasticity to the age of the scar, and it can be inferred that it can take a long time indeed for a scar to reach full maturity.

In an immature scar histologically, there are an increased number of inflammatory cells. After 2 weeks or so, the predominant inflammatory cells are macrophages with scattered lymphocytes and an occasional mast cell. There are increased numbers of fibroblasts including myofibroblasts, increased numbers of blood vessels, and for a period of up to a few months epidermal hyperplasia. The visual appearance is a scar that is erythematous and slightly raised due to increased fluid in the tissues and increased collagen as well as increased cellularity.

9.2 Mature Scar

In undergoing the transition from an immature scar to a mature scar, the key visual marker is resolution of erythema (◘ Fig. 9.2). At this point, the inflammatory cells, endothelial cells, and most of the fibroblasts have undergone apoptosis, and the epithelium looks completely normal as compared to the adjacent unwounded

Table 9.1 Scar Classification

Scar type	Description
Immature scar	Pink slightly raised
	Sometimes itchy
	Firm but not hard
	Begins soon after injury, months to resolve
	Peaks at a few weeks after injury
Mature flat scar	Flat scar without erythema, stable
	No symptoms
Hypertrophic linear scar	Ropy (elevated) and pink or red
	Evolves from immature scar within several weeks
	Progressive enlargement for months before slow decrease in activity
	Often itchy or slightly sore to touch
	Resolution results in a persistently elevated scar that is no longer pink
Hypertrophic wide scar	Elevated, pink or red
	Arises from widespread injury such as a burn
	Frequently with severe pruritis and can be tender
	Very stiff with limitation of mobility across joint surface
Minor keloid	Round or elevated, extends beyond scar
	Most often at site of pierced earring or surgical incision
	Strong genetic component which is different than hypertrophic scars
	Simple surgical excision with very high rate of recurrence
Major keloid	Elevated, large often irregular in shape (i.e., butterfly appearance)
	Frequently seen in multiple locations on person
	Initial injury can be very minor
	Often symptoms of pain and pruritis are debilitating
	Treatment options are limited

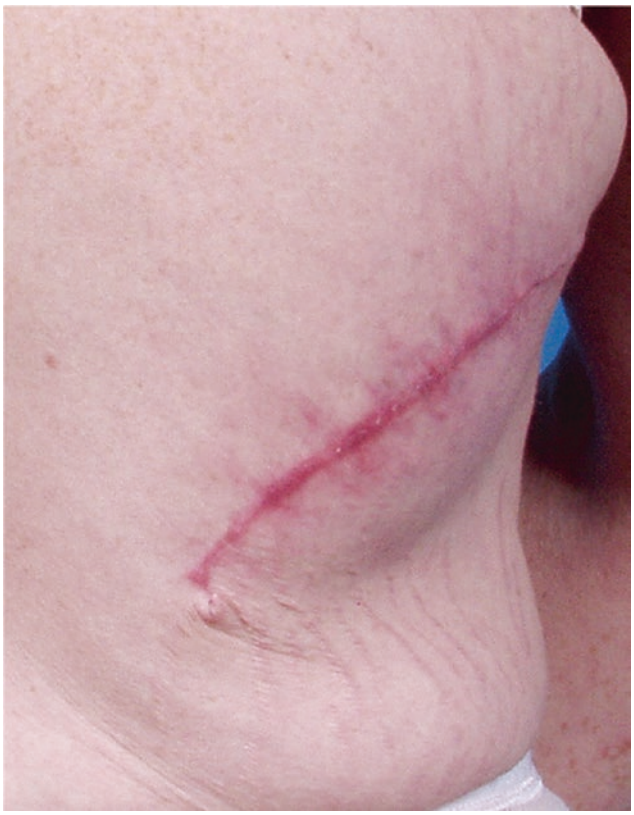

Fig. 9.1 Immature scar

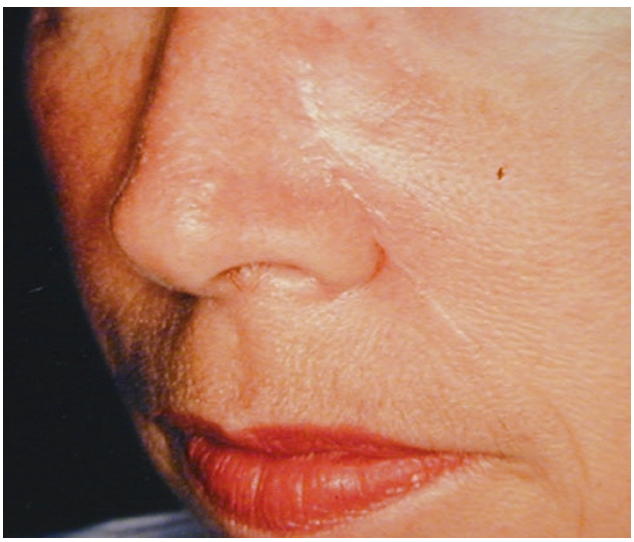

Fig. 9.2 Mature scar

skin. What is left is a band of collagen fibers that are clearly demarcated from the surrounding dermis histologically lacking the completely ordered collagen organization characteristic of normal skin. The collagen fibers go in multiple directions giving the scar stiffer biomechanical properties and are of variable width depending on the genetics of the patient and the underlying tension placed on the healing immature scar. There is no longer any increased fluid in the tissues (edema) and so the scar is flat. The color of the scar ranges from white (absence of melanocytes) to hyperpigmented (often characteristic of ethnicities with increased melanocytes

in the basal layer of the epidermis such as Asian, South Asian, Middle Eastern, Mediterranean, and Latin American or patients with brown skin).

9.3 Atrophic Scar

In some cases, a scar will become depressed or thinned as it transitions from an immature scar (Fig. 9.3). This can occur when collagen synthesis is depressed and inflammation is less than usual. Examples of atrophic scars are the stretch marks or striae that can be a complication of systemic steroid excess either from exogenous steroids or Cushing's disease or in some scars after radiation therapy.

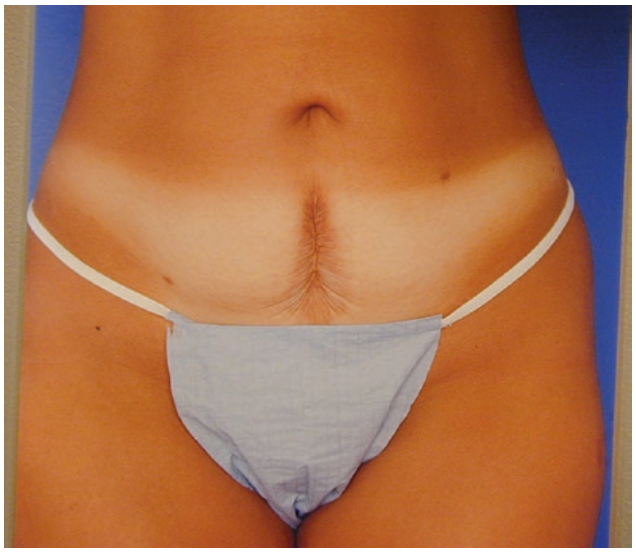

Fig. 9.3 Atrophic mature scar

9.4 Linear Hypertrophic Scar

In many cases, scars fail to transition normally from immature to mature with resolution of inflammation and an equilibrium of collagen synthesis and breakdown. Collagen continues to accumulate, and the scar widens and becomes elevated or ropy in appearance and the erythema fails to resolve. This active process of scar growth can continue for many months but eventually slowly resolves, with resolution of erythema that can take years. The collagen accumulation stabilizes but with a residual scar that is elevated and wider than a normal mature scar (Fig. 9.4). During the period of active collagen accumulation and erythema, the scar can be itchy and/or painful. The residual scar is less elastic (stiffer) than normal skin and, if it crosses a joint, can limit motion. A key feature of hypertrophic scar (versus keloid) is that the scar tissue remains within the confines of the original scar (although it may be widened). Hypertrophic scars are more common in patients of color, particularly East Asians, and the susceptibility to hypertrophic scars is often inherited. Prolonged inflammation for any reason (delays in epithelization, blocked sebaceous glands, ingrown hairs, and tension) contributes significantly to the incidence of hypertrophic scars. Frequently portions of a scar will be hypertrophic in hair-bearing areas, while the adjacent scars evolve into normal mature scars.

9.5 Widespread Hypertrophic Scar

In many cases, most notably from burns, the initial injury is not linear but covers a larger area (Fig. 9.5). In general, when epithelization (complete epithelial resurfacing) is not completed within 2 weeks, the risk of

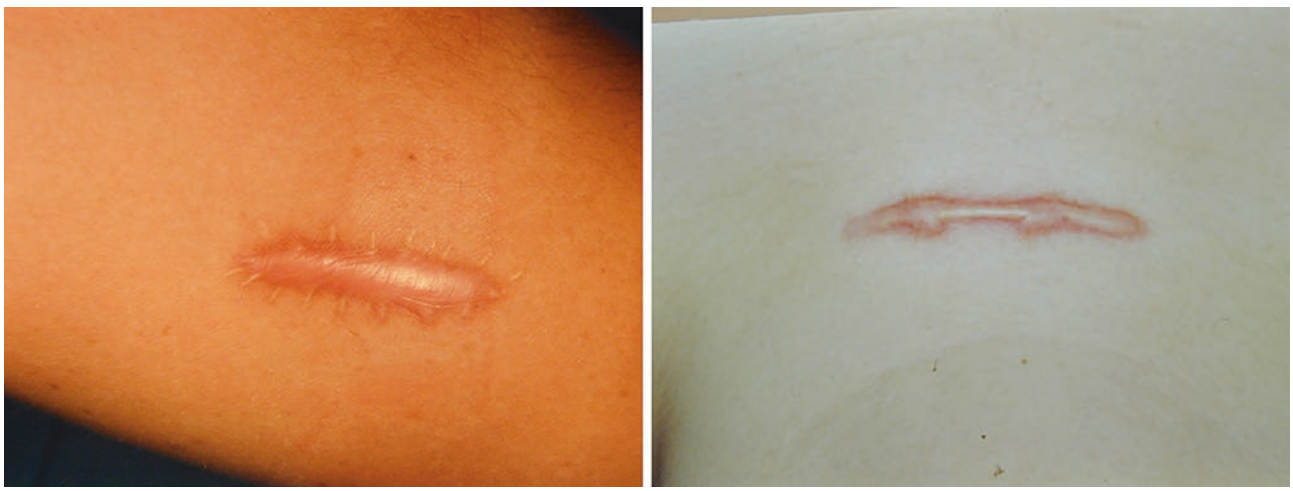

Fig. 9.4 Linear hypertrophic scar

hypertrophic scar increases, particularly in children and in adults under the age of 40. In a hypertrophic scar, the period of collagen accumulation is prolonged up to 6–12 months resulting in a scar that is elevated and thickened and is very stiff. Erythema will be prolonged and the scars are often intensely pruritic or even painful.

9.6 Keloid

A keloid unlike a hypertrophic scar behaves more like a tumor in that growth can occur even years after the original injury and extend far beyond the confines of the original scar. The keloid often has a mushroom or cauliflower type of appearance. Keloids are frequently symptomatic with pain or itch. The genetics of keloids are quite complex and beyond the scope of this chapter, but many are familial and are much more common among many African tribes and to a lesser degree among Asians. The central portion of a keloid is very dense fibers with a characteristic pattern histologically and relatively acellular, while the active spreading edge has a significant inflammatory and cellular component.

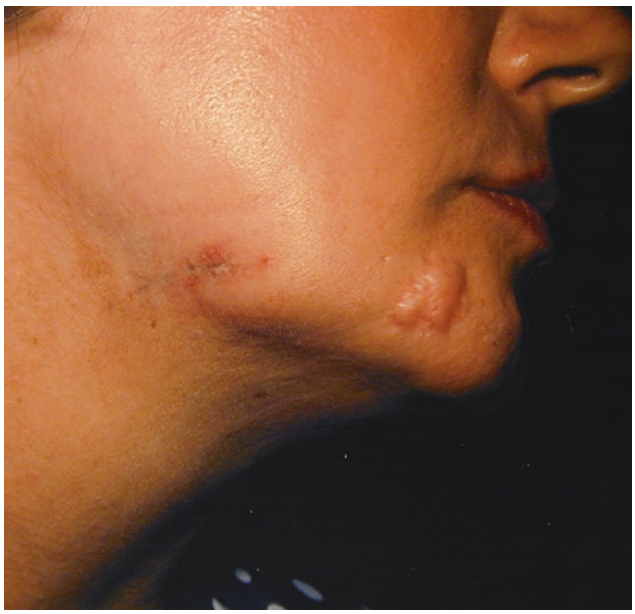

Fig. 9.5 Hypertrophic broad scar

9.6.1 Minor Keloid

Most keloids arise from localized injuries such as a pierced ear (the most common location of minor keloid), and although they extend beyond the margins of the original scar, their growth stabilizes and allows more options for treatment including surgical excision combined with other modalities such as steroid injections or radiation therapy (Fig. 9.6).

9.6.2 Major Keloid

In extreme situations in patients with a very strong genetic predisposition, keloids can extend into large plagues with a very actively growing outer edge that in some areas has a characteristic butterfly pattern (Fig. 9.7a) due to forces on the keloid exerted by the surrounding skin. The peripheral edge of the keloid is active, while the central portion is less active with less cell proliferation. Often the original injury can be as minor as a scratch or seemingly spontaneous (Fig. 9.7b Keloid arising from small tracheotomy

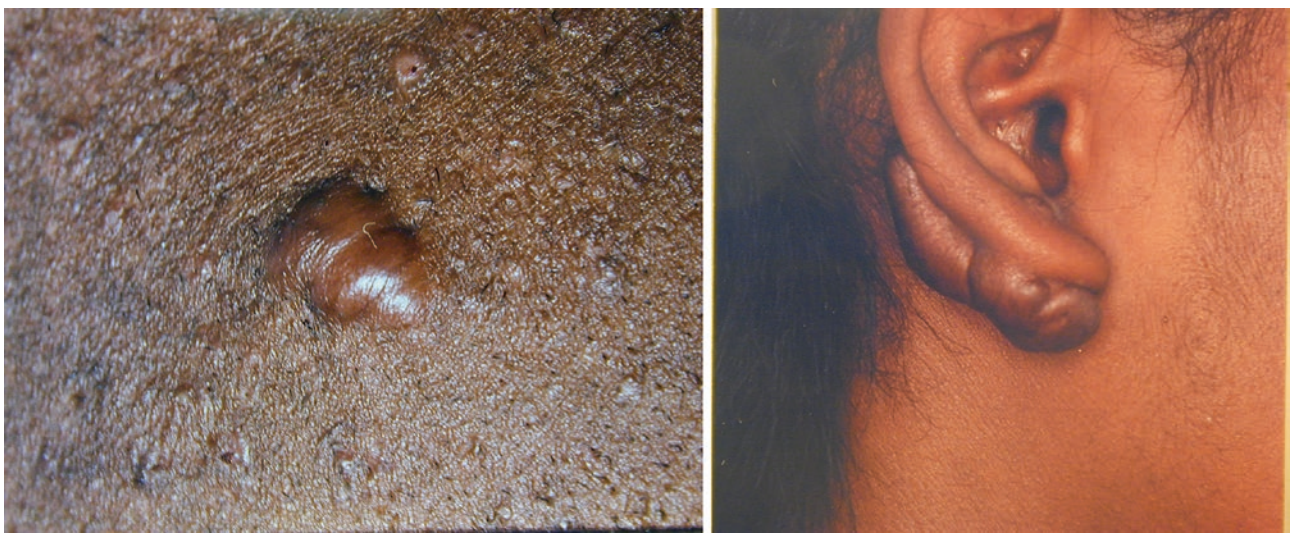

Fig. 9.6 Minor keloid

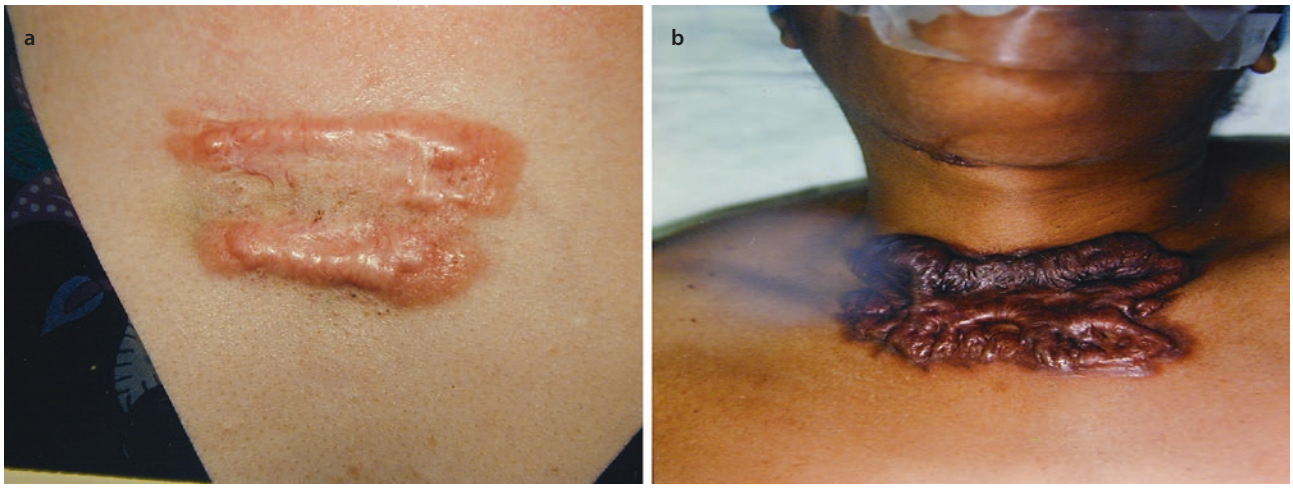

Fig. 9.7 Major keloid. **a** Chest keloid with typical butterfly pattern. **b** Major keloid

scar), and the unfortunate patients with major keloids can form them all over their body. These are extraordinarily difficult to treat and are both deforming and debilitating. Intensive research on the defining genetic characteristics and pathogenesis of keloids continues, and in a few cases genetic loci have been identified, but the genetics are complex, as well as the pathogenesis.

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Scar Symptoms

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Scar Symptoms: Pruritus and Pain

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10.1 Pain: Definition and Subtypes

Pain is defined as a distressing sensory experience associated with potential or actual tissue damage with cognitive, emotional, and social components [1]. Pain can be classified into acute and chronic, based on the duration of symptoms as well as nociceptive and non-nociceptive subtypes with regards to the neurophysiological processes involved.

Acute pain is the predicted physiological response to an adverse mechanical, thermal, or chemical stimulus and most frequently occurs after traumatic injury/surgery as part of the inflammatory response. Chronic pain is defined as pain lasting for three or more months showing no resolution to treatment [1].

Nociceptive pain can be defined as pain arising from the sensitization/activation of peripheral nociceptors and will only continue if the inciting stimulus is maintained [2]. Non-nociceptive pain can be classified into neuropathic and psychogenic pain. Neuropathic pain denotes a primary anatomical or biochemical abnormality arising within the CNS, resulting in persistent and chronic sensory disturbance following the initial injury [3]. It occurs as a result of damage to neural tissue in peripheral and central nervous system and relates to aberrant somatosensory processing. While a detailed account of psychogenic pain is outside the remit for this review, we will elaborate extensively on neuropathic phenomena since they are frequently observed in scar practice.

10.2 Pain Pathway

10.2.1 Peripheral Receptor Activation

Specialized sensory nociceptor fibers in peripheral tissues are activated by a broad spectrum of stimuli including mechanical, thermal as well as chemical with the most frequent being acetylcholine, bradykinin, adenosine triphosphate, and prostaglandins [4].

10.2.2 Ascending Pathway

First-order neuron pathways are responsible for carrying impulses to the dorsal column initially and then other parts of the CNS as part of the ascending pathway and comprise the following different subtypes [5].

A-beta fibers: These are low stimulation threshold, myelinated fibers, activated by vibration and touch; under normal conditions, they convey nonpainful stimuli; nevertheless, they play a crucial role in carrying painful sensations in chronic neuropathic pain.

A-delta fibers: These thinly myelinated fibers have a high threshold potential and are involved in the initiation of the reflex response associated with painful stimuli; they transmit pain faster than unmyelinated C fibers and contain the neurotransmitter L-glutamate.

C-fibers: These fibers are unmyelinated, have a high threshold for activation, and their stimulation causes delayed perception of pain that is often described as diffuse stabbing or burning. As well as glutamate, they contain other neurotransmitters like substance P (SP) and calcitonin gene-related peptide (CGRP).

Second-order neurons start from the dorsal horn and cross over to the contralateral side of the ascending spinothalamic tract to reach the thalamus and pons. The components of the dorsal horn involved in nociception express several receptors including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), voltage-gated calcium channels, N-methyl-D-aspartate (NMDA), as well as gamma-aminobutyric acid–alpha (GABA-A) receptors [4].

Third-order neurons start at the thalamus and end at a number of different cerebral loci.

Processing regarding the magnitude and spatial characteristics of painful stimuli is provided by the somatosensory cortex and the ventral posterior thalamic nuclei. At the same time affective and motivational aspects of pain are processed by the ventromedial posterior thalamic nucleus and its cortical connections [6].

Furthermore, positron emission tomography studies have proposed that pain-related activation of anterior cingulate cortex (ACC) has a direct relationship with an individual's emotional and behavioural reactions to pain [7]. Midbrain periaqueductal gray matter, the region responsible for fight or flight response has also been shown to have interconnections with the ACC [8].

10.2.3 Descending Pathway

The dorsal horn of the spinal cord receives input from higher centers, which can modulate the peripheral nociceptor input barrage by the descending pathway.

The descending pathway starts at the limbic system of the brain area, namely the periaqueductal gray/parabrachial area, rostral ventromedial medulla, and nucleus raphae magnus, whose stimulation, in turn, inhibit nociceptors in the laminae of the spinal cord. Key transmitters involved include noradrenaline, serotonin, as well as endogenous endorphins and encephalins [9].

Aside from descending signals, nociceptive impulses can also be modulated by segmental input from A-beta fibers under the gate control theory of pain. In other words, non-nociceptive fiber signals carried by the large diameter A fibers can interrupt the transmission of pain indirectly by inhibiting the effect of pain fibers ("closing the gate") [10].

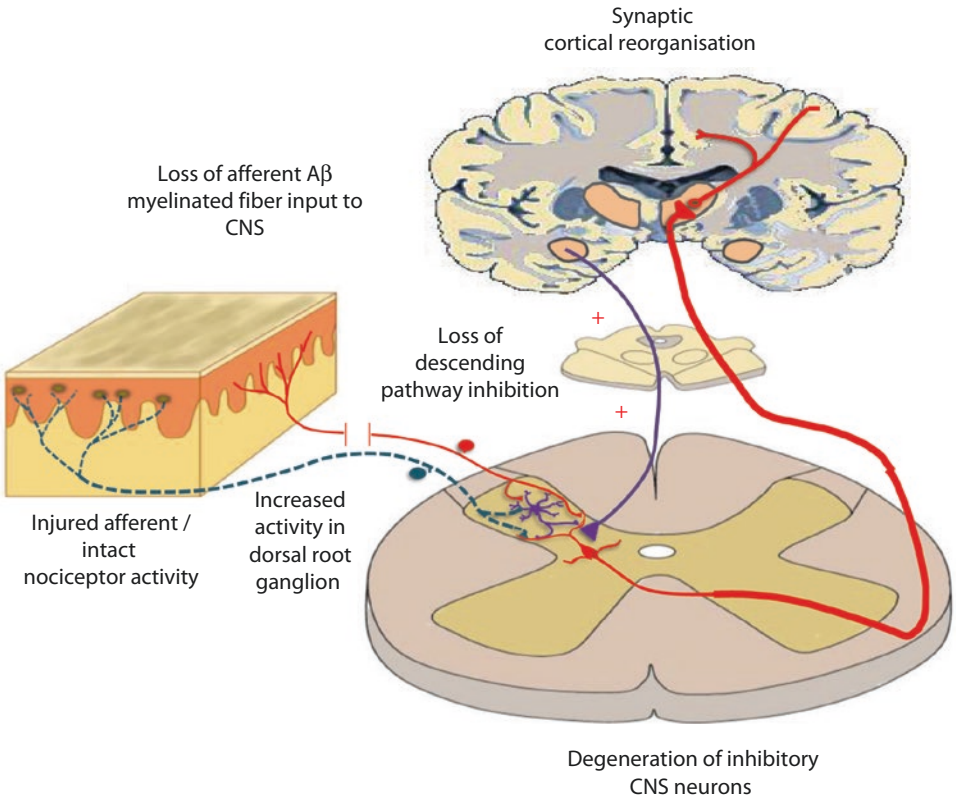

Fig. 10.1 Schematic diagram of several mechanisms of peripheral and central nervous system neuropathies. Peripheral sensitization include injured afferent hypothesis when a neuroma formed by injury to peripheral afferent fibres causes increased sesitvity to different stimuli resulting in abnormal excitability [11]; intact nocioceptor hypothesis in which spontaneous activity may develop in the nocioceptors that survived peripherally after injury innervating the region of the transected nerve secreting agents altering the activity of uninjured afferents [12] Central sensitization include increased activity in of the dorsal horn projection neurons in the dorsal root ganglion after a peripheral nerve injury causing the release of excitatory neurotransmitter glutamate [13]; loss of Aβ-myelinated fibers input causing loss of afferent inhibition resulting in more noxious stimuli reaching the CNS (Deafferentation theory) [14]; degenration of inhibitory CNS neurons (GABA interneurons) in the dorsal horn resulting in decreased inhibtion of nociceptive pathways causing chronic pain [15]; loss of anti-nociceptive descending pathways resulting in increased excitability to the CNS resulting in increased pain [16]; abnormal cotical input as a result of misdirected axonal growths at the site of injury causing reorganization of the somatosensory cortex with distorted skin mapping of the area innervated by the injured afferent [17]

Neuropathic pain refers to a type of non-nociceptive pain, which has many neurophysiological phenomena central to its genesis and symptom maintenance. These can involve the central nervous system primarily or secondarily due to changes to the peripheral nervous system components (sensitization). Figure 10.1 provides a pictorial representation of key processes involving the peripheral and central nervous system in neuropathic states.

10.2.4 Peripheral Sensitization

Different mechanisms have been proposed for the occurrence of abnormal signals in the peripheral nervous system capable of ultimately sensitizing the central system, including:

- Injured afferent hypothesis: According to this theory, a neuroma formed by injury to the peripheral afferent fibers causes growth of unmyelinated C fibers from damaged axons and results in abnormal excitability. This spontaneous activity occurs due to increased sensitivity to mechanical, chemical, and thermal stimuli [11, 12].
- Intact nociceptor hypothesis: This concept proposes that intact nociceptors (i.e., those surviving the original injury in the periphery and innervating the region affected by the transected nerve fibers) develop spontaneous activity [11]. Changes in ion channels, expression of receptors, and secretion of agents like prostaglandin, bradykinin, and tumor necrosis factor-alpha have the potential to sensitize nociceptors, thereby altering the properties of uninjured afferents [12].

10.2.5 Central Sensitization

The following mechanisms have been proposed to underlie central sensitization:

- Increased activity of dorsal horn projection neurons: There is an upregulation of $\alpha_2\delta$ subunit of calcium channels in the dorsal root ganglion and spinal cord after a peripheral nerve injury; this results in increased release of excitatory neurotransmitter glutamate [13].
- Deafferentation theory (loss of afferent inhibition): Tissue injury causes loss of Aβ-myelinated fibers input, which is the primary mechanism promoting hypoactivity of interneurons. These interneurons primarily inhibit nociceptive afferents resulting in more noxious stimuli reaching the CNS centers [14].
- Loss of CNS inhibitory neurons: γ-Aminobutyric acid (GABA) interneurons in the dorsal horn nerve fibers undergo degeneration, causing decreased inhibition of the nociceptive pathway contributing to chronic pain and hypersensitivity [15].
- Loss of descending inhibition: Inhibition of the anti-nociceptive descending pathways can result in increased excitability of the CNS, and this is thought to cause loss of sensory input following peripheral nerve injury [16].
- Synaptic reorganization: Acute deafferentation in the nervous system is thought to stem from peripheral nerve transection resulting in a misdirected axonal growth at the site of injury and cause abnormal cortical input. This mediates somatosensory cortex reorganization with distorted skin mapping originally innervated by the injured afferent [17].

The sensitization phenomena described above appear to play a key role in the generation and maintenance of chronic sensory phenomena in burn scars (see the following section) as well as keloid scars. It is interesting to note that the clinical profile of symptoms in keloids is such that pain in keloid is felt at the center while itch is mostly felt at the periphery raising the suspicion of a small fiber neuropathic state. Its severity has been suggested to correlate with pruritic intensity with a disproportionate number of regenerating unmyelinated C fibers at the periphery causing itch. Keloids with itch have also demonstrated an overall lower epidermal innervation density pointing toward mechanisms of peripheral nervous sensitization [18, 19]. Another study reporting a large number of thinner nerve fibers in deeper layers of keloidal skin has hypothesized the presence of the intensive fibrous compression (entrapment neuropathy) accounting for painful symptoms [20].

10.2.6 Pruritus: Definition and Subtypes

Pruritus is derived from the Latin word *prurio*, which means "to itch" and can be defined as the unpleasant sensation, which leads to the desire to scratch [21]. It can be divided into acute and chronic as well as into different subtypes based on the pathophysiological processes involved. In terms of chronicity, the acute itch has been proposed to last up to 6 months post-injury/insult to the skin in burns patients, corresponding to the early remodeling phase of wound healing [22]. Pruritic sensations in the healing wound could potentially be explained on the basis of histamine release as part of the inflammatory response and partly by virtue of abundant mast cell present in hypertrophic scars [23]. Nevertheless, the persistence of these symptoms beyond the wound healing and into scarring phase could not be solely explained on a histaminergic basis (see below).

Twycross et al. [24] has classified pruritus into the following four main subtypes:

- Pruritogenic: Arising in the skin because of injury/inflammation
- Neuropathic: Stemming from within the afferent neurologic pathway
- Neurogenic: Having a central nervous system origin in the absence of neurologic pathology
- Psychogenic: Associated with psychiatric conditions

While a number of non-skin pruritic disorders may appear to consistently fit in one discreet category, the scar-related itch is thought to have a number of non-pruritogenic origins.

10.2.7 Pruritic Pathway

10.2.7.1 Peripheral Receptor Activation

A wide variety of substances have been implicated in the generation and propagation of antegrade pruritic stimuli including:

Histamine

A number of histamine receptors have been described in the literature. The surface of sensory nerve endings have H1 and H2 receptors that are activated by histamine stored in the keratinocytes and mast cells [25]; H3 and H4 receptors are also found on peripheral and central neurons regulating neurotransmitter release and mast cells [26, 27]. As a by-product of collagen production, histamine synthesis is increased in the healing wound, and this can account for the generation of pruritic stimuli in the healing wound/freshly formed scar [28].

Acetylcholine

Human keratinocytes have been shown to synthesize, store, and release acetylcholine, which, through the activation of M3 muscarinic receptors in the skin, can produce an itch-associated response [29, 30].

Bradykinin

Histamine release can be caused by bradykinin secretion through mast cell degranulation [31]. It also stimulates the release of calcitonin gene-related peptide, substance P, and prostaglandin E2 at the site of tissue injury resulting in inflammation [32].

Proteinases

Dermal mast cells synthesize proteinases, including tryptase and chymase, which interact with proteinase-activated-receptor-2 located on C fibers neurons, contributing to impulse generation [33].

10.2.8 Peripheral Nerve Fibers (PNF)

A specific group of "unmyelinated C fibers" appears to be responsible for the transmission of itch; they start at the dermo-epidermal junction and reach the spinal cord via the dorsal root ganglion. These fibers have a characteristic slow conduction velocity (0.5 m/sec) with a prolonged histamine response and extensive terminal branching. The main transmitters released include substance P and calcitonin gene-related peptide [34].

10.2.9 Spinal Cord/Itch Specific Neurons

Andrew and Craig, in their experiments on cats, showed "itch-specific" neurons to be located in the superficial part of the dorsal lamina I of spinothalamic tract [35]. They are characterized by their lack of ongoing discharge and low conduction velocities and terminate at the thalamus before crossing over to the contralateral side in the spinal cord.

10.2.10 Thalamocortical Level

The exact parts of the brain activated by the pruritic pathway are still not fully characterized; lamina I of the spinothalamic tract was originally postulated to terminate in the medial dorsal and ventral medial nucleus of the thalamus in primates [36]. However, positron emission tomography studies have failed to show any subcortical activation in healthy individuals and instead show significant activation in contralateral somatosensory cortex and in both ipsilateral and contralateral motor areas (premotor cortex, primary motor cortex, and supplementary motor area). The cingulate gyrus and prefrontal cortex have also been implicated in neuronal transmission and this may potentially be the reason for the associated emotional component seen in scratching behaviour of patients suffering from pruritus [37].

The generation and maintenance of pruritic symptoms into a chronic state has been postulated to relate to a state of central nervous system sensitization, based on a combination of clinical, neurophysiological, as well as pharmacological data [38]. The salient observations supporting a neuropathic state in chronic pruritus in burns patients are summarized below.

(a) Emerging pharmacological evidence behind the effectiveness of antihistamines at different time-points during rehabilitation indicates that in the later phases of healing, wounds and scars become unresponsive to antihistamine therapy [39, 40, 41]. This may point toward the involvement of the central nervous system in the maintenance of these symptoms and is further supported by the superiority of centrally acting agents including gabapentin and pregabalin [34, 35, 42, 43] and transcutaneous electrical nerve stimulation modalities in symptom management [41, 44].

(b) Neurophysiological studies in burn scars show that phenomena similar to those occurring in chronic neuropathic pain exist in terms of the presence of increased sensitivity to stimuli (hyperalgesia/hyperkinesis) on the background of otherwise overall decreased sensibility. This finding provides some evidence of possible deafferentation as a mechanism for CNS sensitization [44, 45].

(c) Clinical presentation highlights a pattern of symptom exacerbation at night time, which is found typically in neuropathic states [46, 47].

(d) The neurological pathways of both symptoms share common features including the role of substance P and CGRP as well as similar areas of the central nervous system activated in the generation of symptoms as in neuropathic pain [48, 49].

(e) Neuropeptide expression data. Hypertrophic scar biopsies in patients with pain and itch demonstrated a higher density of neuropeptides (SP and CGRP) compared to controls, whereas these were absent in non-hypertrophic scars providing a link between neuropeptide expression and impulse transmission. Interestingly, SP immunoreactivity was present in the densely packed areas of scar hypertrophy [50].

Another study in grafted burn skin showed the coexistence of overall decrease in axonal population and a preferential increase in SP fibers correlating with pruritic symptoms; this provides a link between a state of SP hyperinnervation in a milieu of deafferentation possibly leading to a neuropathic state [32]. Furthermore, neuropeptides like SP are thought

to play a key role in perpetuating fibroproliferative pathology establishing a cycle of nociception and scar hypertrophy [50, 51].

Other authors have proposed the role of opioids in the generation of pruritic impulses in hypertrophic burn scars [52].

10.2.10.1 Incidence/Prevalence of Pain and Itch in Scars

Pain is a major sensory disturbance and has been described as contributing to the "hidden cost" of cutaneous scars. According to a study based on semi-structured interviews in a UK scar specialist service, it has been identified that 26% and 44% of patients reported pain and itch in association with their scars, affecting their physical comfort and functioning [53].

In a corroborative study, pain and itch have been found to correlate with physical impairment ($P \leq 0.001$) in a study of 100 patients with keloid and hypertrophic scarring attending a German dermatology department using the Questionnaire on Experience with Skin Complaints. Similar work utilizing the Dermatology Life Quality Index (DLQI) tool confirmed that keloids have a statistically significant effect on the quality of life compared to physiologic scars ($p < 0.001$); additionally, they are associated with a statistically significant increase in pain and itch disturbances ($P < 0.01$ and 0.001 respectively) [54].

A cross-sectional health-related quality of life (HRQL) assessment study focused on indicators of the burden for 106 keloid patients using one disease-specific (Skindex-29) and two generic (SF-36 and EQ-5D-5L) HRQL measures; results indicated that pain and itch were the strongest predictors of impairment and related to low mental and emotional status [55].

A study evaluating chronic pain due to central sensitization in burn scars showed a 35% prevalence of pain in scarred tissue one or more years after injury [56, 57]. Additionally, work evaluating 98 burn survivors, reported 25% of patients having painful scars and 20% experiencing shooting pain more than 30 years post-injury [21]. A retrospective review involving 72 patients suggested that the first complaint of neuropathic pain presents on average at 4.3 months after injury and that there is a qualitative progression pattern; symptoms are initially reported as "pins and needles," then being predominantly stabbing or burning pain followed by "shooting" sensory qualities [58].

A multicenter cohort involving 510 patients was used to evaluate the incidence and prevalence of burns itch. In this long-term prospective study, 64% of individuals reported itch to be a significant problem over a 2-year period. At three months, 87% of individuals reported severe itching; this fell to 70% at 12 and 64% at 24 months respectively. Predictors of itch at three months post-burn included total burned surface area (TBSA), female gender, number of surgical procedures (deep dermal injury), and post-traumatic stress disorder (PTSD) symptoms at two weeks post-injury. Interestingly, at 24 months the only predictors for itch complaints were the latter two (PTSD at two weeks post-injury and the presence of deep dermal injury). The authors proposed that acute itch (up to 6 months) corresponding to the early remodeling phase of wound healing effects, both partial and full-thickness burn injuries. Chronic itch, on the other hand, affects patients with certain predisposing factors, providing a link between the chronicity of symptoms and markers of injury severity as well as psychological stress [59].

Another multicenter, large cohort study of adult burn survivors, reported high prevalence and severity of post-burn pruritus. Two cohorts of individual with burns were studied; the first included 637 patients followed prospectively over a 2-year period and identified that pruritus initially affected more than 90% of individuals and persisted in more than 40% of burn survivors in the long term. The second cohort comprised 336 patients who sustained burn injury 4–10 years before assessment using the 5-D itch scale. Pruritus was reported as severe in 76% patients within this group, moderate in 29%, and mild in 52% [60].

Schneider et al. [61] conducted a retrospective review of 430 pediatric burn survivors with a mean TBSA of 40.8%. Findings included that pruritus is present in most children (93%) and is of moderate intensity at discharge. The frequency and intensity of symptoms decreased over time; nevertheless continued to affect 63% of children at two years post-injury; furthermore, regression analysis showed significant correlations between pain and itch intensity at each time point. Most interestingly, no association was identified between pruritic intensity and burn etiology, age, gender, or burn size.

10.2.10.2 Management of Symptoms

Sensory symptoms in scars can be managed using a variety of approaches; undoubtedly, the most important initial step toward successful management relies on reliable and consistent monitoring of symptoms. A plethora of clinical measurement scales have been described in the literature; some of the most commonly utilized mono-dimensional scales include verbal, visual, as well as numerical analogue scales [62]. Other evaluation methods like the "itch man scale" incorporate a pictorial element, which makes them more suitable for pediatric patients or those unable to complete analogue scales [63]. Multidimensional tools including the 5-D Pruritus Scale have the advantage of incorporating components of the sensory experience other than intensity, including duration and disability, hence offering the opportunity

to capture the degree of disturbance in a more comprehensive manner [64].

A variety of pharmacological and non-pharmacological adjuncts are available and frequently using a combination of modalities provides an optimal therapeutic approach.

10.2.11 Non-pharmacological Adjuncts

10.2.11.1 Psychological Support

A multidisciplinary approach toward treating sensory disturbances in scars is vital, and psychological support has been suggested as an integral part of the management plan [65]. This is particularly pertinent given the association between psychological stress and perseverance of sensory symptoms into a chronic state [38].

10.2.11.2 Cooling

The application of cooling agents as part of wound care and scar management can help temporarily relieve pruritic sensations. The beneficial effect of cooling can be explained by the temperature-sensitive activation of certain excitatory ion channels, including vanilloid receptor 1 as well as ascending pathway C fibers [34, 66].

10.2.11.3 Hydration/Moisturization

Two recent literature reviews have found that there is limited and low-level evidence behind the optimal choice of a moisturizing and hydrating product for burn scars [67], with a small number of studies investigating the value of different products available. The rationale for moisturization of a scar relates to addressing the increased rate of transepidermal water loss (TEWL) seen in scars and potentially inhibits the fibrogenic action of fibroblasts by virtue of the hydrating effect [68].

The ideal moisturizer should have both occlusive as well as humectant ingredients. Occlusive substances (e.g., oils) function to impede water loss, whereas humectants (e.g., glycerin, propylene glycol, etc.) attract water from the dermis into the stratum corneum. The presence of a defective barrier against transepidermal water loss in scarred skin implies that a humectant-only-based preparation would enhance fluid loss, hence should be avoided [69].

A small randomized study has indicated that mugwort lotion is a promising topical agent for the relief of an itch in burns hypertrophic scarring [70]; additionally, a non-prescription moisturizer containing a blend of protease enzymes (Provase) applied every 8 hours for four weeks has been shown to reduce itch severity parameters as well as the affective burden significantly [71].

A similar randomized controlled study among 52 patients with postburn itch found that a preparation of beeswax and herbal oil had a statistically significant better effect on itch compared to aqueous cream ($P = 0.001$); additionally, symptoms recurred later comparatively ($P \leq 0.001$), and the use of antipruritic medications was lower ($P = 0.023$) [72].

A different literature report compared the effects of hydrocolloid dressing versus moisturizer in 20 patients with keloid and hypertrophic scars over a 2-month period in a randomized controlled prospective manner. Results indicate that both products achieved a similar reduction in itch ($P < 0.03$) and pain ($P < 0.08$) presumably by virtue of scar hydration [73].

One of the most interesting reports in the literature focused on the comparison between a hydrating gel-cream and three fluid silicones in a group of healthy volunteers. The moisturizer Alhydran (BAP Medical, Belgium) has been found to have an equivalent effect on hydration and occlusion suggesting that these may be the most important in topical scar care preparations as opposed to active substances like silicone, which have become extremely popular in recent decades [74].

10.2.11.4 Massage

Massage has been shown to be effective for the management of pain, itch, and anxiety associated with scars in a number of studies [75–77]. The first randomized study included 20 patients in the remodeling phase of scar formation; these were divided into either a 30-minute massage with cocoa butter to a moderate-sized scar tissue area twice a week for five weeks or standard therapy (cocoa butter application to scars applied by physical therapists without massage motions). The massage therapy group showed reduced pain, itch (both measured using visual analogue scales), as well as anxiety scores consistently throughout the study period [75]. Similar results were obtained in a study with a comparable design with regards to pain, itch, and anxiety in adolescent burn victims [78].

A Korean group investigated the effects of skin rehabilitation massage for three months in a group of 18 burn survivors; this involved the combination of light stroking movements followed by acupressure using oil as a medium applied for 30 minutes once a week for three months. Results indicated a statistically significant improvement of pruritus in the massage group ($t = -2.942$, $p = 0.006$) as well as depression ($t = -2.920$, $p = 0.007$) [76]. The underlying mechanisms of action of massage include the principles of the "gate theory" of pain modulation as well as the increased vagal activity, reducing stress hormone levels in the recipient [10, 79, 80].

10.2.11.5 Silicone Gels/Sheets

Silicone is widely used for the treatment of symptomatic hypertrophic scars. The proposed beneficial mechanisms involved include increased skin hydration (by virtue of occlusion) and a decrease in fibroblastic activity [81, 82].

The literature contains a number of high-quality studies regarding the role of silicone for the prevention of hypertrophy including a randomized placebo-controlled, double-blind prospective trial on sternotomy wounds showing a statistically significant effect on pain and itch symptoms [83].

Topical application of silicone gel versus placebo gel has been investigated in a randomized within-subject comparative clinical trial. Results suggested that silicone gel promoted maturation of early burn scars (mean age of scars in the study 4 months) and a decrease in itch symptoms in a statistically significant manner [84]. Similar beneficial effects were reproduced in a different study employing silicone gel application to burns hypertrophic scarring showing a significant difference in terms of scar vascularity starting at the first month of application [85].

Another study utilized silicone gel sheets in the conservative management of six keloid patients for 24 weeks. Symptoms of pain and itch showed a decrease after four weeks of the gel sheeting application and disappeared after 12 weeks. After 24 weeks, a histological decrease in the number of mast cells was observed, which may explain the therapeutic benefit seen by virtue of a decreased concentration of mast cells derived mediators [86].

A number of comparative studies exist in the literature, which aimed to elucidate the role of silicone products in the scar care arena.

A randomized clinical trial of 45 post-traumatic hypertrophic scars found that silicone gel sheeting applied 24 hours/day for six months was superior to 15-minute-long daily massage in reducing scar thickness in a statistically significant manner ($p < 0.001$); of particular note is that pain and itch reduction did not reach statistical significance in this study [87].

A separate prospective single-blinded study compared the efficacy of 585 nm flashlamp-pumped pulsed dye laser and silicone gel sheeting and control in the management of 20 patients with hypertrophic scars; results showed an overall reduction of blood flow, volume, and pruritus for all the study subgroups but failed to show any statistically significant difference between treatment and control groups [88].

A prospective split sternotomy scar study [89] involving 14 patients randomized to treat one-half of the scar with triamcinolone acetonide (TAC) and the other with silicone gel sheeting worn for 12 hours for 12 weeks. The primary outcome of patient preference was analyzed, and recruitment was terminated after 11 patients had completed the study, 10 of whom favoured silicone gel treatment. The average time for the symptomatic improvement of silicone-treated patients was 3.9 days as compared to triamcinolone acetonide, which was 6.8 days ($p < 0.05$). The authors proposed that the enhanced compliance to silicone-based treatments relates to the painless and noninvasive nature of silicone-based adjuncts.

10.2.12 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS involves the application of low-voltage electrical impulses to the nervous system by means of electrodes placed on the skin [90]. The underlying mechanism of action involves the stimulation of rapidly conducting A-fibers, which inhibit the transmission of noxious stimuli carried by the slower C fibers according to the "gate theory of pain" [10].

A pilot study involving 20 patients with healed burns complaining of severe itch following burns demonstrated a statistically significant change in the reported visual analogue scale compared with placebo over a 3-week period [90].

10.2.13 Pharmacological Adjuncts

10.2.13.1 Capsaicin

This is a naturally occurring alkaloid compound, which interacts with the transient receptor potential V1 receptor resulting in the depletion of neuropeptides from peripheral nerves. Despite the fact that capsaicin forms one of the mainstay topical agents in many chronic pain services, a double-blind placebo-controlled randomized trial using 0.025% capsaicin cream on 30 patients with pruritic wounds revealed no significant effects on pruritic symptom relief [91, 92, 93]. Further work is warranted involving preparations with different concentrations of this agent in order to elucidate its exact role in the management of symptomatic scars.

10.2.13.2 Antihistamines

Antihistamines have traditionally been used as first-line agents for the management of pruritus. First-generation compounds (diphenhydramine, hydroxyzine, cyproheptadine, and chlorphenamine) act on histaminic, serotonergic, muscarinic, and alpha-adrenergic receptors. Second-generation compounds, like cetirizine, have minimal activity on non-histaminic receptors and hence have a more favourable side effect profile as well as a longer duration of action [94, 95]. The pharmacological action of antihistamine relates primarily to a reverse agonist action at histaminic receptors as well a central nervous system sedative effect (the latter action refers to first-generation compounds).

One of the initial studies involving 35 burns patient complaining of severe itching after discharge assessed the efficacy of three first-generation antihistamines,

namely chlorpheniramine, hydroxyzine, and diphenhydramine. The results of the study pointed toward no significant difference in therapeutic efficacy between the three compounds and only a 20% complete relief of symptoms in the cohort [96].

10.2.13.3 Gabapentin/Pregabalin

Gabapentin is a useful agent for the management of neuropathic pain associated with a variety of conditions, including post-herpetic neuralgia [97].

The mechanism of action of gabapentin involves a number of mechanisms, including:

1. Blockade of the $\alpha_2\delta$ subunits of voltage-gated Ca channels resulting in a reduced release of excitatory neurotransmitters [98].
2. Increased synthesis and release of γ-aminobutyric acid in the CNS [99].

A comparative study appraised two different therapeutic protocols for the management of burns pruritus in patients with healing and healed burns in a UK burn center incorporating a mixture of antihistamines and gabapentin; the authors concluded that gabapentin as monotherapy as well as in combination with another two antihistamines was more efficacious compared to chlorpheniramine alone and in combination with another two antihistamines ($t = 3.70$, df = 89, $P < 0.001$ for monotherapy and $x^2 = 12.2$, df = 1, $P = 0.001$ for polytherapy). Additionally, patients with higher initial pruritus scores needed a combination of pharmacological agents for effective symptomatic relief. This study raised the value of centrally acting agents in itch management and proposed the combination of peripherally and centrally acting agents in the treatment for burns pruritus [41].

Another landmark study comprised a four-arm, double-blind, randomized and placebo-controlled study of pregabalin in the management of postburn pruritus. Pregabalin is a newer analogue of gabapentin with comparatively better anxiolytic and pharmacokinetic properties. The study compared the following four groups: pregabalin; cetirizine and pheniramine maleate; the combination of pregabalin, cetirizine, and pheniramine maleate; and placebo. Results indicated that for moderate to severe pruritus (VAS 6-10) a centrally acting agent like pregabalin is indicated to significantly decrease itch; patients with milder itch (VAS 4-5) are best served with the addition of pregabalin even if massage and antihistamines can provide some control because of quicker, predictable response with the added benefit of anxiolysis [77].

10.2.13.4 Steroids

Steroid delivery to hypertrophic and keloidal scars is a well-established modality for the alleviation of scar-related symptoms, including pain and itch, and their beneficial effects were first recorded in literature in the 1950s [100]. The international advisory panel in 2002 recommended triamcinolone acetonide (TAC) as the first-line treatment modality for keloid and second-line treatment for linear hypertrophic scar in reducing subjective symptoms associated with keloid and hypertrophic scar like pain and pruritus [101].

In 2014, a protocol re-evaluation was undertaken, which reinforced the prominent position of steroids in scar management albeit supported a combined approach incorporating the use of other agents including 5 fluorouracil, cryotherapy, laser, and silicone products [102].

Darvi evaluated the use of intralesional triamcinolone acetonide in treating hypertrophic and keloid scars in 65 patients with a 10-year follow-up. The dosage of TAC for 1–2 cm^2 of scar surface area was determined to be 20–40 mg, 40–80 mg for 2–3 cm^2, and 60–120 mg for scar surface area of 4–6 cm^2. In this study four injections of TAC were given for the total dose delivered to the scar at 1–2-week intervals with an ensuing symptomatic relief seen in 71% of patients; furthermore, a dramatic improvement of symptoms with full flattening of hypertrophic scars was seen in 50% and 71% in patients with keloid scars [103].

Manuskiatti [104] and colleagues performed a randomized controlled trial comparing the effects of intralesional triamcinolone acetonide with 5-fluorouracil or alone with 585 nm pulse dye laser. TAC-treated scars had better improvements in clinical symptoms (pain, itching) and scar induration, although the results were not statistically significant. Intralesional triamcinolone acetonide treatment, however, did produce side effects, including skin atrophy, telangiectasia, and hypopigmentation in 50% of the TAC-treated group. Boutli-Kasapidou and colleagues [105] evaluated a polytherapy protocol, including three triamcinolone acetonide intralesional injections every month combined with 12 monthly cycles of cryotherapy and 12-hour silicone dressing for 12 months. Patient satisfaction scale was used to grade the appearance cosmetically and subjective symptoms (pain, burning, and tension post 12 months). Similarly, an investigator satisfaction scale was used as well. The results showed that compared to monotherapy, polytherapy group had a major improvement in control of symptoms and appearance, reported by the patient and observed by the physician ($P < 0.01$). They concluded the beneficial effects of each treatment acting synergistically: Steroids downregulating the excessive collagen expression in keloids and making it softer, ischemic destruction and subsequent necrosis of keloids with cryotherapy, and silicon downregulating mastocytes.

Tan and colleagues [106] conducted a patient-controlled prospective study for 12 weeks with patients receiving intralesional triamcinolone acetonide (40 mg/mL), silicone gel sheeting, or no treatment (control).

The dose of triamcinolone acetonide varied between 0.1 ml to 0.5 ml of 40 mg/mL of TAC depending upon the size of the lesion. In this trial, 12% of silicone-treated keloids showed a significant reduction (>50%) in size compared with 94% of triamcinolone acetonide group (RR: 33.00, 95% CI: 2.14–509.33). There was also a significant improvement in erythema (RR: 21.00, 95% CI: 1.33–332.06). The improvement in itch and pain was not statistically significant when compared to control.

Martin et al. studied the combination of carbon dioxide fractional laser (10,600 nm), a pulsed dye laser (585 nm), and triamcinolone acetonide (40 mg/ml) injections monthly for seven sessions in a cohort of keloid scars; they reported favourable results in regards to pruritic relief [107].

Steroids can also be delivered to scars in the form of tape application. Advantages of this modality include the noninvasive nature and the ability to maintain a continuous level of steroid concentration to the symptomatic scar, which can ameliorate the inflammatory milieu responsible for the bulk as well as sensory symptoms [108].

10.2.13.5 Botulinum Toxin

Botulinum toxin is a protein neurotoxin produced by the spore-forming bacteria Clostridium Botulinum; it works by preventing the release of acetylcholine at the neuromuscular junction and causing chemoimmobilization as well as affecting a variety of cell types including fibroblasts [109]. It is an established adjunct in a variety of medical and aesthetic interventions and over the last number of years has been trialed in the scar management arena. The rationale for its use rests on the ability to decrease muscular tension underlying a scar as well as the ability to alter a host of fibroblast related pathways, including their proliferation and cell cycle [110].

A randomized, double-blind comparative trial [111] involving 24 females with idiopathic or post-traumatic keloids employed the use of either intralesional triamcinolone (10 mg/cc), given every four weeks for six sessions or 5 IU/cm^3 intralesional botulinum toxin every eight weeks for three sessions; in both groups, therapy was continued until complete improvement of keloid was noted. The authors concluded that the effects of intralesional botulinum toxin A comparable to that of intralesional steroids with a significant reduction in volume height and redness of scar in both groups ($p < 0.01$). In the 7-month follow up both treated groups had a statistically significant reduction in subjective symptoms of pain and itching with a statistically significant difference in favour of the botulinum toxin A treated group with the added advantage of no side effects which were typically seen in steroid-treated patients.

Another blind study compared the effect of triamcinolone acetonide (maximum of 40 mg dose) plus placebo versus triamcinolone acetonide and botulinum toxin (20IU) for keloid scars injected every four weeks for a total of 12 weeks. Although the difference in height, vascularization, and the pliability were not significant between the two groups, there was a significant difference in favour of the botulinum group in terms of pain and pruritus control (($p < 0.001$) at the end of the study [112].

Similar results in terms of the superior alleviating effect of botulinum toxin have been reached in another randomized, single-blind study in 32 keloid patients [113].

The use of botulinum toxin has been reported in the burns literature as part of a pilot study involving nine patients, eight of which had skin grafts for deep partial-thickness to full-thickness burns, with an average TBSA of 24%. At the beginning of the study, 87.5% of patients rated their burns itch as being severe (>7/10), which fell to 0 at four weeks following the administration of toxin [114].

Further studies are warranted to delineate the exact role of botulinum toxin in scar symptom management.

10.2.14 Emerging Modalities

10.2.14.1 Autologous Fat Grafting

Autologous fat grafting has been widely used for the treatment of contour deformities and increasingly employed to remodel and regenerate tissue by virtue of mesenchymal stem cells present in adipose tissue [115, 116].

The proposed mechanism supporting the alleviation of scar symptoms is suggested to relate to the mechanical release of adhesions, neovascularization, and remodeling of scar tissue architecture [117]. Other mechanisms proposed for controlling neuropathic pain symptoms include blockade of nociceptive impulses and an overall reduction of the signal input to the central nervous system [118].

Fredman et al. [119] in a retrospective case review evaluated the effectiveness of fat grafting in neuropathic burn scars using the patient-reported outcome measurement information system (PROMIS) to assess pain following two fat-grafting sessions eight weeks apart. Results showed a statistically significant improvement in subjective outcomes at 1-year follow-up.

Huang et al. [120] evaluated autologous fat grafting in 13 patients with neuropathic scar pain. Pain evaluations were undertaken using the Visual Analogue Scale (VAS) and Neuropathic Pain Symptom Inventory (NPSI) preoperatively and at 1, 4, and 24 weeks postoperatively. Both VAS and NPSI scores showed a significant decrease starting at one week, alleviating neuropathic scar pain in the short term, which were statistically significant ($P = 0.009$ and $P = 0.007$

respectively). The NPSI score continued to decrease at four weeks ($P = 0.0009$) till 24 weeks ($P = 0.0008$) with the most significant improvement in paresthesia, dysesthesia and evoked pain ($P < 0.001$). They concluded the autologous fat provides insulation and acts as a cushion to block abnormal sensations and prevent stimulation.

Two systematic reviews of the literature pertaining to the use of fat grafting and adipose-derived stem cells in scarring have shown improvements in scar characteristics including texture and size, improved pain profiles, increased angiogenesis, and an earlier return to function [121, 122]. It is clear that the use of fat-derived cells will play an important role in the future of scar treatments in the field of regenerative medicine.

10.2.14.2 Lasers

Laser stands for "Light Amplification by Stimulated Emission of Radiation" and exerts its effect on the tissue through photochemical/thermal/mechanical mechanisms [123].

The photothermal effect or photothermolysis is the most relevant mechanism in scar treatment with the main target being either blood vessels (pulsed dye laser) or water (CO_2 and Er:YAG laser). Lasers can be further subdivided into ablative and non-ablative based on whether the epidermis is affected or not and fractional and non-fractional: based on whether intact columns of skin are left behind or not after the treatment [124].

Pulsed Dye Laser is a vascular specific laser with haemoglobin being the target chromophore. Selective photothermolysis [125] with a short pulse duration leads to selective absorption of heat by haemoglobin, leading to thrombosis and vasculitis [126].

Ebid et al. [127] in a double-blind, randomized, placebo-controlled trial, compared the effects of pulsed high-intensity laser in the treatment of post-burn pruritus. They showed that a combination of a long period of high-intensity pulsed laser, antihistamine, and massage could effectively control moderate to severe burn pruritus, raising the value of incorporating laser modalities in antipruritic protocols.

Vasheghani and colleagues [128] showed that low-level laser therapy in second-degree cutaneous burns decreases the total number of mast cells in the remodeling phase while increasing the number of mast cells in the proliferative and inflammatory phases. Increased level of growth factors and anti-inflammatory cytokines and decreased level of pro-inflammatory cytokines like interleukin alpha and beta have been shown after treatment with laser therapy [129] elucidating potential mechanisms for the action of laser on pruritic pathways. Other proposed mechanisms include the direct action on reactive oxygen species, inhibition of cyclooxygenase (COX) and prostaglandin E2 [130], as well as the fast axonal flow and microtubule disruption of Aδ and C fibers transmission [131].

Alster and Williams [132], in an investigator-blinded split scar study of patients with keloid scarring, performed two sessions of flash pump 585 nm pulse-dyed laser treatment to half of the scar at 6–8-week intervals. They reported a significant improvement in the texture of the skin surface, scar height, erythema, pruritus with coarse, loose collagen, and increase number of mast cells seen histologically in the laser-treated side.

A prospective randomized controlled trial investigated the outcomes following ablative fractional CO_2 laser on 19 patients with burn scars (minimum age of scars for inclusion six months). Results demonstrated that three treatments of ablative fractional CO_2 laser (Deep FX setting on UltraPulse®, Lumenis; treatment parameters: single pass of 300 Hz, 5% density, and 50 mJ energy) significantly improved scar pain, itch based on Patient and Observer Scar Assessment Scale (POSAS) scores ($p = 0.047$ and <0.01 respectively). Additional findings included an improved dermal architecture at six weeks post-treatment [133].

10.3 Conclusion

Pain and itch represent the most common sensory symptoms accompanying scars and can have a significant impact on patients' quality of life. Over the last number of decades, our understanding of the pertinent pathophysiological mechanisms has improved considerably, especially with regards to the contribution of the central nervous system in the generation and maintenance of nociceptive and pruritic stimuli. Consistent and reliable monitoring of symptoms combined with a multimodal approach to treatment should be integral parts of holistic scar management.

Take-Home Messages

- Itch and pain can have a significant impact on individuals with scars.
- The contribution of the central nervous system in the generation and maintenance of symptoms is paramount.
- Accurate assessment and monitoring of symptoms are central to successful scar management.
- Multimodal approaches which target both peripheral and central nervous system components and incorporate non-pharmacological adjuncts are recommended.

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Scar Symptom: Erythema and Thickness

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_11

Definition

Erythema is derived from the Greek *erythros*, which refers to the redness of skin or mucous membrane. Erythema is common in pathological scars (hypertrophic scar and keloid) and premature physiological scars where inflammation-induced angiogenesis and capillary dilation are mostly responsible. Different from the temporary and self-relieving redness in normal skin caused by allergy or mechanical friction (such as massage), the existence and severity of erythema in scar tissues are consistent with their maturity and inflammation state inside, serving as a convenient monitor of scar quality and treatment response. Scar thickness indirectly reflects the extent of scar development by collagen deposition.

11.1 Mechanisms of Erythema in Scar

In general, the common causes of erythema can be roughly categorized into four groups: inflammation, mechanical stimulation (massage, waxing, and tweezing of hairs), radiation (sunburn, radiotherapy), allergies and other chemical agents. Despite the pervasive nature of erythema in both physiological and pathological scars, the development mechanisms remain to be relatively less explored and therefore limited effective treatment options are available. However, previous studies demonstrated that inflammation, vascularization, and sometimes epidermis defect are the three major mechanisms that contribute to the erythema in scars.

11.1.1 Inflammation-Induced Capillary Perfusion Is Crucial for Erythema Initiation

Accumulated studies have confirmed that the inflammation induced by various reasons (infection, foreign body, immune dysfunction, etc.) is greatly associated with the formation of scars, especially hypertrophic scars and keloids [1]. Stimulated by inflammatory cytokines, capillaries constrict to increase the local blood flow and vessel permeability, resulting in erythema and sometimes elevated skin temperature [2]. It was shown that significant increase of blood flow values was detected in erythematous scars when compared to healthy skin [3, 4]. Besides, erythema (measured by colorimetry) is often interpreted as an indirect measurement of the blood flow in clinical practice as it indicates the hyperemia in superficial capillaries. Bae-Harboe *et al.* first introduced the term "postinflammatory erythema" (PIE) in 2013 to describe erythema often seen after the resolution of inflammatory acne or other inflammatory skin conditions [5]. To be specific, the symptom of erythema persists all along the inflammatory stage of wound healing and plays multiple roles in this process.

11.1.2 Vascularization Dynamically Participates in the Erythema Development

The chronic inflammatory stimulation and hyperproliferation of scar tissues deteriorate the local hypoxia and promote the secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and hypoxia-induced factor 1 (HIF-1) [2, 6]. As reported by Amadeu *et al.*, hypertrophic scars contain an increased number of dilated vessels in papillary and reticular dermis compared to normal skin [7]. The increased capillary density and dilated vessel diameter then contribute to the formation of erythema, in line with the study of Fullerton, who stated that erythema is determined by the blood volume under a given area, and not by the product of erythrocyte velocity and concentration [8]. Clinically, erythema disappears on finger pressure (blanching), which also suggests that the vascular remodeling is involved.

Scar erythema, blood flow, microvessels, and redness are four features of scar that are often interchangeably used under the item "vascularization" or "vascularity." However, by directly measuring erythema with colorimetry, blood flow with laser Doppler imaging (LDI), vessels with immunohistochemistry, and subjective scale of redness with POSAS, respectively, Jaspers *et al.* found only significant relevance between erythema and subjective redness, but no correlations between the others. In contrast, Mermans *et al.* found that erythema was associated with blood flow, but this correlation was not consistent at different test moments [9]. Moreover, Kischer *et al.* reported that most microvessels were occluded in hypertrophic scars due to an excessive number of endothelial cells [10, 11]. And the higher hematocrit and the enlarged vessels would then result in a more sluggish blood velocity and lower blood flow values. Taken together, it is now understood that the term "vascularity" describes a dynamic process, and the four criteria mentioned above can attribute to the redness either independently or interact with each other at different stages of scar development. These exploration studies express well the complexity of erythema formation and enlighten us to view this process dynamically instead of simply putting them under the umbrella of "vascularization," especially in clinical practice.

11.1.3 Thinner Epidermis Is Directly Responsible for the Transparency in Erythematous Scars with Skin Barrier Defect

The epidermal thickness and collagen synthesis are directly associated with the transparency of skin. Oliveira *et al*. and Busch *et al*. identified a thinned-out skin texture in burn scar that makes the intense circulation of blood becoming more apparent [3, 12]. They argued that increased skin redness is not only considered as an inflammatory symptom but also the structural modification of subdermal components. And the induction of percutaneous collagen (IPC) and angiogenesis therapies (medical needling and fractional laser) has been proven to be effective to adjust the skin color after repetitive treatments [12].

Different from the thinner epidermis in physiological scars resulting from normal wound-healing process, keloids and hypertrophic scars are characterized by extra collagen deposition and increased epidermal thickness [13]. But recent studies also hypothesized a skin barrier defect in keloid scars, which may possibly alter the opacity of epidermis [14].

11.2 Contributions of Erythema to Scar Development and Associated Clinical Symptoms

The wound-healing process contains three chronological but partially overlapped phases: inflammatory stage (day 1–6), proliferation stage (day 4–week 3), and remodeling stage (week 3–1 year). Parallel with this process, Van Der Wal *et al*. reported that the erythema index scores of scars reduce significantly within 12 months [15] as a result of the common pathological mechanisms they shared. To be specific, the alleviation and deterioration of erythema are closely associated with the scar development since they indirectly reflect the inflammatory state and angiogenic activity beneath the skin. And since the redness of erythema (from pink to scarlet to purple) is the result of different proportion of hemoglobin (the red oxygenated state, absorbed at 660 nm) and deoxyhemoglobin (dark red, absorbed at 940 nm) in the capillaries of the dermis, the color of scarred skin can serve as a monitor of local hypoxia, angiogenesis, and microcirculation.

Although the most commonly used principles for measuring scar color are narrow-band reflectance spectrophotometry and tristimulus reflectance colorimetry [4], researchers found statistically significant correlation between erythema values (colorimetry) and subjective redness assessment (Patient and Observer Scar Assessment Scale, POSAS) ($r = 0.403$, $p = 0.030$) [4], proving the reliability of subjective erythema measurement in clinical practice.

Similarly, erythematous scars are more likely to suffer from pain or pruritus as a result of inflammatory stimulation and suspicious vulnerability of scar fibroblasts (previous studies detected an elevation of α-adrenoreceptors expression on keloid fibroblasts and predicted that it might be related to paresthesia in scar tissues [16]).

Elevated temperature is directly associated with overperfusion of vessels especially arteries in deeper layer of the skin [4] and is not common in thickened scar tissues, but the existence of which could be explained as a sign of infection or active inflammatory state.

Generally, erythema reflects the inflammation and angiogenesis activity, as well as structural remodeling of scar tissues to serve as a monitor of scar maturation and quality. Since patients and clinicians often determine the success of treatment by the visual appearance of a scar, erythema measured by POSAS could be an accessible method to evaluate the treatment response and help to set the endpoint for the course.

11.3 Scar Erythema and Scar Thickness

There is no direct relation between scar erythema and scar thickness, because the former reflects the level of inflammation and angiogenesis process, whereas the latter indicates the extent of cell proliferation and extracellular matrix production and deposition. Such phenomenon has been frequently observed in clinical practice that a highly inflamed scar with sever erythema might be thin and soft in texture, whereas a dark-colored keloid could be thick and abundant with collagen. However, enhanced erythema by strong angiogenesis provides nutrition for fibroblast proliferation and matrix production, and therefore reducing erythema also helps to prevent scar thickening.

11.4 Clinical Measurement of Scar Redness and Thickness

Colorimetric plate along with photography is the conventional methodology to semi-objectively measure the redness of scars. Doppler ultrasound can detect blood flow inside a scar, but it reflects activity in a relatively deep blood vessel. For superficial blood flow inside the

surface capillaries, laser speckle might be the technique to quantitatively measure the erythema change.

Manual measurement is the conventional way to assess scar thickness. With advances in technology, ultrasound and nuclear magnetic resonance can quantitatively provide data of scar thickness. In addition, 3D scanner not only provides the gross view of a thick scar, but also provides quantitative data of scar thickness and volume.

11.5 Clinical Relevance

11.5.1 Clinical Treatment Strategies of Erythema in Scars

Traditional clinical treatments of erythema in scar tissues mainly target on anti-inflammation and anti-proliferation, such as topical glucocorticoid and compression garments. The spreading applications of laser treatments and medical needling provide therapists with powerful arms that can interfere with erythema formation from various perspectives. Besides, systematic elements including imbalanced diets, stressful lifestyles, and even genetic predisposition may also be responsible.

11.5.1.1 Anti-inflammation Strategies to Alleviate Erythema and Hinder Scars Development

Inflammation is one of the major risk factors of both scar development and erythema. Since corticoid can effectively reduce the production of pro-inflammatory mediators and inhibit inflammatory processes in the dermis, the intralesional triamcinolone acetonide (TCA) injection has been widely used alone or as an adjuvant therapy to treat hypertrophic scars and keloids [17]. Besides, although the application of triamcinolone tapes is limited by its penetrating ability, it can be stuck to the scar area and release the drug all day long. Moreover, clinical studies observed a better performance of triamcinolone when combined with 5-Fluorouracil [17]. Other topical anti-inflammation treatment such as silicone gel sheeting that increases the elasticity of burn scar tissue also showed a reduction in pruritus, erythema, and scar thickness [18]. Systematic glucocorticoid application is not recommended for risks of complications such as diabetes, infections, and Cushing's syndrome.

11.5.1.2 Laser Treatments to Interfere with Erythema from Multiple Perspective

Laser therapy is one of the most widely used methods to treat erythema in scars. Ablative fractional lasers that create columns of vaporized tissue with surrounding eschar and coagulated tissue can improve various features of burn scars including erythema. Kawecki *et al*. observed that 31% of hypertrophic burn scar patients had resolution of erythema with resulting normal skin tone after ablative fractional laser treatment [19]. Coagulating microvessels with the selective photothermolysis of wavelengths around 595 nm, pulsed dye laser (PDL) can decrease inflammation and edema in erythematous scars and shows satisfactory outcomes in color repair. Similarly, Q-switched Nd:YAG lasers with a wavelength of 1064 nm in very short pulses are promising solutions to superficial angiogenesis of erythematous skin, especially in decreasing the vascular prominence in PIE [17, 18, 20]. Studies have demonstrated minimal side effects including atrophic scarring (0.8%), hyperpigmentation (1%), hypopigmentation (2.6%), and dermatitis (2%), among 500 patients treated with PDL [21]. Notably, although PDL and Nd:YAG have shown good results in reducing the red color of scars, skin erythema itself is one common adverse effect of laser treatment, which suggests that the laser therapy should be carefully selected and be practiced with cautions especially in patients with a history of post-treatment erythema or scar constitution.

11.5.1.3 Compression Therapy

Compression therapy (or occlusive dressings) has been widely applied to hypertrophic scar patients as a first-line agent with good results in decreasing erythema, thickness, and hardness of burn scars [22, 23]. A total of 60% of patients treated with compression devices showed 75–100% enhancement in scar condition according to previous studies [17]. The anti-scar effects of occlusive garments are thought to be related to occlusion and hydration [7, 17]. Some literature reported that this change is likely because of the inhibition of transforming growth factor (TGF)-β1 release and ultimately decreased fibroblast activity [24].

11.5.1.4 Medical Needling

Although sounding contradictory, the bleeding process of medical needling can influence vascularization by stimulating angiogenesis in the post-wound healing cascade and improve the vital thickness of the epidermis (directly related to skin transparency) by inducing percutaneous collagen synthesis.

Based on the outcomes of objective measurements, medical needling achieves a normalization of the skin color and an adjustment to healthy skin after repetitive treatments [12], and it has clinically shown to improve the abnormal vascular proliferation that occurs in PIE. Similarly, fractional resurfacing lasers have been used to induce structural remodeling and skin regeneration.

11.6 Clinical Treatment for Thick Scar

Contracture and functional disability caused by hypertrophic scars need surgical interventions. As for thick keloids, surgical therapy is also preferred. In addition, intralesional injection with 5-fluorouracil and steroid, cryotherapy, pressure therapy, and radiotherapy are all potential therapeutic options for thick scars, and these will be introduced in various chapters of this book and thus will not be the focus of this chapter.

11.7 Conclusion

The scar erythema is a burden for patients, as it amplifies the cosmetic problems and is associated with other unpleasant feelings such as pain and itching. Moreover, the development of erythema parallels with the dynamic process of inflammation, angiogenesis, scar formation, and thickening. Although most studies consider erythema as a concomitant byproduct following wound healing, it also promotes scar development via enhancing angiogenesis to provide scar fibroblasts essential nutrition for collagen production and deposition, and thus it has become an important therapeutic target as well. Although many issues remain to be explored such as what determines erythema presence, persistence, and disappearance, the erythema/redness itself can serve as a visible symptom reflecting treatment response and thus help both patients and therapists to set a relevant endpoint.

Take-Home Messages

Both erythema and thickness are key characteristics of scar, which can be used to monitor scar development and therapy efficacy. Angiogenesis represented by scar redness is a key contributor to pathological scar development due to enhanced inflammation, which can also serve as an important therapeutic target.

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Scar Symptoms: Pigmentation Disorders

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Background

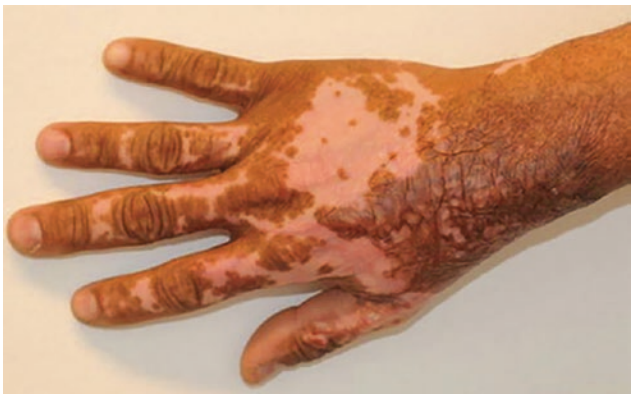
To a significant degree, vascularization and pigmentation determine the color of scars. Pigmentation problems are often even more persistent than deviations in vascularization. Pigmentation problems are a common consequence after partial and full-thickness burns, skin pathology such as vitiligo, other skin trauma, and surgical procedures. Almost all these patients experience at least some pigmentation problems. Both hypopigmentation and hyperpigmentation can cause esthetic and psychological issues which affect the quality of life of patients. Information on the role and pathways of melanocytes in pigmentation problems and the changes that occur during scar maturation is increasingly more understood. Different subjective and objective methods are available to determine scar color. Hypo- and hyperpigmentation management options include surgical and nonsurgical techniques.

12.1 Pathophysiology and Epidemiology

Altered skin pigmentation, or pigmentation disorders, can result from increased or decreased melanin, abnormal melanin distribution, decreased hemoglobin, or deposition of exogenous substances. Melanin is produced by melanocytes, specialized cells of neural crest origin that reside in the basal layer of the epidermis. The biosynthesis of melanin occurs in lysosome-like organelles called melanosomes, which are transported to the cell periphery and transferred from the dendritic tips of the melanocytes to the surrounding keratinocytes. Each melanocyte is associated with approximately 36 basal keratinocytes to form the so-called "epidermal melanin unit."

12.1.1 Hypopigmentation

Hypopigmentation is characterized by skin becoming lighter than the individuals own color, but not completely lacking pigment (■ Fig. 12.1). This should not be confused with depigmentation, which is the absence of all pigment. Hypopigmentation is common and approximately 1 in 20 have at least one hypopigmented macule [1]. Common causes include vitiligo, postinflammatory hypopigmentation, pityriasis versicolor, pityriasis alba, and halo naevi. Hypopigmentation disorders may be congenital or acquired. Acquired hypopigmentation may be the result of inflammatory conditions or trauma like a burn injury. In burn scars, hypopigmentation is a frequent pathology. Although the condition often improves over time with scar maturation, lasting depigmented or hypopigmented lesions may remain.



■ **Fig. 12.1** Hypopigmentation in a hand after burn injury

Data on the prevalence of these conditions after burn injury are scarce.

Vitiligo is an autoimmune disease where melanocytes are affected. The condition affects approximately 0.5–1% of the population, occurs in patients of all ages, equally affects men and women, with an early onset in many cases (<20 years). There is no difference in prevalence with respect to skin type or race.

12.1.2 Hyperpigmentation

Hyperpigmentation is the darkening or increase in the natural color of the skin and results from overproduction or abnormal release of melanin in the epidermis and/or dermis in response to either endogenous or exogenous inflammatory conditions [2]. Superficial hyperpigmentation is located in the epidermis and causes a light- to dark-brown discoloration. As soon as the pigment lies deeper in the skin (dermal pigmentation), the hyperpigmentation acquires a gray-brown to gray-blue glow. Like hypopigmentation, hyperpigmentation disorders may be congenital or acquired.

Postinflammatory hyperpigmentation is a reactive hypermelanosis of the skin that occurs as a sequela of cutaneous inflammation. Common causes of include acne vulgaris, eczematous dermatoses, and burn injury. Postinflammatory hyperpigmentation may also occur as a complication of a chemical peeling.

Although this pigmentary change can be observed in all skin types, it more frequently affects individuals with higher degrees of skin pigmentation (meaning Fitzpatrick skin types IV–VI) due to increased reactivity of melanocytes within the skin. The modified Fitzpatrick skin type classification system contains six categories with types I–IV describing different types of white skin and type V "brown" and type VI "black" skin.

Severe burns significantly affect the process of pigmentation as it is tightly regulated by cell proliferation

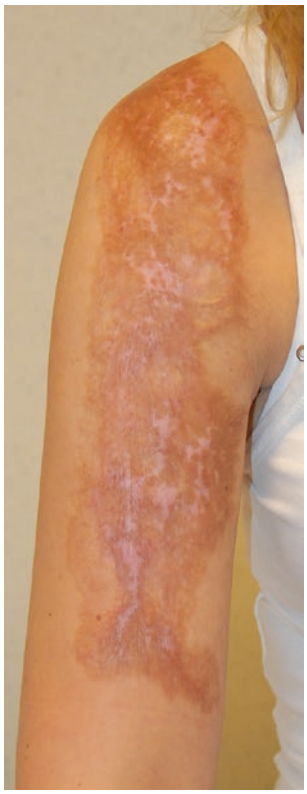


Fig. 12.2 Burn scar with hyperpigmented and hypopigmented areas

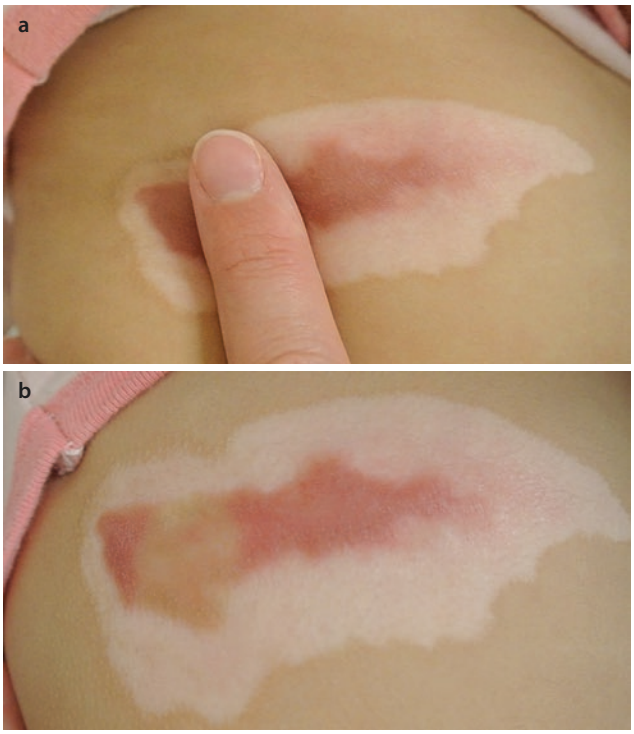


Fig. 12.3 (**a**) Pressure on the scar with a finger reduces blood flow in the scar. (**b**) Immediately after release of the pressure, level of pigmentation of the scar is visible

and differentiation of melanocytes and melanocyte stem cells which are located in the epidermis and hair follicles of the skin. Almost all burn patients with deep partial-thickness wounds and full-thickness wounds experience at least some pigmentation problems (Fig. 12.2). Superficial burn wounds generally heal without pigmentation problems. Although scar-related hypo- and hyperpigmentation are not harmful, it can cause significant cosmetic problems and become a great psychological burden for patients which influences their quality of life.

12.1.3 Maturation

Maturation is the fourth and final stage of the wound healing process and is commonly referred to as remodeling. The cellular changes that occur during scar maturation are increasingly understood. They are associated with remodeling of the extracellular matrix as well as normalization of the ratio of type III to type I collagen. However, the process of scar maturation with regard to changes in clinical appearance over time is the least understood part of wound healing. Most studies suggest a mean maturation period of 1, 2, or several years. In this active stage it can be difficult to determine to what extent deviant skin color is caused by vascularization and/or pigmentation. By pressing the scar with a finger or transparent ruler like made from plexiglass, the blood flow is reduced and degree of pigmentation can be better established (Fig. 12.3).

Van der Wal et al. performed the first longitudinal study on the maturation pattern of individual scar characteristics and predictors of severe scarring in a representative burn population [3]. They conducted a detailed analysis on the clinical changes of burn scars in 474 patients following a longitudinal scar assessment protocol. The observations of the POSAS Observer Scale (see ▶ Sect. 2.2) showed that all scar parameters, except vascularization, become more apparent in the first 6 months after the injury. After 12 months, mean POSAS scores were significantly lower for vascularization, pigmentation, and pliability compared with the 6-month follow-up. Statistical significant improvement at 12 months was also found for the parameters vascularization and pigmentation compared with the 3-month evaluation.

12.2 Measurement Techniques

For the diagnosis, evaluation of progress of disease and/or therapy it is of major importance to be able to measure skin or scar color in a noninvasive, valid, and reliable way. Outcome measures receive more and more attention to evaluate therapies on an individual basis as

well as at group level for efficacy studies. For this, validated techniques are a prerequisite.

To determine scar color, different subjective and objective methods are developed and available.

12.2.1 Objective Measurement Instruments

Several instruments are available to measure skin or scar color. The output is generally a combination of redness (erythema) and melanin (pigment). Most instruments use either narrow band spectrophotometry or reflectance colorimetry. The tristimulus reflectance colorimetry measures color through three broad wavelengths filters representing brightness, redness, and pigmentation. This system is suitable to measure any kind of color in the standard color space defined by Commission Internationale de l'Eclairage (CIE), where the output in L∗a∗b coordinates is defined as CIELAB color space values [4]. The LAB values express color as three values: L∗ for the lightness (black to white), a∗ from green to red, and b∗ from blue to yellow.

Narrow-band reflectance spectrophotometers measure erythema and melanin index, representing vascularization and pigmentation, based on differences in light absorption by hemoglobin and melanocytes, respectively, in selected bands of the light spectrum corresponding to hemoglobin and melanin absorption spectra.

Van der Wal et al. performed a study where the reliability, validity, and feasibility of narrow-band reflectance spectrophotometry and tristimulus reflectance colorimetry on normal skin and scar tissue were studied [5]. All three devices included in this study, Mexameter (narrow band spectrophotometer) and Colorimeter (tristimulus reflectance) (both from Courage & Khazaka Electronic GmbH, Cologne, Germany) and DSM II ColorMeter (narrow band spectrophotometer) (Cortex Technology, Hadsund, Denmark), obtained reliable results after a single measurement, performed by one observer.

Some aspects of these measurements need to be considered when using skin color data for therapeutic evaluation: Skin color is generally adapted to seasonal differences and is likely to be different on various anatomical regions of the body. Therefore, measurements of skin or scar lesions on specific locations need to be compared to the relevant normal skin of a nearby or contralateral comparative anatomical region. For narrow band spectrophotometric measurements, this needs to be performed by subtraction of the data of the normal skin from the lesional data. Furthermore, for the narrow band spectrophotometers, some caution is needed in interpretation of the data from highly pigmented skin: There is some influence on the erythema index by the melanin index, in that the erythema index apparently increases with increasing melanin index. Also, the melanin index is influenced by the oxygen saturation level of hemoglobin, since reduced hemoglobin absorbs more red light than oxyhemoglobin. For example, lowering the arm of a subject to be measured will lower the oxygenation, and give an increase in both erythema and melanin indices. Therefore, a standardized position for the measurements is recommended.

12.2.2 Scar Assessment Scales

Today, many scales exist to evaluate skin and scar characteristics [6]. One of the earliest and frequently reported is the Vancouver Scar Scale (VSS) [7]. Despite the fact that it is frequently used as a scale, especially the items "erythema" and "pigmentation" are nominal categories rather than ordinal ones. For the item "pigmentation" categories are normal, hypo, mixed, or hyper pigmentation; and for the item 'erythema' they are normal, pink, red, and purple. The VSS gives no intensity value of these parameters and therefore the numbers that are often attributed to these categories cannot be added to give a "severity score" for total scar characteristics. This is specifically important for pigmentation problems, since "hypopigmentation" cannot generally be considered to be less severe than "hyperpigmentation," which would be a consequence if the VSS categories would be used as a true scale.

To overcome these difficulties, the Patient and Observer Scar Assessment Scale (POSAS) was designed and validated [8]. The POSAS questionnaire represent the severity of burn scar quality including parameters that indicate skin color and pigmentation on a numerical 10-point rating scale. Furthermore, the categories "pale, pink, red, purple, mix" and "hypo, hyper, mix" are added for each assessment. Within these categories, the numerical data can be added to present an overall scar severity score.

12.3 Therapies

12.3.1 Hypopigmentation

12.3.1.1 Nonsurgical Techniques

Laser Therapy

Laser therapy can be used to treat pigment disorders in a scar. If there is hypopigmentation of a scar, it can be treated with the Excimer laser (308 nm) [9]. This laser produces a stimulation of melanocytes, thereby correcting hypopigmentation in the scar tissue.

Other pigment lasers mainly focus on the presence of hyperpigmentation and induce pigment reduction.

Dermatography

Dermatography, also known as medical tattooing, is an alternative method to improve the scar color, particularly in hypopigmented areas. Chemical-based pigments are injected into the dermis, as with other sorts of tattooing. Dermatography can be repeated if the color fades over time.

Camouflage Therapy

Camouflage therapy offers a temporary solution to hide a (hypopigmented) scar or make it less visible. Often a cream, spray, or powder that is close to the original skin color is used. Once the correct color has been determined, the application can be used independently in the home situation.

12.3.1.2 Surgical Techniques

Dermabrasion

Dermabrasion can help to treat the hypopigmentation of a scar.

By abrasion, the epidermis and a very small layer of the dermis are removed layer by layer, resulting in a superficial wound.

Normally, the abrasia is done until the whitish dermal layer is exposed with no more than fractional bleeding present.

Dermabrasion is performed as a single treatment modality or in combination with other treatments such as skin transplantation or cell spray. If it is used as a single treatment modality, the superficial wound has to recover by itself. In those cases abrasia must be carried out carefully to prevent wound-healing problems if the wound becomes too deep. This method is mainly used in case of hyperpigmentation where the excess pigment is shaved off and the new epidermis hopefully has a more balanced pigment and therefore color (see below).

In hypopigmentation the dermabrasion is mostly combined with a method to transplant melanocytes from healthy skin to the depigmented regions like skin grafting or cell therapy.

Skin Grafting

Skin-grafting techniques include split-thickness skin grafts, full-thickness skin grafts, punch-grafting, and epidermal grafts, such as grafts from suction blisters.

The split skin graft (SSG) contains the entire epidermis with only a thin layer of dermis. The skin is harvested with a dermatome preferably from a suitable, color-matching concealed donor site. A pigmented donor area with a thickness of 0.15 mm is identified to achieve optimal outcomes as the basal layer of the epidermis and a complement of melanocytes remain intact.

The full-thickness graft provides better functional and cosmetic outcomes in terms of scarring compared to the SSG. The entire epidermis and dermis are transplanted. For correction of pigment disorders, this is only indicated if the general quality of the scar is unacceptable/problematic and the scar area is limited.

In skin grafting, selecting a donor site of healthy skin with suitable normal pigmentation is key to ensure optimal outcomes.

Small full-thickness punch biopsies are harvested from healthy skin from a concealed body part, normally the upper arm or upper leg. The size of the biopsies can be 1–4 mm in diameter. Repigmentation occurs in 70% of the cases. Melanocytes migrate from the punch biopsies into the adjacent area in a centrifugal manner. A disadvantage of punch grafting is the cobblestone appearance that may remain in the long term.

Grafting of suction blisters is an interesting and successful technique for the treatment of hypopigmentation disorders. Negative pressure is exerted on healthy skin of the patient to create epidermal blisters. Devices such as a suction pump, vacuum bottle, hoses, or suction cups can be used for harvesting. This blister is harvested subsequently and transplanted to the depigmented area.

The donor site generally heals spontaneously with no or minimal scarring. Minor adverse effects such as donor site hyperpigmentation and color mismatching may be encountered.

Cell Therapy

An autologous epidermal cell suspension spray can be used to enhance repigmentation. The suspension can be sprayed on top of the wound after dermabrasion or injected in the hypopigmented area. This was studied by Falabella et al. already in 1971 and measured both by clinical score and by melanocyte counts, but the difference between the groups was not statistically significant in either case [10].

Later the RECELL® Autologous Cell Harvesting Device (AVITA Medical Europe Ltd., Melbourne, UK) became available, which uses an on-site device to isolate epidermal cells from a small piece of split skin graft.

Similar to the treatment of vitiligo, melanocytes are directly isolated and harvested from skin grafts prior to transplantation to the depigmented injured area. These cell-based treatments can be divided into (i) non-cultured cell suspension, (ii) cultured melanocyte suspension, (iii) cultured keratinocyte/melanocyte suspension, (iv)

tissue-engineered melanocyte grafts. For current clinical practice mainly the non-cultured cell suspension is used. The other, more sophisticated options may be interesting but are rarely used as clinical therapy so far. These therapies are expensive and laborious and currently it has not been conclusively demonstrated that they are cost effective.

A limitation of cell transplantation is a potentially uneven cell dispersion across the recipient site. Furthermore, poor attachment of transplanted melanocytes to the recipient skin and unfavorable wound conditions may also affect cell survival and outcome.

Microneedling

Microneedling is a relatively new therapeutic modality in dermatology. It has shown promising results as an adjuvant therapy for enhanced drug delivery in the treatment of atrophic scars, alopecia, actinic keratoses, and disorders of pigmentation such as melisma [11]. The efficacy in treatment of vitiligo remains limited.

Excision

Excision of the hypopigmented area can be performed and needs to be combined with a technique for wound closure. For small areas direct wound closure is the first choice. For larger areas and in the case of considerable tension on the wound edges, additional closing techniques such as the skin stretching technique or tissue expansion can be performed.

The skin stretch technique is suitable for closing defects after excision of scars and wounds of limited size. The skin stretcher is a device that can stretch two widely spaced wound edges together. The force with which this goes can be set, but is usually in the order of 30 Newton. The best result is obtained when working in cycles of 4 minutes of stretch and 1 minute of rest. After a few cycles, the wound tension has dropped and the wound can be closed under acceptable tension. In a large study, the number of wound dehiscence was limited [12].

With the help of a tissue expander large areas of scar can be normally excised. The tissue expander technique is widespread and is frequently used for reconstruction of large scar areas such as alopecia areas of the hairy head. During the first operation, an expander is placed under flexible skin in the area of the scar area that needs to be reconstructed. This extension is a special balloon with a filling port. The filling port is also placed under the skin. The fill port can be triggered through the skin so the balloon can be filled in tempi until sufficient texture has been expanded for the scar reconstruction. However, despite good results, two interventions are needed, the total procedure may take several weeks to months with frequent visits to the clinic to fill the balloon.

12.3.2 Hyperpigmentation

12.3.2.1 Nonsurgical Treatment

Topical Treatments

Hydroquinone, either as monotherapy or in combination with alpha-hydroxy acid, ascorbic acid, retinoids, corticosteroids, and antioxidants, is a commonly used depigmenting agent [2]. Its working mechanism is thought to inhibit melanogenesis by acting as an alternative substrate for the enzyme tyrosinase. Hydroquinone may also result in inhibition of DNA/RNA synthesis, destruction of melanocytes, and degradation of melanosomes.

Topical retinoids, including tretinoin (all-trans-retinoic acid), tazarotene, and adapalene, are also used as monotherapy for treatment of hyperpigmented lesions. Retinoids are supposed to act by inhibition of tyrosinase, induction of melanocyte apoptosis, and acceleration of epidermal cell turnover.

Also azelaic acid is thought to inhibit tyrosinase and decrease melanogenesis.

Chemical Peels

A commonly used acid against hyperpigmentation is the use of lactic acid. Lactic acid is particularly known to prevent the formation of tyrosinase so that pigment cells can form less pigment. In addition, the accelerated exfoliation of the skin cells fades the pigment cells present. The mechanism of this effect might be due to epidermal remodeling and accelerated desquamation, which would result in quick pigment dispersion.

Laser Therapy

Hyperpigmentation can be treated with laser therapy, based on selective photothermolysis. Selecting the right wavelength can tackle pigment selectively. Selective photothermolysis suggests that laser therapy would allow discriminating destruction of pigment without injuring the surrounding tissue. Selective melanin photothermolysis can be obtained with any laser light having a wavelength in the absorption spectrum of melanin and sufficient energy levels to target melanosomes (mostly used: the Q-switched ruby laser (694 nm), Q-switched Nd:YAG laser (532 nm, 1064 nm), and the Q-switched alexandrite laser (755 nm)). Laser induces extreme heating of melanosomes with subsequent thermal expansion, local vaporization and generation of acoustic waves that damage the nucleus and eventually destroy the pigment-laden cells. The released melanin is then removed through transepidermal elimination or phagocytosis by dermal macrophages. To be effective and specific, wavelengths that avoid absorption by other skin chromophores and penetrate to the desired depth have to be used [13].

12.3.2.2 Surgical Treatment

Dermabrasion

As mentioned above, dermabrasion can help to reduce hypo- and hyperpigmentation of a scar. In the case of hyperpigmentation, dermabrasion is usually performed as a single treatment modality, that is, it is not combined with another treatment such as skin transplantation. The idea is to easily remove the epidermis including the melanocytes and the pigment and let it heal spontaneously resulting in an epidermis with a lower concentration of melanocytes. It is not recommended to go too deep because the regeneration capacity of the skin is limited in scars, due to lowered presence or even absence of hair follicles and sweat glands. If the wounds are too deep and stay open too long, problematic new scars can occur.

It is advisable to perform dermabrasion in the fall or winter season to anticipate low UV light exposure to reduce the risk of excessive new pigmentation. It is also recommended to start dermabrasion with a small test area, preferably in an area that can be easily evaluated by the patient.

Excision

Excision and closure is also a feasible therapeutic option for hyperpigmented lesions that are limited in size (see above under hypopigmentation). It should be taken into account that a (linear) scar will remain and that outcome may be more severe than the original situation.

12.4 Conclusion

Pigmentation problems are an important feature of scar quality and partly determine the visual characteristics of a scar. Both hypopigmentation and hyperpigmentation can cause aesthetic and psychological issues which influences quality of life. Pigmentation disorders are difficult to treat. Treatment options include camouflage therapy, topical treatments, chemical peels, laser therapy, dermatography, dermabrasion, microneedling, skin grafting, cell therapy, and excision. It is advised to first try the conservative options and to dose the treatment to prevent overshoot and complications.

Take-Home Messages

- Pigment abnormalities are divided into hyperpigmentation and hypopigmentation.
- Pigmentation disorders are difficult to treat.
- Nonsurgical and surgical options are available.
- Wait until the area has matured.
- First try the conservative options. If possible, first test the response to the therapy in a test area.
- Dose the treatment to prevent overshoot and complications.

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Scar Contractures

Marguerite Guillot Masanovic and Luc Téot

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_13

13.1 Introduction

The prevalence of contractures is high, especially after burns and may vary, depending on the age, the depth of the initial burns, and the time between burns and the occurrence of the contractures. Young patients and children are more likely candidates to develop contractures. When skin grafting after burn is performed in due time, the prevalence is lower. Contractures are more likely to occur in more severe burns, flame burns, children, females, on the cervical spine and in the upper extremity. The absence of physiotherapy and an abnormal long period awaiting spontaneous healing without skin grafting will progressively induce severe contractures. This is still frequently observed on the upper limbs in burn patients in developing countries. Early excision and skin grafting is the best option to reduce the incidence of contractures. Other causes of contractures are less frequently observed, but may be seen after trauma or infection, linked to noncompliance, a too long immobilization, a joint destruction, an epiphysiodesis in children. This chapter proposes to give an overview of the functional limitations of the skin contractures and the need for an adapted early rehabilitation program starting during the healing stage and carried on during the next 2 years post burns and other causes of skin limitation.

13.2 General Features

Incidence of contractures has been recently analyzed [1, 2] on patients presenting acute burns across or adjacent to the neck, shoulder, elbow, wrist, hip, knee, and ankle. Passive range of motion was measured at 3–6–9–12 months after burn. Limited range of motion of non-operated burned joints was restored back to normal within 6–9 months. From the operated burned joints, 58.6% demonstrated a limited range of motion at 3–6 weeks declining to 20.9% at 12 months. The upper part of the body was affected more often by scar contracture than the lower part. Reconstructive surgery was performed in 13.3% of the operated burned joints. This study confirms that a quick skin grafting is a good option to prevent severe contractures, but not enough to prevent all of them.

Contractures may clinically present with different characteristics, like bands of skin partially limiting the range of joint movements to a complete impossibility to move, all joints being glued in deep stiffness. Contractures are more or less severe, depending if the deep structures (tendons, aponeurosis, subcutaneous muscles, or fascia) are involved in the process, and the type of contracture, static or dynamic.

Skin capacity is particularly limited in burns of the dorsal aspect of the hand, if an adapted rehabilitation program including staged splinting of the hand before, during, and after skin grafting, as well as slow movements during the inflammation stage and more active after some months is not properly done. The usual limitation is observed at the level of the metartarsophalangeal joints (in flexion) and the grip is impacted.

Contractures may variably limit the amplitude of movements, some of them being only observed during full movements, others imposing a severe stiffness and a blockade of any movement. Neck contractures may simply affect the extreme degrees of lateral movements or realize a vertical contracture (chin to thorax) imposing strong difficulties to maintain the horizontal sight, a situation extremely difficult to live with.

Web contractures may limit multidirectional movements on the neck or the shoulder, others will limit opening of orifices (mouth, nostrils, perineal areas) with concentric contractures, a cause of difficulties to feeding.

Contractures may vary along time. An early inflammation is frequently observed in children or young adults after burns, lasting some months especially on mobile areas like the thorax and the upper limb. This situation may be transiently observed during the first 2 years and may disappear afterward. This period should be covered by adapted physiotherapy programs, aiming at an augmented range of movements and a less red skin.

13.3 Contractures of the Neck

Neck skin is extremely mobile over the underlying structures. This mobility will be quickly limited in burns, due to a skin retraction linked to wound healing and particularly to the mechanical action of myofibroblasts, but also to the pain during movements inducing a voluntary restriction of movement during the healing stage. These combined factors induce a centripetal retraction and may lead to different situations, ranging from a single line of skin tension in the lateral movements (Fig. 13.1) to severe vertical and horizontal loss of movements. The subcutaneous muscles, embedded in the scarring process,

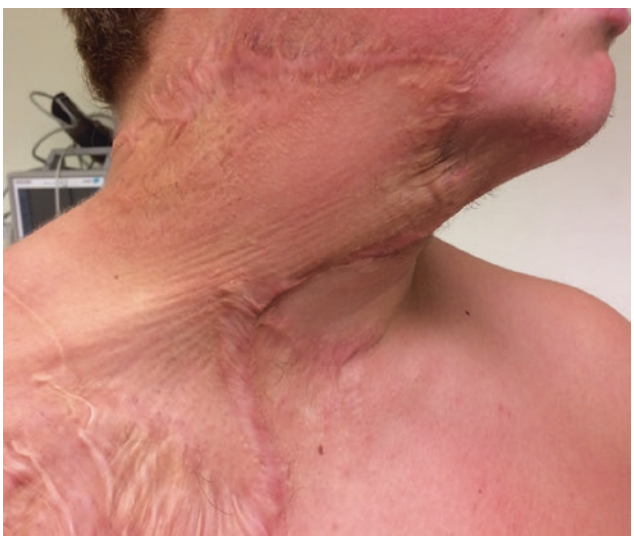


Fig. 13.1 Neck contracture persistent in spite of several surgical procedures

contribute to skin limitation. In severe situations the horizontal sight may be impacted, bending permanently the neck and imposing a difficult surgery.

13.4 Axillar Contractures

Three different areas may be impacted by retractile scars, the anterior and posterior pillars, and the central axilla. Skin contractures may affect any one or the three of these areas, with different possible extensions on the anterior or posterior thorax. The shoulder is mobile anteriorly, posteriorly, and laterally, needing a full skin mobility in all aspects of the region. A large range of functional deficits may be encountered in burns, with a good reactivity to early physiotherapy and specifically to range axilla orthotic, as demonstrated [3] (◘ Figs. 13.2, 13.3, and 13.4).

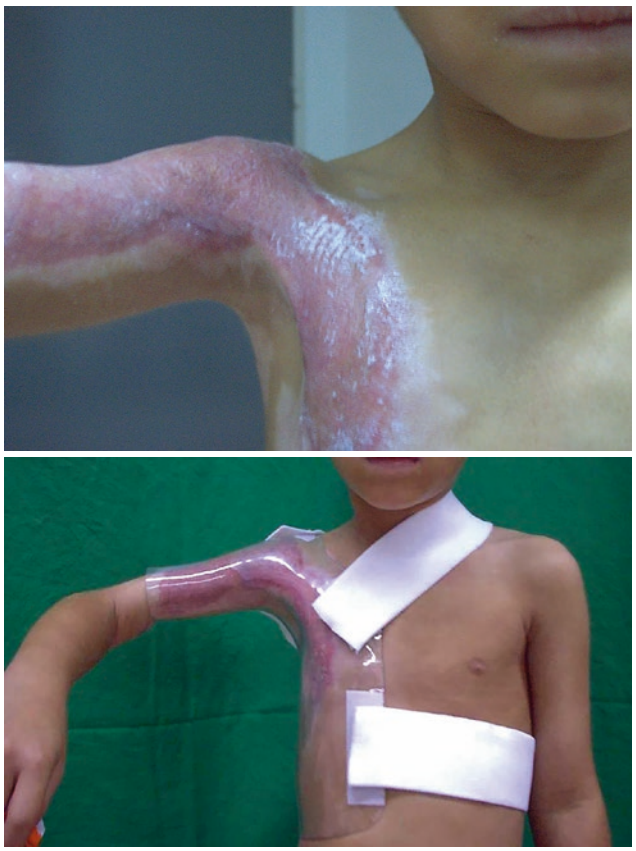
13.5 Hand Contractures

Burns usually affect the dorsal aspect of the hand, with a centripetal retraction impairing the complete combined flexion of all digits together. The deficit in terms of grip may be crucial; other situations may limit one or two digits in flexion. When the situation has become chronic, tendon shortening and bone deformities may be observed, imposing complex surgical procedures including bone shortening, joint arthrodesis, and tendon lengthening to restore function.

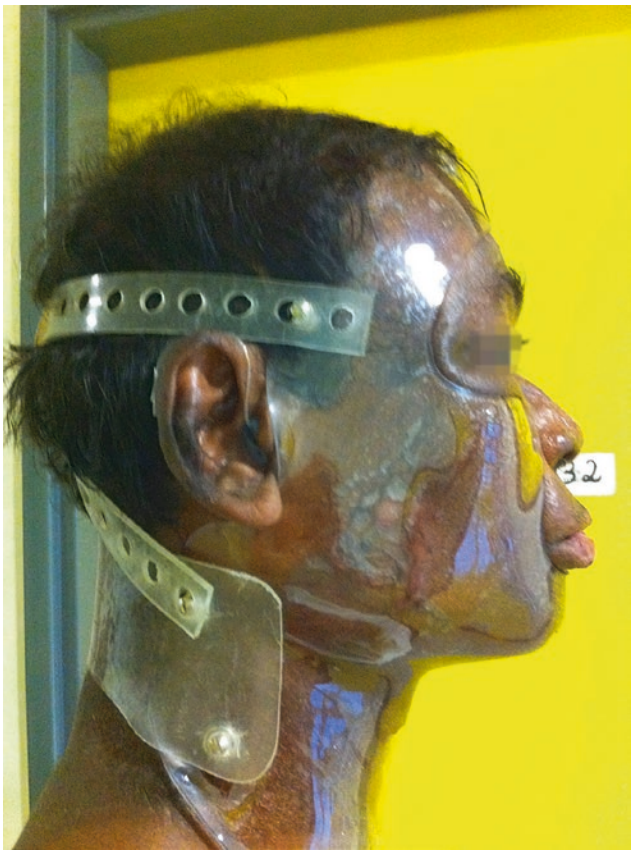
The dorsal aspects of the interdigital webs are frequently involved, with consequences on the separate movements of each digit, a quadrige effect often observed in poorly managed deep burns.

The palmar aspect of the hand is less frequently touched but more frequent in children, but the very deep scarring tissues may sometimes reach more than 2 cm depth, inducing tendons blockade. Usually these severe scars embed totally the underlying structures, nerves, vessels, tendons, and muscles (◘ Fig. 13.5).

Persistent contractures observed in young adults having been submitted to burns that occurred during childhood, with retracted wrists and elbows or completely locked axillas, which sometimes require bone resection or amputation, are less observed now with the development and diffusion of NGO programs acting in underdeveloped countries.



◘ **Figs. 13.2 and 13.3** Postburn axillar contracture treated by an orthotic orlen realized at fashion



◘ **Fig. 13.4** Severe postburn neck contracture on a young female treated by an orthesis worn initially 24/7 during 2 months and then at night

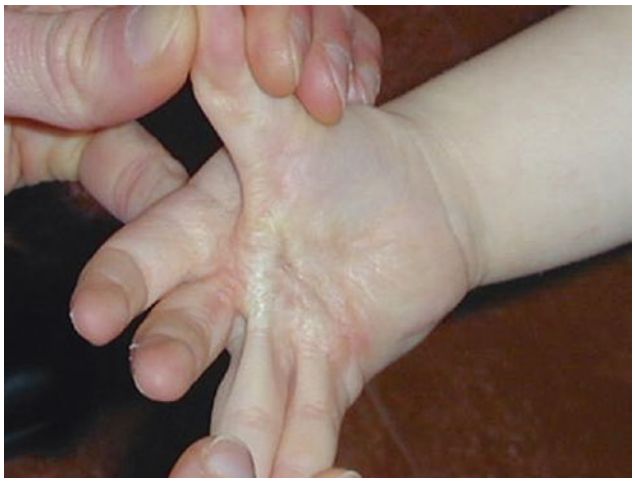


Fig. 13.5 Palmar contracture embedding the whole palmar area, creating a maximal web between the I and the IV. Surgery is needed

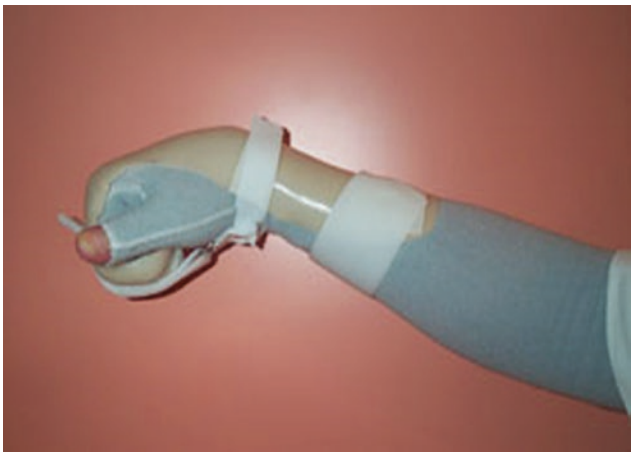


Fig. 13.6 Hand splint in complete digital flexion used for mechanical tension over the dorsal aspect

13.6 Other Anatomical Sites of Scar Contractures

Lower limbs may develop contractures at the level of hips (in flexion), knee, and foot (dorsal positioning of toes). These contractures are better managed by an adapted rehabilitation, completed by surgical procedures if needed.

13.7 Rehabilitation Programs

During the wound-healing stage, splinting of the burned hands, the neck, the axillar, and the lower limbs are needed to prevent contractures. Most of the burns centers benefit of a specific rehabilitation team included in the organization of the center. Passive movements during the dressing change and positioning of joints into adapted customized splints in position of maximum extension capacity will efficiently limit the development of contractures (Fig. 13.6). Exercise is allowed as soon as the inflammatory period is under control, immobilization being the most anti-inflammatory agent.

After skin closure, active and passive movements will be encouraged but it is essential not to exert an excessive mechanical tension on contractures, relayed and completed by the design of compressive garments, and mechanical compression of the involved areas. Specific rehabilitation centers for severely burned patients exist in some countries, proposing multiprograms to soften the scar, manipulate joints, and efficiently prevent the occurrence of the contractures using positioning, especially on the axillar region, the neck, and the hands (Figs. 13.7 and 13.8).

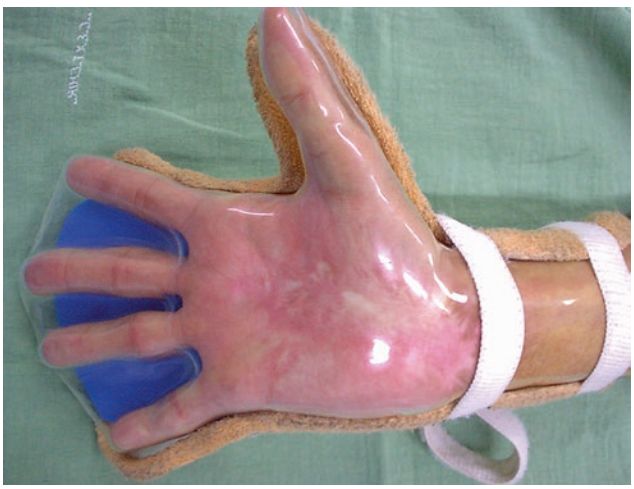


Fig. 13.7 Hand splint in complete digital extension used for mechanical tension on the palmar aspect. In case of contracture touching both the aspects of the hand, alternative positioning in flexion during night and in extension during the day may be proposed

Pruritus and the risk of stretching are prevented using hydration and drugs. Capsaicin and cooling are frequently used to limit pain and inflammation. These programs are long, painful, and psychologically demanding. A limited compliance of the patients may explain some of the poor results sometimes observed, but most of the patients get benefit of these treatments.

Once the inflammation stage is completed, more active compressive techniques like endermology, motorized skin manipulations (LPG), stretching posture, high power jets, or other types of physiotherapy are proposed, with good results at 2 years. More than 90% of the patients come back to a normal function if the program is done properly.

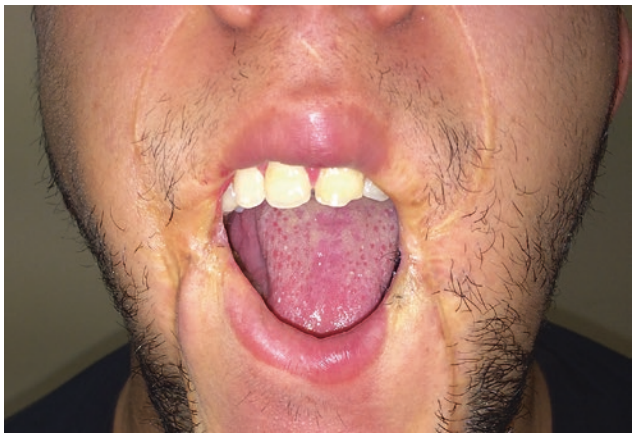


Fig. 13.8 Bilateral contracture of the mouth web, combined with a red lip loss of substance. Surgery using W–Y-5 plasties, plus advancement of the mucosa will be proposed

Despite clear international recommendations [4] the studies on the modalities of application and the type of splints cover only a limited number of cases, therefore the evidence for these strategies is limited [5].

13.8 Surgical Strategies

Contracture release creates a large skin defect, and the aim of surgery is to restore as far as possible a full skin disponibility after surgery and to prevent recurrence.

13.9 Z Plasties

Z plasty is the most frequently used surgical technique [6]. Based on the principle of skin disponibility and softness of adjacent areas, the triangles designed by the Z-shape incisions break the linear scar contracture with a new scar without any mechanical tension. The cosmetic result is usually acceptable. Linear contractures are better managed using Z plasties, multiple Z plasties. Web contracture may be treated using W–Y 5 plasties combing 2 Z plasties and an advancement flap, or omega plasties using the contracted skin but needing two small full skin grafts on the edges.

13.10 Skin Grafts

Skin grafts are by definition free skin transfers from one site to another without any vascular connection. Depending on their thickness, skin grafts form two different techniques, split-thickness skin grafts (STG) limited to epidermis and a thin layer of dermis, harvested using a dermatome and full-thickness skin grafts (FTG), which include the epidermis and the entire dermis; harvested with a scalpel and needing a defatting before application. The donor sites of STG heal by rapid re-epithelialization (like a superficial abrasion) while the donor site of FTG must be closed primarily for healing, so their use is limited to smaller defects. The main disadvantage of STG is the lack of dermal component, meaning a risk of recurrence higher than when using a flap.

13.11 Dermal Substitutes

Since three decades the introduction of acellular dermal substitute has changed the profile of skin grafting. The dermal component brought by the use of collagen (and elastin) inside the dermal substitute limits the secondary retraction of the thin skin graft applied to cover it, even if some shrinking is sometimes observed [7]. Different devices are proposed, with or without elastin, the collagen coming from different animals like cows, sharks, or pigs with different combination with elastin, and with or without a protective film in silicone, depending if the product is immediately covered by skin graft or secondarily after 3 weeks, the device being slowly incorporated in the new dermis before skin coverage. Hori et al. recently compared the contraction capacity, pores size, and shape of the different proposed devices [7] which may induce a secondary contraction.

13.12 Flaps

Large contractures have to be excised and replacement using different types of flaps.

Random skin flaps are frequently used [8], coming from the adjacent area when scar-free, but pedicled fasciocutaneous flaps bring a rich vascular network. Branches from this plexus reach the skin as direct or indirect perforators. They can be used locally or regionally, and rotated into the defect [9].

Perforator flaps, more recently developed, are based on a fine dissection of the perforator vessels going through the fascia to vascularize the overlying skin island. This increases the range of motion of these pedicled flaps and it reduces significantly the donor site morbidity.

Free flaps enlarge even further the armamentarium for tissue transfer. In principle, all axial flaps can be transferred as a free vascularized flap: the artery and the vein (eventually also the nerve) are transected at the donor site and re-anastomosed microsurgically with a recipient vessel at another part of the body. Till recently, free fasciocutaneous flaps and perforator flaps were most frequently used for coverage of contracture defects. Both can however result in significant donor site morbidity by harvesting structurally important fascia.

13.13 Conclusion

In summary, contractures after burns are difficult to prevent, some areas like axilla, neck, and upper limbs being predominantly affected. Early skin grafting may prevent contractures, but an adapted rehabilitation program should be established and redefined during the regular check-up done by the burns team. When constituted, a precise analysis of the lacking skin surface should be done by the surgical team, issuing to a covering program depending on the area involved and the expertise of the team. Function may efficiently be restored using different techniques, skin grafting and dermal substitutes being more adapted in term of volumes, flap providing a suppler skin.

Take-Home Message

Contractures may form a severe functional deficit. Early prevention is mandatory, with a combination of exercise and positioning to prevent skin retraction. In specific situations like the burned hand immobilization can be done in both positions: flexion during the night and extension during the day. Treatment is difficult, and a balance should be sought between surgery, which always means a restart in the rehabilitation process, and the rehabilitation limits which should be established in close conjunction together with the team in charge. Recurrence is a risk if the postoperative management is not properly realized.

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Scar Assessment Scales

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Scar Assessment Scales

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14.1 Background

Over the last decades, standardized measurements of medical treatment outcome have become increasingly important. First of all, application of evidence-based medicine requires that the research field evaluates the effectiveness of new and existing treatments. Therefore, no clinical trial can exist without the appropriate outcome measurement instruments to determine the study outcomes in a reliable and valid way. These outcome measurement instruments are not only vital in the research setting but also indispensable in daily clinical practice to monitor scars in individual patients. Furthermore, standardized scar measurements are performed and recorded in clinical registries with the aim to improve the quality of care and patient health outcomes.

Scar outcome measurement instruments can be either measurement devices or scar assessment scales. Measurement devices are often seen as objective instruments that provide solid quantitative analyses of scar characteristics. However, measurement devices have to be purchased for sometimes high prices and can only be used at one place at a time. Another disadvantage may be that most devices are only able to evaluate one scar characteristic. In addition, cutting-edge measurement technologies often involve time-consuming measurements and analyses that require training of the observer, which might be appropriate in research settings but is less suitable in clinical practice. Contrary to measurement devices, scar assessment scales are qualitative evaluations of multiple scar characteristics provided by an individual, either the patient or the clinician/researcher. Scar assessment scales are sometimes criticized by their subjective nature. However, advantages of scar assessment scales are their ability to provide fast evaluation of multiple scar characteristics, their (usually) free and easy accessibility, and their ability to capture the patient's view on their scars. The latter is especially important as nowadays patients are receiving more information about treatment options and are getting more involved in making treatment decisions and in reporting treatment outcomes. In this chapter, an overview of the content and development of most frequently used scar assessment scales is provided.

14.2 Domains

Scars can influence patients in several health domains, ranging from appearance to quality of life. These different domains require different levels of measurements. Measurements acquired with clinician-reported scales are limited to observable aspects of the scar, such as appearance, physical characteristics, and functional impairment of the scar. On the other hand, patient-reported scar scales allow for the evaluation of additional health domains that cannot be observed by clinicians, such as scar symptoms and quality of life.

14.3 Scar Assessment Scales

Table 14.1 provides an overview of consecutive developed scar assessment scales, the constructs measured, and whether it is reported by the patient or clinician. Table 14.2 shows which scar aspects are assessed in the most frequently used scales. The first concepts of scar assessment scales were reported in the late 1980s, but the first widely used, validated scar scale was developed in 1990 by Sullivan et al., which became widely known as the Vancouver Scar Scale (VSS) [1]. The VSS consists of four items: vascularity, pigmentation, thickness, and pliability. Since this first introduction to scar assessment scales, the development of many other scales followed. Various authors modified the original version of the VSS by adding extra items to the scale or altering the answering categories of the existing items [2–4]. This resulted in an abundance of modified VSS versions—of which the modified VSS by Baryza et al. is the most widely used [2]. The Seattle, Hamilton, and Manchester scar scales were consecutively developed from 1997 to 1998 [5–7]. The Seattle and Hamilton scales were both developed for photographic evaluation of scar [5, 6]. The Manchester scar scale introduced two new items: an "overall assessment," rated on a VAS scale (0–10), and if the scar appeared matte or shiny [7]. Until 2000, the focus remained on the clinician/observer, as all developed scales were clinician-reported, focusing on visual and physical scar characteristics. This changed when Nedelec et al. added a symptomatic assessment (i.e., items of pain and itch) to the original VSS [3]. However, it was not until 2004 that in addition to symptoms such as pain and itch, the patient's opinion on visual and physical scar characteristics was incorporated into a scar assessment scale called the *Patient and Observer Scar Assessment Scale* (POSAS) [8]. The POSAS captures both the clinician's (observer's) and the patient's perspective on multiple-characteristics scar quality. A few years after the introduction of the POSAS, Bock et al. made it possible to evaluate the quality of life of patients with keloid and hypertrophic scars by the development of the *Bock Quality of Life Scale* [9]. This was the first patient-reported scar scale measuring at the level of quality of life. Around the same time, the *Stony Brooks Scar Evaluation Scale* was introduced, which is a clinician-reported scar scale specifically designed for the assessment of surgical scars [10]. Therefore, it included an item to evaluate the presence of suture marks. The *Patient Scar Assessment Questionnaire*, *Patient-Reported Impact of Scars Measure* (PSAQ), and *Brisbane Burn*

Table 14.1 Overview of consecutive developed scar assessment scales

Scar scale	Year	Clinician-reported	Patient-reported	Type of scars	Construct
Vancouver Scar Scale	1990	X		Burn	Physical characteristics and appearance
Modified Vancouver Scar Scale by Baryza et al.	1995	X		Burn	Physical characteristics and appearance
Seattle Scar Scale	1997	X		Burn	Physical characteristics and appearance
Hamilton Scar Scale	1998	X		Mix	Physical characteristics and appearance
Manchester Scar Scale	1998	X		Mix	Physical characteristics and appearance
Modified Vancouver Scar Scale by Nedelec et al.	2000	(X)		Burn	Physical characteristics and appearance, scar sensation
Patient and Observer Scar Assessment Scale	2004	X	X	Mix	Physical characteristics and appearance, scar sensation
Bock Quality of Life	2006		X	Hypertrophic/keloid	Quality of life
Stony Brooks Scar Evaluation Scale	2007	X		Surgical	Scar characteristics and appearance
Patient Scar Assessment Questionnaire	2009		X	Surgical	Scar characteristics and appearance, scar sensation Consciousness (body image and confidence)
Patient-Reported Impact of Scars Measure	2010		X	Surgical	Scar sensation Quality of life
Brisbane Burn Scar Impact Profile	2016		X	Burns	Scar characteristics and appearance Scar sensation Quality of life
Scar Cosmesis Assessment and Rating scale	2016	(X)		Surgical	Scar characteristics and appearance Scar sensation
Scar Q	2018		X	Mix	Scar characteristics and appearance Symptoms Psychological problems

(*X*) = Clinician-reported scale in which the presence of pain and itch is included

Scar Impact Profile (BSSIP) are more recently developed patient-reported scales which measure aspects of quality of life, in addition visual and physical scar characteristics, symptoms, and/or satisfaction [11–13]. Most recently, the *Scar Q* was developed for the evaluation of physical characteristics, scar appearance, symptoms, and physiological problems [14].

14.4 Measurement Properties/Clinimetrics

To evaluate the quality of available scar assessment scales, several measurement properties must be considered, i.e. ,validity, reliability, and responsiveness [15]. The most important property is content validity. Content validity is the degree to which the content of a measure is an adequate reflection of the construct to be measured [15]. Good content validity means that all items included in the scale are relevant and no relevant items are missing for the construct of interest (within a specific population and context of use). Furthermore, it means that patients should understand the content as intended. Lack of content validity can influence all other measurement properties [16]. To ensure good content validity, it is important that well-designed scale development studies are performed that use qualitative methods to gain patient/professional input on the content of the scale. In addition, the draft scale must be pilot tested to ensure its content is relevant, comprehensive, and comprehensible for patients. In Table 14.3, it is noted if

Table 14.2 Overview of the content of most frequently used scar assessment scales

	VSS	Modified VSS by Baryza et al.	Manchester Scar Scale	POSAS (2.0)	Bock Quality of Life	SBSES	PSAQ	PRISM	BBSIP	Scar Q
Number of subscales	1	1	1	2	1	1	5	2	10	2
Number of items[a]	4	4	6	14	15	5	39	37	66	24
Visual and physical scar characteristics										
Vascularity	X	X		X			X			
Pigmentation	X	X		X			X			
Color			X	X		X	X		X	X
Thickness	X	X	X	X		X	X		X	X
Pliability/ hardness	X	X	X	X					X	X
Roughness							X		X	
Surface irregularities				X			X		X	X
Distortion			X	X						
Shiny surface			X				X			
Hatch marks						X				
Width						X	X			X
Length							X			X
Overall appearance			X	X		X	X			X
Symptoms										
Pain				X			X	X	X	X
Itch				X	X		X	X	X	X
Stinging								X		
Burning								X		
Discomfort							X		X	

	VSS	Modified VSS by Baryza et al.	Manchester Scar Scale	POSAS (2.0)	Bock Quality of Life	SBSES	PSAQ	PRISM	BBSIP	Scar Q
Numbness							X			X
(Hyper) Sensitivity								X	X	X
Tingling							X	X		X
Tightness							X		X	X
Impaired movement					X				X	X
Dryness									X	X
Sensitive to temperature (changes)					X			X	X	
Swelling										X
Inflammation								X		
Open wounds									X	
Tiredness									X	
Psychosocial										
Self-consciousness							X	X		
Self-confidence					X			X	X	
Embarrassment					X			X		X
Unhappy feelings								X	X	X
Angry feelings								X	X	
Sexual concerns					X			X		
Feeling unattractive					X			X		
Not accepting scars					X					
Hiding scars					X		X			

(continued)

Table 14.2 (continued)

	VSS	Modified VSS by Baryza et al.	Manchester Scar Scale	POSAS (2.0)	Bock Quality of Life	SBSES	PSAQ	PRISM	BBSIP	Scar Q
Avoid talking about scars					X					
Reactions of others					X		X	X	X	
Impact on social interactions and activities					X			X	X	
Impact of scar treatments									X	
Suicidal thoughts					X					
Satisfaction										
Overall satisfaction										
Appearance							X			
Symptoms							X			

[a]Not all items included in the scales are scored in this table. *VSS* Vancouver Scar Scale, *POSAS* Patient and Observer Scar Assessment Scale, *SBSES* Stony Brooks Scar Evaluation Scale, *PSAQ* Patient Scar Assessment Questionnaire, *PRISM* Patient-Reported Impact of Scars Measure, *BBSIP* Brisbane Burn Scar Impact Profile

Table 14.3 Methods used for the development of most frequently used scar assessment scales

	VSS	Modified VSS by Baryza et al.	Manchester Scar Scale	POSAS (2.0)	Bock Quality of Life	SBSES	PSAQ	PRISM	BBSIP	Scar Q
Scale development										
Literature search		X		X	X		X	X	X	X
Expert opinion	X	X	X	X	X	X	X	X	X	X
Patient interviews							X	X	X	X
Pilot testing					X		X	X	X	X

VSS Vancouver Scar Scale, *POSAS* Patient and Observer Scar Assessment Scale, *SBSES* Stony Brooks Scar Evaluation Scale, *PSAQ* Patient Scar Assessment Questionnaire, *PRISM* Patient-Reported Impact of Scars Measure, *BBSIP* Brisbane Burn Scar Impact Profile

these requirements were met for the included scar assessment scales. Besides content validity, reliability is an important clinimetric property. Reliability refers to the extent to which scores for patients who have not changed are the same for repeated measurements [15]. Reliability and measurement error are related but distinct measurement properties. Reliability refers to the ability of a measure to distinguish between patients, and measurement error refers to the systematic and random error attributed to the measurement instrument [17]. The responsiveness is the ability of a scale to detect changes over time in the construct to be measured (e.g., scar quality) [15]. All measurement properties should be evaluated in the specific population in which it will be used. The context of use, referring to the application of use (i.e., discriminative, evaluative, or diagnostic application) and to the setting (e.g., hospital or at home), should also be taken into account. Furthermore, the instrument must be practical and user-friendly in order to be easily applicable in clinical practice: an aspect which is defined as feasibility [18]. It is crucial to consider the measurement properties, the context of use, and the feasibility when choosing a measurement instrument. Measurements obtained by poor-quality or non-validated instruments are not trustworthy, and thus, studies that utilize these instruments yield unreliable results and invalid conclusions.

14.5 Conclusion

Scar assessment scales are useful tools to measure various domains of scars. This chapter provides an overview of the most frequently used scar scales, including their content and development. It is of paramount importance to evaluate the clinimetric properties of an instrument prior to using it for scar assessments for clinical or research purposes in order to prevent measurements obtained by poor-quality instruments.

Take-Home Messages

- Scar assessment scales are important to evaluate the effectiveness of scar treatments and to monitor patients over time.
- Traditional scar scales are clinician/researcher-reported, focusing on the appearance and physical characteristics of the scar, while more recently, developed scales are patient-reported scales which measure aspects of quality of life.
- (Content) Validity, reliability, and responsiveness are important measurement properties which must be evaluated prior to using a scale for scar assessments.

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Japan Scar Workshop (JSW) Scar Scale (JSS) for Assessing Keloids and Hypertrophic Scars

Rei Ogawa

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_15

15.1 Background

The Vancouver scar scale [1], the Manchester scar scale [2], and the Patient and Observer Scar Assessment Scale (POSAS) [3] are all very well-known scar evaluation methods. These tools are based on a number of scar variables, including color, height, and pliability. However, since all were mainly developed to evaluate burn scars, they are difficult to use in clinical practice for keloids and hypertrophic scars. This is because these pathological scars require both differential diagnosis and a way to evaluate their response to therapy. Since the Japan Scar Workshop (JSW) was established in 2006, it has sought to develop a scar assessment scale that meets these clinical needs. The first version of this scar assessment tool was named the JSW scar scale (JSS), and it was reported in 2011 [4]. In 2015, the revised second version was reported (Table 15.1 and Figs. 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, and 15.7) [5]. This chapter introduces the JSS and discusses its clinical importance and usefulness in scar research.

15.2 JSW Scar Scale (JSS) 2015

The JSS consists of two tables. One is a scar classification table that is used to determine whether the scar is a normal mature scar, a hypertrophic scar, or a keloid. This grading system helps the user to select the most appropriate treatment method for the scar. The other table in the JSS is an evaluation table that is used to judge the response to treatment and for follow-up. Both tables contain sample images of each subjective keloid/hypertrophic scar item that allow the user to evaluate each item without hesitation (Figs. 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, and 15.7). Japanese guidelines for the prevention and treatment of keloids and hypertrophic scars [6] include JSS 2015.

15.3 Classification Table

The classification table consists of two parts: risk factors and the present symptoms. The risk factors consists of six items, each of which has 2–3 categories: (1) human race (African, Other, Caucasian), (2) whether there is a familial tendency (Clearly exists, Does not clearly exist), (3) the number of scars (Multiple, Solitary), (4) the body region the scar is on (Anterior chest/scapular-shoulder/suprapubic, Other), (5) the age at onset (0–30, 31–60, ≥60 years), and (6) the cause(s) (Unknown/minute, Specific type of wounding such as surgery). The present symptoms also consist of six items, each of which has 2–3 categories: (7) scar size (>20 cm^2, <20 cm^2), (8) whether there is vertical growth (Clearly exists, Does not clearly exist), (9) whether there is horizontal growth (Clearly exists, Does not clearly exist), (10) the shape of the scar (Characteristic shape, Others), (11) whether there is erythema around the scar (Clearly exists, Does not clearly exist), and (12) whether there are subjective symptoms (Always exist, Intermittent, None). Thus, the classification table consists of 12 items in total. The categories in each item are weighted: for example, in Human race, African, Caucasian, and Other races are weighted 2, 0, and 1 points, respectively. The minimum and maximum number of points in the classification table are 0 and 25, respectively. If the classification score is 0–5, the scar is deemed to have mature scar characteristics. If the score is 6–15 or 16–25, the scar is deemed to be a hypertrophic scar and a keloid, respectively.

This grading system is thus used to differentially diagnose keloid and hypertrophic scars. It is necessary to have this system because there are many cases in which the scar bears the growth and histological features of both hypertrophic scars and keloids; as a result, it can be difficult to differentially diagnose these scars in real clinical practice. This reality is not mirrored by the current dogma about pathological scars. Thus, many classical textbooks consider keloids and hypertrophic scars to be completely different types of scar. Clinicians define hypertrophic scars as scars that do not grow beyond the boundaries of the original wound, whereas keloids are defined as scars that spread into the surrounding normal skin. Pathologists have their own definitions; they make a histological distinction between keloids and hypertrophic scars on the basis of thick eosinophilic (hyalinizing) collagen bundles called “keloidal collagen”: these are present in the former scar type but rarer in the latter. However, we have observed many cases that do not fit these dichotomic definitions. For example, scars with hypertrophic growth characteristics can bear considerable keloidal collagen. Indeed, it is possible that hypertrophic scars and keloids are manifestations of the same fibroproliferative skin disorder and just differ in the intensity and duration of inflammation. These inflammatory features may be shaped by genetic, systemic, and local risk factors [7].

15.4 Evaluation Table

The evaluation table consists of six items: (1) Induration, (2) Elevation, (3) Redness of the scar, (4) Erythema around the scar, (5) Spontaneous and pressing pain, and (6) Itch. Each item has four intensity categories, namely, None, Weak, Mild, and Strong. These categories are weighted 0, 1, 2, and 3, respectively. There are sample

Table 15.1 JSW Scar Scale (JSS) 2015 (Classification and Evaluation of Keloids and Hypertrophic Scars)

Classification (for grading and selection of appropriate treatment methods)			Evaluation (for judging treatment results and for following-up)			
Risk factors			1. Induration			
1. Human race	Africans	2	0: None	1: Weak	2: Mild	3: Strong
	Others	1				
	Caucasians	0	2. Elevation (Fig. 15.5)			
2. Familial tendency	Clearly exists	1	0: None	1: Weak	2: Mild	3: Strong
	Not clearly	0				
3. Number	Multiple	2	3. Redness of scars (Fig. 15.6)			
	Solitary	0	0: None	1: Weak	2: Mild	3: Strong
4. Region	Anterior chest, scapular-shoulder, suprapubic	2				
	Others	0	4. Erythema around scars (Fig. 15.7)			
5. Age at onset	0–30 y/o	2	0: None	1: Weak	2: Mild	3: Strong
	31–60 y/o	1				
	60 y/o	0	5. Spontaneous and pressing pain			
6. Causes	Unknown or minute	3	0: None	1: Weak	2: Mild	3: Strong
	Specific wound type such as surgery	0				
Present symptoms			6. Itch			
7. Size (cm^2)	Over 20 cm^2	1	0: None	1: Weak	2: Mild	3: Strong
	Under 20 cm^2	0				
8. Vertical growth (elevation) (Fig. 15.1)	Clearly exists	2	Total 0–18			
	Not clearly	0	Remarks			
9. Horizontal growth (Fig. 15.2)	Clearly exists	3	Weak: symptoms exist in less than 1/3 of the area, or are intermittently			
	Not clearly	0	Strong: symptoms exist in the entire region, or are continuous			
10. Shape (Fig. 15.3)	Characteristic shape	3	Mild: between weak and strong			
	Others	0				
11. Erythema around scars (Fig. 15.4)	Clearly present	2				
	Not present	0				
12. Subjective symptoms	Always exist	2				
	Intermittent	1				
	None	0				
Total 0–25						
Remarks						
0–5	Character like matured scars (intractability, low risk)					
6–1	Character like hypertrophic scars (intractability, middle risk)					
16–25	Character like keloids (intractability, high risk)					

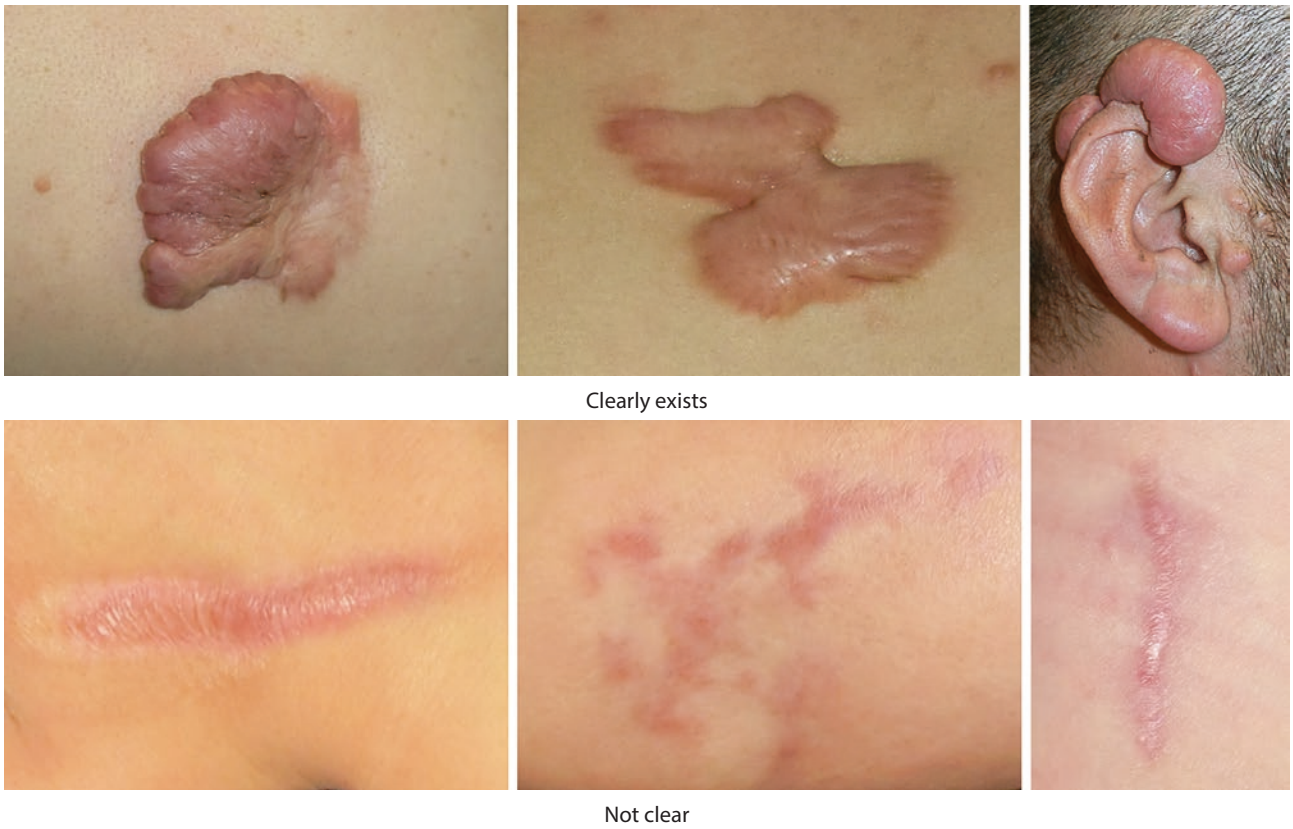

Fig. 15.1 Vertical growth (elevation)

images of each category in each item that helps the user judge the items. The minimum and maximum total points in the evaluation table are thus 0 and 18, respectively. When the symptoms improve, the total score decreases.

15

15.5 Clinical Suitability and Usefulness of the JSS

We evaluated the clinical suitability of the classification table of JSS2015 with 50 consecutive scar patients in our clinic. The scores of the patients were evenly distributed between 0 and 25 points (Fig. 15.8). This distribution closely reflects our subjective experiences in our scar clinic and those of other Japanese plastic surgeons. As a result, the JSS became a standard classification and evaluation tool for keloid and hypertrophic scars in Japan. The JSS has since been used to evaluate scar severity in several clinical research projects [8–10]. It was also used in a study in Taiwan [9]. However, in our experience, different regions of the world vary in terms of the severity of keloids and hypertrophic scars: in particular, keloids appear to be singularly severe in Africa and East-South Asia, while being rare in western countries. Therefore, in the future, the JSS2015 should be modified to cover other regions of the world.

15.6 Conclusion

The Japan Scar Workshop (JSW) developed the JSW scar scale (JSS) to evaluate keloids and hypertrophic scars. The JSS consists of two tables; one is a scar classification table that is used to determine whether the scar is a normal mature scar, a hypertrophic scar, or a keloid, and the other table is an evaluation table that is used to judge the response to treatment and for follow-up. The JSS became a standard classification and evaluation tool for keloid and hypertrophic scars in Japan. In the future, the JSS5 should be modified to cover other regions of the world.

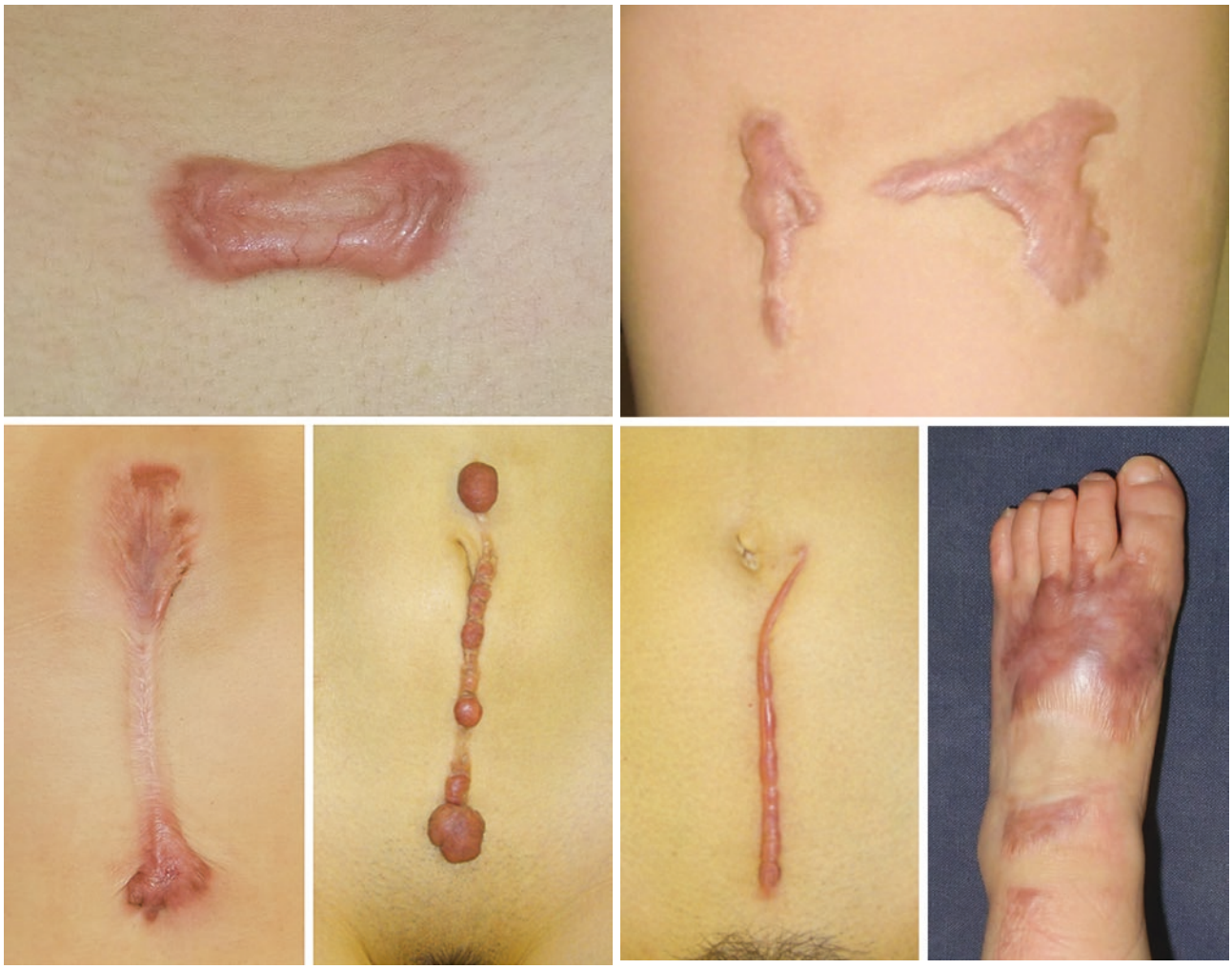

Fig. 15.2 Horizontal growth

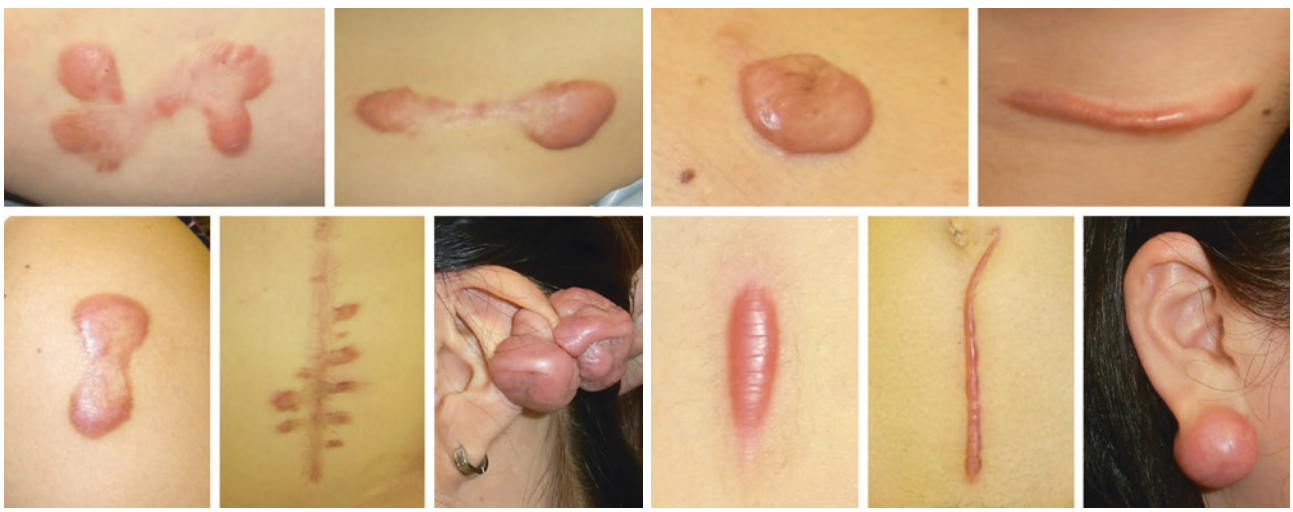

Fig. 15.3 Shape

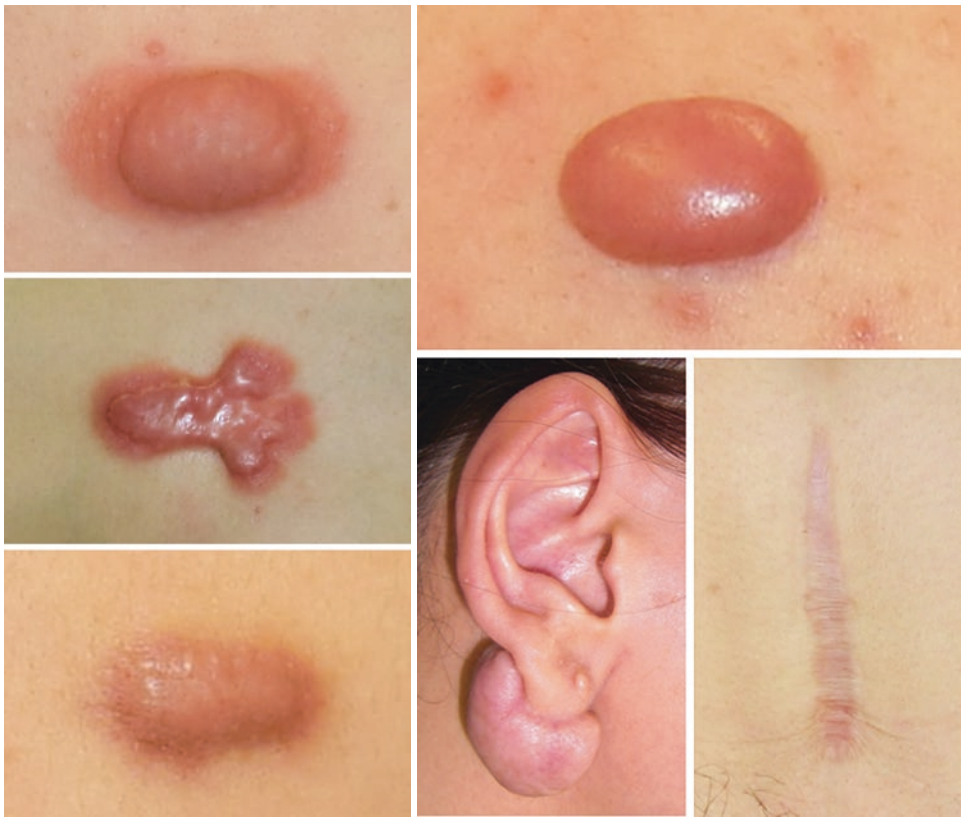

Fig. 15.4 Erythema around scars

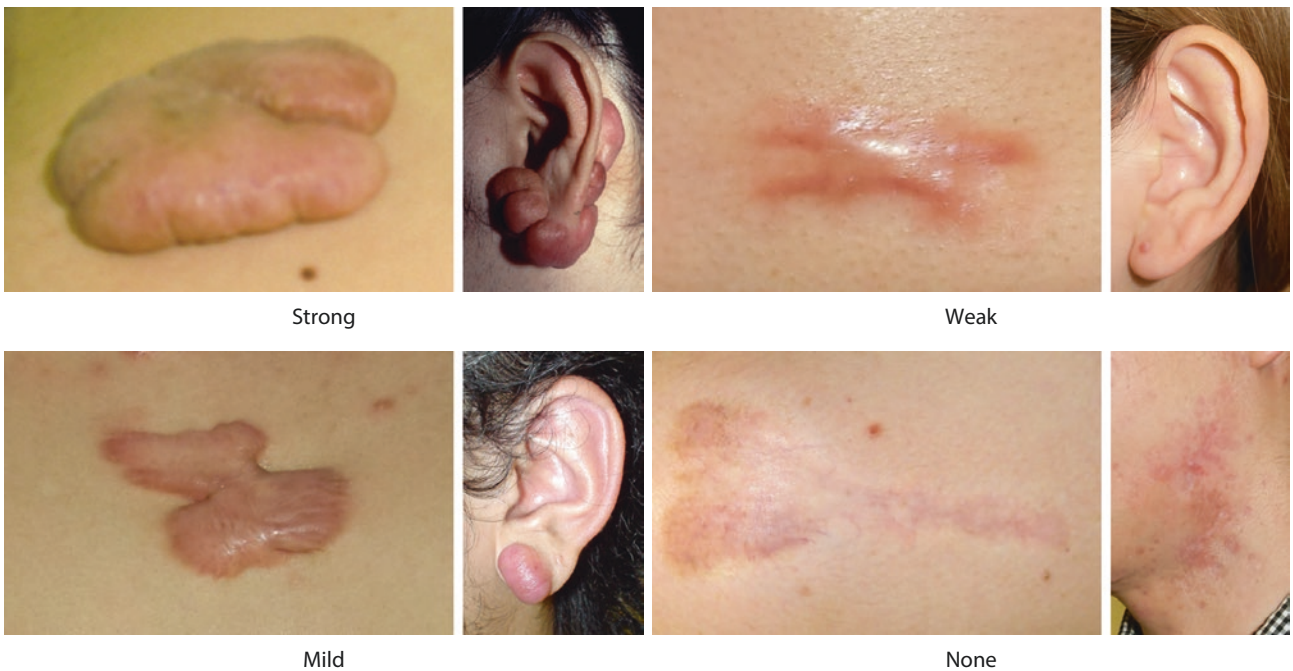

Fig. 15.5 Elevation

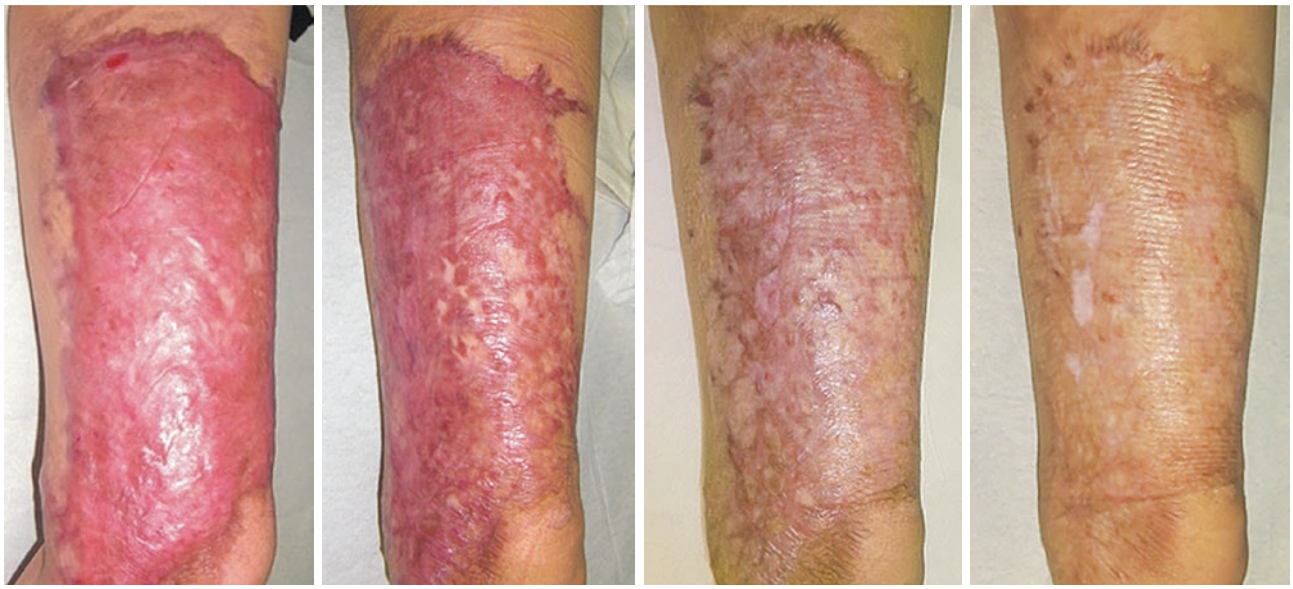

Fig. 15.6 Redness of scars

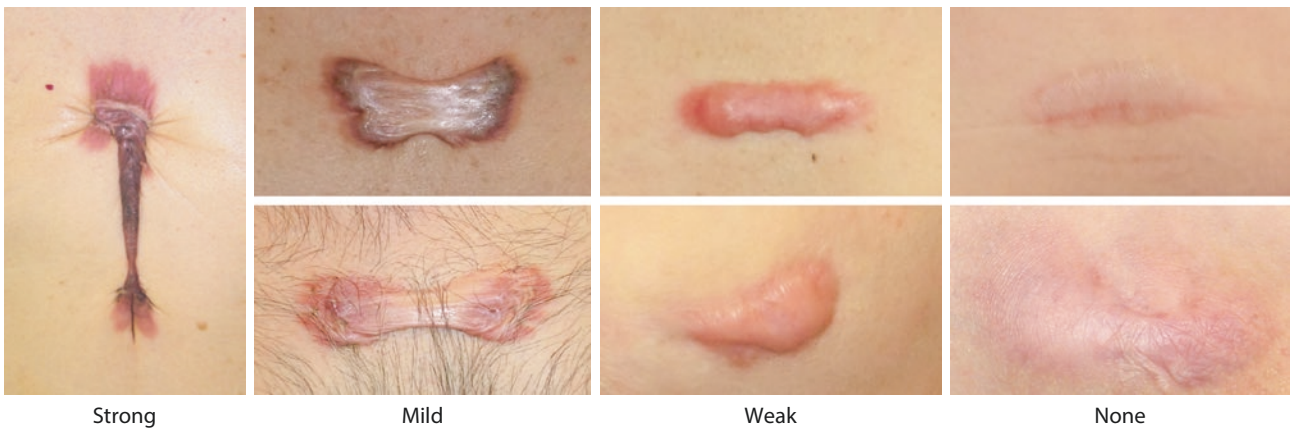

Fig. 15.7 Erythema around scars

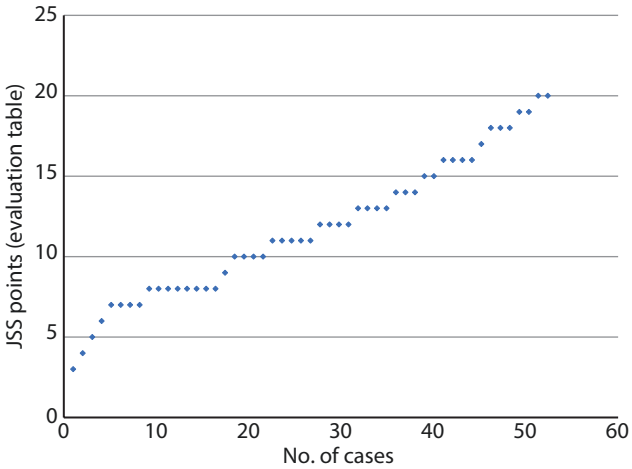

Fig. 15.8 *Clinical suitability* of the classification table of JSS2015 in consecutive scar patients. We evaluated the clinical suitability of the classification table of JSS2015 by applying it to 50 consecutive scar patients in our clinic. The scores of the patients were evenly distributed between 0 and 25 points. This reflects our general clinical experience

Take-Home Messages

- The Vancouver scar scale, the Manchester scar scale, and the Patient and Observer Scar Assessment Scale (POSAS) were mainly developed to evaluate burn scars.
- The Japan Scar Workshop (JSW) developed the JSW scar scale (JSS) to evaluate keloids and hypertrophic scars.
- The JSS consists of two tables; one is a scar classification table that is used to determine whether the scar is a normal mature scar, a hypertrophic scar, or a keloid, and the other table is an evaluation table that is used to judge the response to treatment and for follow-up.
- The JSS contains sample images of each subjective keloid/hypertrophic scar item that allow the user to evaluate each item without hesitation.

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Objective Assessment Technologies (Cutometer, Laser Doppler, 3D Imaging, Stereophotogrammetry)

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Objective Assessment Technologies: General Guidelines for Scar Assessment

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16.1 Background

Comprehensive scar treatment is becoming more and more readily available. Both the awareness of medical professionals regarding the impairments of severely scarred patients and their knowledge of treatment options for scars have increased significantly during recent years. Those developments have been made possible by extensive research of new treatment options and continued reevaluation of long-established ones.

However, large numbers of studies continue to rely predominantly on subjective evaluation methods like scales and questionnaires to gauge the success of their treatment. Objective scar evaluation technology, too, has shown an immense development throughout recent years, and researchers and clinicians alike can now choose from a large arsenal of options to document treatment progress and failure [1].

But while this newfound selection of tools for objective scar analysis has helped to improve research, it has also introduced new problems.

With many different manufacturers offering many different devices for analysis of a vast number of parameters, researchers are left with the dilemma to choose the right tools for their individual projects with little evidence-based recommendations available. Oftentimes, devices will not be able to measure in standardized units but will provide measurement results in the manufacturer's own proprietary format that offers little comparability with results from different research groups with different measurement tools. The process of measuring the desired parameters reliably in the oftentimes hectic environment of everyday clinical routine can be daunting too and can lead to problems with recreating measurements and making sure that repeated measurements yield comprehensible results.

In this chapter, we want to focus on the basics of objective measurement technologies that allow researchers and clinicians to find the right tools for their desired analyses, to make comprehensive plans about how to document their patients' scars in a way that can both easily and reliably be reproduced, and to understand the value and impact of the results of their measurements.

Obtaining and cultivating this knowledge can then not only lead to improving the level of evidence in scar research but also help in everyday clinical treatment scenarios where in-depth scar analysis might provide physicians with a sensitive gauge for the success or failure of their applied treatment.

16.2 Choosing the Right Tools for Each Scar

Before planning a research project or the documentation of clinical results in scar therapy based on objective assessment technology, care must be taken to identify the tools best suited for each specific undertaking. Since scar documentation as well as the consecutive sorting, assessment, and evaluation of data is considerably time-consuming, superfluous measurements should be avoided.

The first step is identifying the scar parameters that require documentation and afterward choosing the tools suitable to assess the development of the chosen parameters. When trying to assess the influence of a certain treatment option on scars, parameters most likely affected positively or negatively (e.g., side effects) should be selected.

When choosing the most suitable assessment technology, a thorough literature research should be performed to identify assessment options that have been well established and are used by other researchers as well to ensure both the suitability for the task and, later, comparability of the results between different research groups.

Ideally, comparability does not require different researchers to use identical hardware but rather that different hardware uses the same units of measurement. While this is common in ultrasound technology where most, if not all, units are able to perform measurements based on SI units, more specialized tools for profilometry or colorimetry specifically designed for application in aesthetic medicine often employ proprietary units of measurement that are difficult to compare with other researches.

While this does not necessarily mean those options are unsuited for research applications, it should be taken into consideration beforehand.

16.3 Optimizing the Measurement Process

16.3.1 Preparing the Surroundings

The room where measurements are conducted should be light, cool, and dry. Illumination through natural light should be minimized so that it does not influence photographic and colorimetric testing where changing outside lighting could act as a disruptive factor. The ambient temperature should neither be too warm or too cool since physiological reactions to extreme temperature (e.g., sweating, goose bumps) can influence measurements, especially regarding physiological skin parameters. Furthermore, extreme temperatures, just like humidity, could also influence the functionality and longevity of the measurement instruments. Some manufacturers even provide ambient condition sensors to monitor parameters like temperature or humidity and save the values together with the measured results. This can guarantee both superior awareness of the lab ambience as well as improve comparability of the achieved measurement results.

16.3.2 Configuring and Calibrating the Assessment Tools

Reliable measurements are paramount in every clinical and/or research setting. This starts with making sure that the assessment instruments are properly cared for and calibrated.

Most devices come with extensive instructions on how to calibrate them, and adhering to those recommendations is important since even small discrepancies in the measurement process can yield significantly altered results, especially with modern, highly sensitive equipment.

Instruments that have direct contact with the skin, for example, devices that measure skin elasticity, color, or physiological properties, should be cleaned regularly as sebum, hairs, and makeup can accumulate on the measuring probes and alter measurements as well as hinder successful calibration.

Photography-based systems require regular cleaning too, so that there are no specks on the lens or projector systems (e.g., PRIMOS system).

Most devices allow for a variety of parameters to be configured that can greatly influence how the measurements are conducted and what the results are going to be. Those parameters need to be defined beforehand and require standardization so that subsequent measurements can be compared. Photography-based devices that use different exposure times or white balances during measurements will result in significantly different looking images, skin elasticity values will differ greatly when on and off times of the suction probes of the Cutometer are changed, and the same is true for many other devices, too. Especially when more than one researcher is working with a certain device, care should be taken to check all the relevant parameters before measurements are performed.

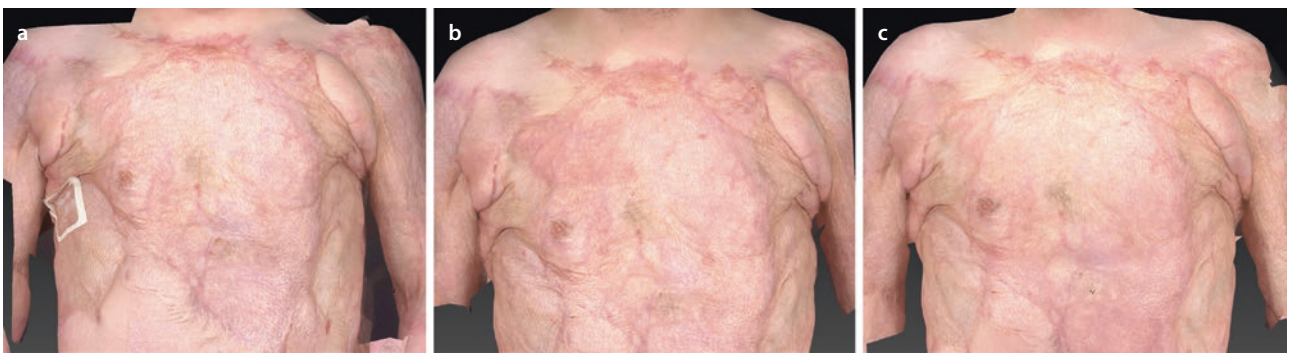
16.3.3 Preparing the Patient

The areas to be measured should be clean and free of makeup, skin-care products, or therapeutic agents (like ointments, gels, silicon sheets).

Throughout the measurement process, patients should remain in a neutral, predefined position so as not to alter certain measurement results due to their pose. Especially during measurements regarding skin texture and relief or elasticity, identical positioning for subsequent measurements is crucial in ensuring comparability of the results. Scars that run close to or over joints are greatly affected when those joints are moved, and elasticity results, for example, might reveal drastically different results when said joints are fully flexed or extended. It can therefore help when the positioning of the patient is predefined (e.g., patient standing, arms hanging loosely on his sides) and said positioning is kept throughout all measurements (◘ Fig. 16.1).

16.3.4 Performing the Measurements

After all the preparations have been made, calibrations have been performed, and configurations have been checked, the measurements are performed. Here, it is important to ensure subsequent measurements are performed similarly. Camera-based systems often provide integrated overlay functions that allow the examiner to achieve identical captures during successive assessments, and some devices offer integrated software solutions to stack subsequently taken images to only measure the common areas; however sometimes, such solutions are not offered. It can therefore help to define anatomical landmarks for orientation and to fashion templates so that positioning of the measuring probe or the camera system remains constant [2].



◘ **Fig. 16.1** Canfield Vectra X3 imaging before **a**, 3 months after **b**, and 6 months after **c** one session of fractional ablative laser treatment of the upper right chest. The patient had been instructed to maintain a standardized pose (standing upright, arms hanging loosely by his sides, facing forward) to ensure comparability between subsequent images

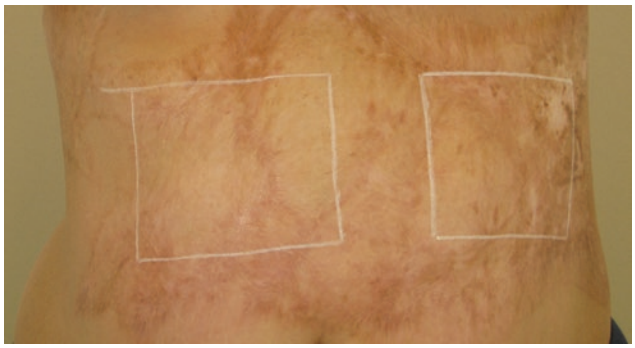


Fig. 16.2 Severe burn scars on the abdomen of a female patient. Note the marked squares where one has been defined as the treatment and the other as the control area. By using a foil template and anatomical landmarks, those areas can be retraced for follow-up measurements which are always conducted within the marked squares to avoid confounding of the results. This course of action ensures that surface profilometry and skin elasticity measurements are always performed on the same area

Devices that measure skin elasticity or color often rely on small probes with relatively small openings through which the individual parameters are measured. This often proves challenging for the examiner since exact repositioning for a subsequent measurement often is difficult if not impossible. Furthermore, especially in widespread scarring, getting representative results from only one measurement is virtually impossible, especially if one cannot ensure that measurements are always taken at the same spot.

These problems, unfortunately, cannot be addressed satisfactorily with devices that are not able to measure the entire scarred surface, and therefore, a compromise that will allow for as great an approximation as possible is necessary. Using an increased number of measuring points in a randomized fashion is a method that has been used in current research, thus ensuring that extreme values do not dramatically alter the overall measurements and including more parts of the oftentimes inhomogeneous scar surface into the measurement [3]. There is, however, no consensus on how many measurements are necessary to adequately represent the results of a larger area. In their research, the authors have commonly used three measurements for an area of 10 cm by 10 cm when measuring skin elasticity or other parameters that rely on assessment through small probes (Fig. 16.2).

16.4 Interpreting Therapeutic Success with Objective Scar Assessment Technologies

16.4.1 Data Assessment and Evaluation

After the measurements, the resultant data needs to be sorted and analyzed. To present the most objective results possible, it is necessary to use the raw absolute data for further analyses. Only including relative changes makes it hard for outside observers to interpret the importance of the findings when absolute baseline values are not known. Furthermore, the level of measurement that is required for certain statistical tests is not sufficient when using relative data.

Then, tests can be performed to elucidate the statistical significance of the findings.

16.4.2 Clinically Important Difference

After performing statistical testing, one must consider whether the results of the measurements constitute a clinically important difference. Currently, there are no clear recommendations on what constitutes a clinically important difference in objective scar assessment in the literature. However, ideally, every modern study on scar treatment and its effects can include its own control to evaluate whether the results are clinically important.

After all, scar treatment should alleviate the patients' symptoms, improve functional impairments, and address aesthetic disfigurements. Therefore, patient-derived questionnaires like the POSAS Patient Scale or the Dermatology Life Quality Index (DLQI) can be included in the research as a control for patient satisfaction [4]. Should those questionnaires show statistically significant improvements, just like the objective assessment tools, then a clinically important difference has been achieved. While the lack of statistically significant results does not necessarily rule out a clinically important difference, it is important to consider just how sensitive modern assessment tools have become. Surface profilometry can measure changes at the micrometer scale, and other technologies boast similar sensitivities. But even if changes can be documented on such a fine scale, statistical significance of such results does not help the patients if they do not register improvements regarding their impairments.

Therefore, defining an absolute clinically important difference for objective scar assessment is neither possible nor sensible. The importance of documented improvements should always be compared to the patients' assessment of the therapeutic results to gauge the overall success.

16.5 Conclusion

Objective scar assessment has come a long way during the recent years. Today, a multitude of options for the documentation of scar treatment is available. From this variety of options, researchers and clinicians have to choose the tools best suited for their individual analysis based on the scar parameters that require documentation and the individual devices' features. Care should be taken to choose

assessment technology that does not rely on proprietary assessment and evaluation formats but that is able to export results in standardized units of measurement so that comparability with other research groups and studies is ensured. Measurements should be performed in a standardized environment with well-maintained and well-calibrated tools, and conditions as well as patient positioning should not differ between measurements.

Objective scar assessment relies on using the most accurate values to represent the results which is why absolute values should always be preferred to relative values. Not only does this ensure comparability of the results, it allows for more complex statistical testing, thus ensuring improved significance of the findings.

A clinically important difference, however, cannot be derived from statistically significant findings alone. Here, the patient's perspective should be taken into consideration. As modern technology is now able to document extremely subtle changes, clinically important differences, despite significant statistical changes, can only be asserted if the patient considers them significant. This further illustrates that neither subjective nor objective scar assessment means alone should be employed. Both clinical and research protocols should include both to profit from additional information and to further characterize their findings.

Take-Home Messages

- Choosing the right objective scar assessment tools is paramount and should be based on the scar parameters that are central to the research.
- Devices that work with standardized units of measurement should be preferred to those that work with proprietary units or formats.
- Maintaining a standardized environment for the measurements both regarding the instruments (regular cleaning and calibration are required; the proper configuration should be checked before measurements are performed) and the patients (standardized posture, identical location for the measurements) is crucial.
- Absolute values should be preferred to relative values to improve the informative value and the statistical significance of the findings.
- The clinically important difference in objective scar assessment is rather a correlation between objective findings and subjective patient satisfaction, than a certain amount of improvement according to technical measurements. Modern assessment technology is oftentimes so sensitive that statistical testing reveals significant improvements before patients notice them.

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Objective Assessment Tools: Physical Parameters in Scar Assessment

M. E. H. Jaspers and P. Moortgat

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_17

Background

Several types of problematic scars can be identified: hypertrophic scars, keloids, contractures, and adherent scars (Fig. 17.1). All these scars require specialized treatment. However, the need for innovation and novel treatment is paramount to further reduce the burden of these scars and to ultimately attain scarless healing. Critical to the development of novel treatment modalities are objective assessment tools that evaluate whether scar treatment is effective and successful. Secondly, assessment tools can be used to monitor the scar's response to interventions. One important aspect to take into account when using tools in clinical practice is to ascertain that the chosen tool is "clinimetrically approved."

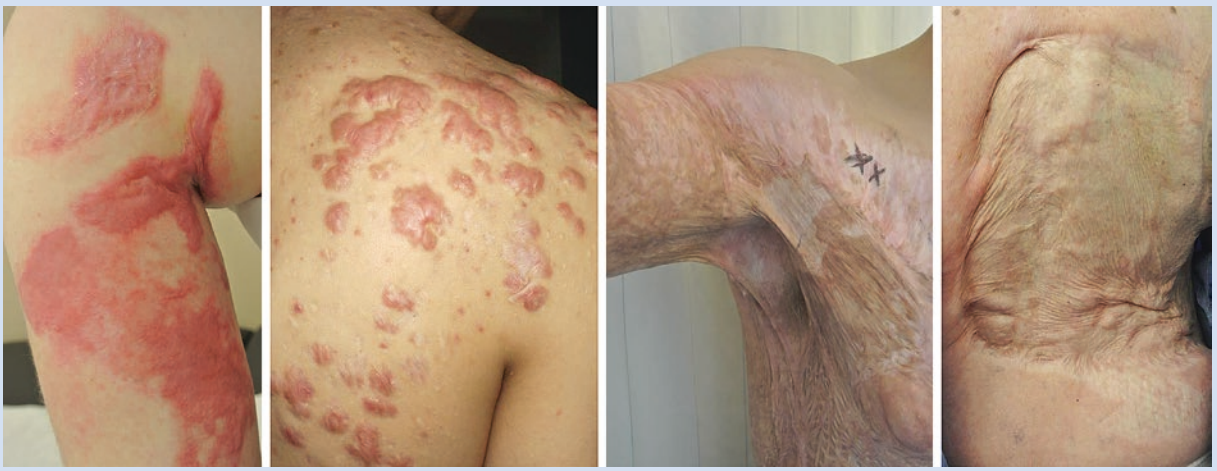

Fig. 17.1 Several types of pathological scars. **a** Hypertrophic scar on the right upper arm, **b** keloids on the right scapula and shoulder, **c** contracture of the right axilla, and **d** widespread adherent scarring on a patient's back and spine. (Reproduced with permission from 'Beyond the skin, new insights in burn care'" by M. E. H. Jaspers, 2017. ISBN: 978-94-6233-852-4.)

17.1 Clinimetrics

The discipline of "clinimetrics" (i.e., measurement in medicine) aims to improve the quality of measurements by assessment of the properties of existing tools or by development of new tools. Before implementation of a new measurement tool in either clinical practice or in research can be considered, two essential properties need to be evaluated: reliability and validity. All measurement tools are required to produce reliable and valid scores.

The general definition of reliability is "the degree to which the measurement is free from measurement error" [1, 2]. In addition, there is an extended definition of reliability: "the extent to which scores for patients who have not changed are the same for repeated measurements under several conditions," which makes clear that repeated measurements are a key point. The variation that may arise between repeated measurements decreases the reliability. This can be attributed either to the measurement tool, the persons performing the measurement, the patients undergoing the measurement, or the circumstances under which the measurements are performed. The measurement error comprises both the systematic and random error of a patient's score that cannot be attributed to true changes in the scar. So, parameters of measurement error are relevant for the measurements of changes in scar status. Moreover, these parameters are of great value for clinicians as they are expressed in the units of measurement, which facilitates interpretation. Finally, to determine whether changes are clinically relevant, the minimally important change (MIC) can be calculated, which is defined as "the smallest change in score which patients, clinicians or relevant others perceive as important" [2, 3]. To monitor the scar of an individual patient, it is of paramount importance that the MIC is smaller than the measurement error of the tool.

Validity is defined as "the degree to which an instrument truly measures what it purports to measure" [1]. Validity can be divided into three types: content validity, construct validity, and criterion validity. Content validity focuses on the correspondence of the content of the measurement tool with the construct that is intended to measure. Content validity is assessed qualitatively during development by pretesting, expert opinion, and literature review. Construct validity is applicable in situ-

ations in which there is no gold standard, and therefore this type of validity refers to whether the measurement tool provides the expected scores, based on knowledge about the construct. Criterion validity focuses on the correspondence of the (new) measurement tool with the gold standard (i.e., criterion). In theory, the gold standard is a perfectly valid assessment, but this rarely exists in practice. Also in scar care, it is challenging to identify a suitable criterion. In light of this chapter and of using tools in the future, it is important to take this into account and to be aware of the reliability and validity of the gold standard or comparator instrument itself.

Over the years, the number of available tools has increased rapidly. However, it is important to realize that not every scar parameter can be assessed and that the use of technologies and corresponding terminology is not standardized yet. Hereby, an overview is provided for three important physical scar parameters that can be assessed by (noninvasive) objective tools: color, elasticity, and perfusion.

17.2 Color

17.2.1 Erythema and Pigmentation

When looking at hypertrophic scars, one could ask the question: Which feature makes these scars so obvious and therefore problematic? Besides increased thickness or an irregular surface, the amount of erythema and pigmentation appear to have a major impact on the judgment of scar quality by both clinicians and patients. Moreover, the assessment of erythema could be imperative to predict the end of the remodeling phase [4]. Therefore, color measurements are an essential part of scar evaluation, and the associated measurement outcomes are common parameters in scar research.

It is beyond the scope of this chapter to state the underlying causes of the formation of erythema and pigmentation. However, it is important to realize how these aberrant scar features are constituted, to consequentially assess them in the right way. Moreover, it is underlined that the terminology regarding color measurements is not standardized yet. In clinical practice and in research, the measurement outcomes blood flow, scar color, erythema, and redness are used interchangeably or often replaced by the umbrella term "vascularization," which is not appropriate [5].

For the purpose of clarity, it is beneficial to provide a detailed description of every feature when assessed by a certain tool. Erythema is a complex characteristic that may be defined as the level of oxygenated hemoglobin measured at 660 nm, which shows to have a correlation with subjectively assessed redness [5]. Furthermore, scar color is also constituted by the amount of pigmentation, expressed by the outcome measurement melanin.

17.2.2 Reflectance Spectroscopy

Reflectance spectroscopy has been in use for over 60 years to assess skin color. At present, many affordable handheld devices are available that can easily be used in daily clinical settings. The most commonly used principles for measuring scar color are tristimulus reflectance colorimetry and narrow-band reflectance spectrophotometry. Both principles determine color by measuring the intensity of reflected light of specific wavelengths. The main chromophores in human scar tissue, hemoglobin and melanin, are primary determinants of the color. It has to be taken into account that these chromophores can be measured separately, but may influence each other. It is suggested that a scar with high hemoglobin values can mask the amount of melanin and vice versa.

17.2.2.1 Tristimulus Colorimetry

Tools based on the principle of tristimulus reflectance colorimetry are the Chroma Meter CR-400 (Konica Minolta Sensing Inc., Osaka, Japan) and the Skin-Colorimeter CL 400 (Courage and Khazaka electronic GmbH, Köln, Germany). This principle was developed to objectively represent color in a manner analogous to how color is perceived by the human eye. As well as with narrow-band spectrophotometry, white light is sent to the skin by LEDs in a probe. Light is scattered in all directions whereas the light reflected from the skin or scar is measured through three particular wavelength filters and expressed accordingly. This technique expresses XYZ-values, which can be calculated into RGB (red/green/blue) values or the related three L∗a∗b components: L∗ (brightness), a∗ (amount of red-green), and b∗ (amount of yellow-blue) [6, 7]. These components are based on the color system of the Commission International d'Eclairage (CIE) Lab system.

Concerning the clinimetric properties, the parameter LAB2 by the Colorimeter shows and ICC of 0.95 for the interrater reliability [6]. The Chroma Meter was first investigated on *healthy skin*, showing ICC values >0.92 for all parameters (L∗, a∗, and b∗) during measurements by two observers, thereby reporting the interrater reliability [8]. The latter study also reports standard error of measurement (SEM) values, which are between 0.38 and 0.59 and thereby low. In addition, a preceding type of the Chroma Meter (CR-221) was evaluated on scar tissue and shows ICC values >0.73 for a single measure-

ment by one observer (test–retest) and ICC values >0.91 when the measurements of four observers are averaged [9]. In this study, SEM values are between 1.26 and 4.33, which is rather high.

17.2.2.2 Narrow-Band Spectrophotometry

Narrow-band tools are based on the fact that hemoglobin and melanin show different spectral curves for the absorption of light. The tools offer read-out of erythema and melanin values as well as CIE L∗a∗b values. The erythema and melanin index values are based on the differences in light absorption of red and green by hemoglobin and melanocytes, respectively. The erythema index is defined as: E = 100 × log (intensity of reflected red light/intensity of reflected green light) and the melanin index can be defined as: M = 100 × log (1/intensity of reflected red light). It has to be taken into account that the index values can be measured separately, but may influence each other.

In the DSM III ColorMeter (Cortex Technology, Hadsund, Denmark) this is achieved by two light-emitting diodes (LEDs) (green 568 nm and red 655 nm) that illuminate a surface and record the intensity of reflected light using a photodetector. The Mexameter MX 18 (Courage and Khazaka electronic GmbH, Köln, Germany) uses 16 light-emitting diodes that emit light at three wavelengths (green: 568 nm; red 660 nm; infrared 880 nm), where after the reflected light is measured by a receiver unit. Erythema is measured by the green and red wavelengths, whereas melanin is determined by the red and infrared wavelengths. Readings are expressed between 0 and 1000, corresponding to white and black respectively.

Both tools are examined in several clinical studies and provide reliable data on scars [10]. The most common reliability parameter examined is the intraclass correlation coefficient (ICC) for ratings performed by several observers (i.e., interrater reliability). Erythema measured by the Mexameter shows an ICC between 0.82 and 0.97 and for the DSM II ColorMeter an ICC of 0.84 is reported [6, 11]. In addition, the DSM II ColorMeter also offers read-out of CIE L∗a∗b values, which will be described in the next paragraph. Investigation of the parameter a∗ by the DSM II ColorMeter shows an ICC of 0.94 [6]. Unfortunately, information on parameters concerning the measurement error of these color tools is lacking. Furthermore, attempts are made to assort the most *valid* parameter of each tool [6]. However, as previously mentioned, it is often difficult to appoint an adequate comparator instrument that exactly measures the same feature (i.e., construct) of a scar as the tool under study. This is underscored by the poor correlations reported between color-measuring tools and scar assessment scales [10, 12]. Overall, the correlation between erythema assessed by a tool and redness assessed by a scar assessment scale is between 0.4 and 0.7 [5, 11, 12].

Ultimately, the DermaLab Combo (Cortex Technology, Hadsund, Denmark) will be mentioned here. This device offers a combination of measurement possibilities. The color probe uses the principle of reflectance spectrometry to measure scar color and all above-mentioned parameters can be reproduced: erythema, melanin, L∗, a∗, and b∗. As previously stated, the parameters erythema and a∗ can be used to indicate scar erythema. A weak to moderate correlation is found between erythema values and redness scored by a subjective tool and in terms of reliability, the ICC varies between 0.66 and 0.84 for measurements by two observers, whereas the test–retest reliability is even lower: 0.29–0.42 [13, 14].

Several studies show that erythema index scores decline over time [15, 16] and all clinical studies report that distinction between scar tissue and healthy skin can be made with color-measuring tools. Therefore, it is stated that objective color measurements appear reliable to determine change over time in a (heterogeneous) study population, which merits their scientific use. However, for the clinical follow up of an individual patient, SEM values need to be very low. Moreover, concerning the validity, it is challenging to define the exact measured construct, which is becoming even more complex given that the tools can reflect various parameters. This has to be taken into account when a color-measuring tool is selected to monitor the scar's response to interventions.

From a practical point of view, it is important to notice that pressure on the scars will change the color toward the white spectrum. Therefore, users are required to lightly put a color-measuring tool on the scar to reduce the influence of pressure. Another limitation, which also accounts for elasticity-measuring tools, is the small size of the probe's measurement area. To comprehensively present the color or elasticity of a scar as a whole, the proposed solution is to work with a predefined algorithm, covering several measurement areas within the borders of one scar. For example, by drawing an imaginary line through the horizontal and vertical axis of the scar, resulting in five measurement points: one on the intersection of both lines and four halfway the intersection and the border of the scar. In this way, also selection bias by the observer is avoided.

17.2.3 Spectrophotometric Analysis (SIA)

To provide information on color outside the visible spectrum, relating to deeper structures of the scar, infrared light can be used. Spectrophotometric intracutaneous

analysis (SIA) can be performed via a clinical device, the SIAscope, which utilizes a probe that exerts radiation ranging from 400 to 1000 nm and produces 8 narrow-band spectrally filtered images of the skin. These images are processed by software algorithms and allow subsequently visualization and quantification of blood, collagen, and melanin. It already has been used to monitor changes in scar tissue in response to treatment [17].

17.3 Elasticity

The second physical parameter that causes poor functional scar quality is a loss of elasticity, which is due to increased collagen synthesis and lack of elastin in the dermal layer. However, as will be emphasized in this paragraph, certain tools quantify the opposite of elasticity, which is tissue *hardness*.

17.3.1 Cutometer

The Cutometer MPA-580 is designed to measure elasticity (i.e., elevation) of the upper skin or scar layer using a predefined negative pressure setting, which mechanically deforms the skin. Negative pressure (i.e., vacuum) is instantly created in the device where after the skin is drawn into the aperture of the probe (Fig. 17.2). Subsequently, after a defined time, the skin is released. Inside the probe, the vertical deformation of the skin is determined by a noncontact optical measuring system. This optical measuring system consists of a light source and a light receptor and two prisms facing each other that project the light from transmitter to receptor. The light intensity varies due to the penetration depth of the skin. The resistance of the skin to the negative pressure (rigidity) and its ability to return to its original position (elasticity) are displayed as curves (penetration depth in mm/time) in real time during the measurement. This measurement principle allows data collection on the elastic and mechanical properties of skin or scar surface and enables objective quantification.

The Cutometer is a feasible device containing a probe, which is available in several aperture sizes (2, 4, 6 and 8 mm Ø) to fit different skin sites and different study requirements (Fig. 17.2). The smaller apertures mainly measure the elastic properties of the epidermis. With a larger aperture (6 and 8 mm), the measurement also comprises the dermal component, which is designated for scar assessment. As with the color-measuring tools, it is important to ensure light contact is made between the scar and the probe to avoid alterations in outcome measure. Measurements can be monitored as live curves on the screen of a connected laptop. The software of the Cutometer MPA 580 allows calculation of many parameters of interest from the different portions of the measurement curve. The two most relevant parameters are labelled as R and U (Figs. 17.3 and 17.4).

R-Parameters:

- R0: Behavior of the skin/scar to force (rigidity), maximum amplitude of the curve in mm
- R1/R4: Ability of the skin/scar to return to its original state, minimum amplitude after relaxation
- R2: Viscoelasticity: Resistance to mechanical force versus ability of returning in %
- R3/R9: Tiring effect (fatigue) visible with repeated suction/relaxation
- R5: Net elasticity: Elastic portion of the suction part versus the elastic portion of the relaxation part in %

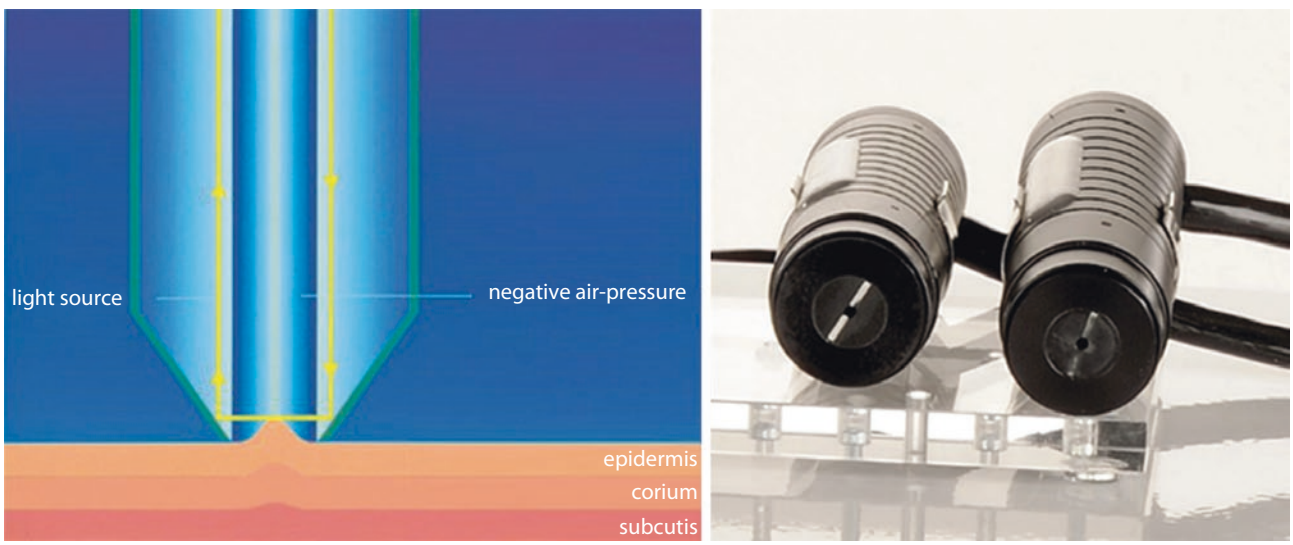

Fig. 17.2 Left: measuring principle of the Cutometer. Right: different aperture sizes of the probes. Reused with permission from Courage + Khazaka electronic GmbH. © All rights reserved

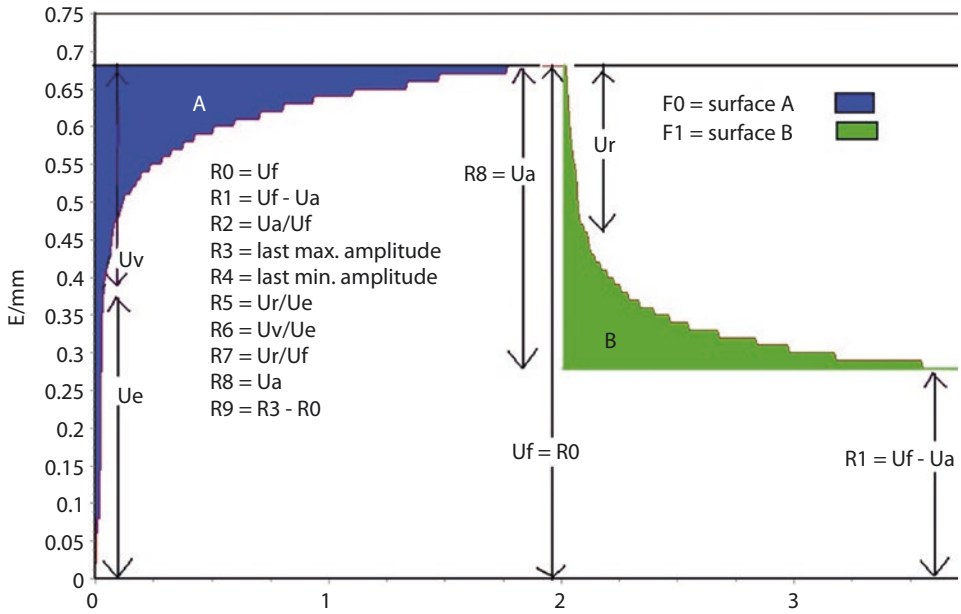

Fig. 17.3 The R-parameters of the Cutometer. Reused with permission from Courage + Khazaka electronic GmbH. © All rights reserved

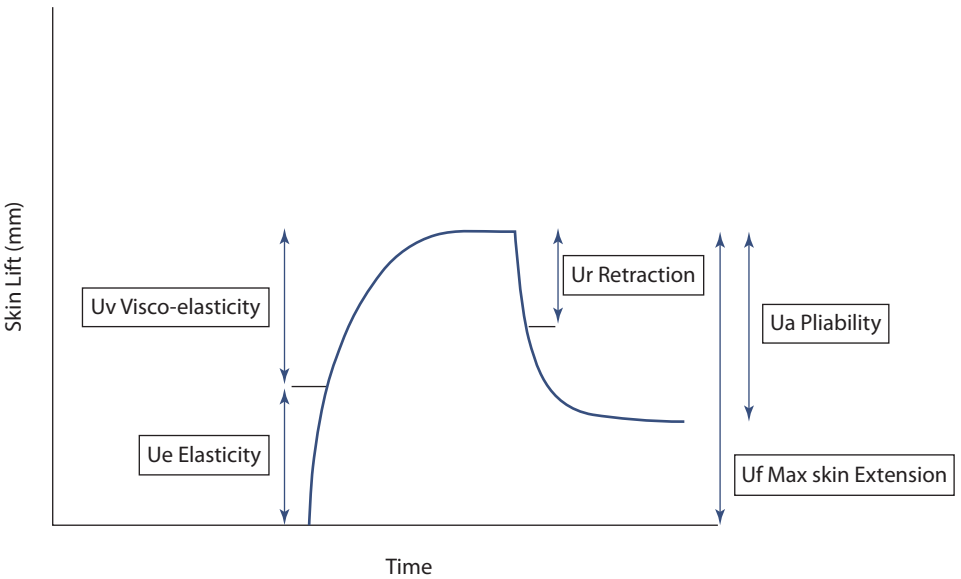

Fig. 17.4 The U-parameters of the Cutometer

17

- R6: Portion of the viscoelasticity of the curve in %
- R7: Portion of the elasticity compared to the complete curve in %
- R8: Complete relaxation after the pressure is removed in mm

U-Parameters:

- Uf (maximal skin extension): Deformation at the end of the vacuum period
- Ue (elasticity): Extent of skin stretching within the first 0.1 s of the vacuum period
- Ua (pliability): Difference between the maximum deformation and the deformation after 1 s of normal pressure
- Ur (retraction): Relaxation of the skin within the first 0.1 s after the ending of the vacuum, that is, the ability of the skin to return to its initial position after deformation and is related to the function of elastic fibers
- Uv (viscoelasticity): Difference between the deformation after the 0.1 s and the maximal deformation

The different parameters and their terms (i.e., elasticity, skin extension, pliability, retraction, and viscoelasticity) suggest that each parameter measures a different aspect of skin or scar deformation. However, the parameters are highly correlated when tested on scars, hence, a sin-

gle parameter is sufficient to use in the evaluation of scar elasticity (see below) [18].

17.3.1.1 Clinimetric Properties

The reliability of a single measurement performed by a single observer is good for extensibility (Uf) and elasticity (Ue) and ranges $r = 0.74–0.76$. For viscoelasticity, pliability, and retraction the reliability is low to moderate: $r = 0.35–0.69$. The Coefficient of Variation (CV = S.E.meas/mean × 100) for measurements on scars, based on the measurements of four observers, shows the lowest variation for extensibility (22.5%), whereas the highest variation is calculated for viscoelasticity measurements (36.0%) [18]. The concurrent validity was estimated by calculating the correlation between subjective evaluation of pliability and each of the Cutometer parameters. The correlations were moderate ($r > 0.46$) and statistically significant for each parameter except for viscoelasticity for which the correlation was low.

In general, it is stated that the reliability of the 2 mm probe is worse than the reliability of larger probes, because the small probe only reflects low values (small skin deformation). This is easily explained by the fact that the ICC or correlation is highly influenced by a wide range in measured values and by a heterogeneous population. So, when higher values or a range of values within a population are measured, this positively affects reliability as expressed by relative parameters. Of all parameters, either maximal skin extension (R0/Uf) or elasticity (Ue) appears to be influenced the least by variations in force applied to the probe and therefore it is the most reliable parameter to detect change in scar elasticity over time or after treatment.

17.3.2 DermaLab

The DermaLab elasticity probe (Cortex Technology, Hadsund, Denmark), which is the successor of the Dermaflex, consists of a light plastic probe that is much smaller than that of the Cutometer. This probe is attached to the skin using double-sided adhesive rings to form a closed chamber. Within this chamber, two narrow beams of light run at different heights parallel to the skin surface and serve as elevation detectors. A controlled vacuum is created in the closed chamber in over 30–60 s. In contrast to the Cutometer, the DermaLab probe measures the amount of suction required (in megapascal, MPa) to achieve an elevation of the skin of 1.5 mm. In pronounced adherent scars, this may cause a problem, as the scar is sometimes too stiff to be elevated sufficiently to reach the level of the detectors. The DermaLab shows an excellent ICC for test–retest reliability on scars (0.76–0.91); however, on healthy skin the ICC is much lower (ICC 0.45) [14].

Both the DermaLab and the Cutometer show advances of being a "hub," to which other measurement probes can be attached. The DermaLab Combo, for example, provides several probes, considering nine skin parameters (e.g., elasticity, color, transepidermal water loss, temperature), including ultrasound measurement of dermal scar thickness.

17.3.3 Tonometers

Tonometry works by exerting pressure on the skin and therefore quantifies predominantly firmness or hardness of tissue. Two types of tonometers can be distinguished: one type is based on air that flows through the system, which is blocked at a certain pressure (e.g., the Tissue Tonometer), and the second type provides an indentation load in the vertical direction (e.g., the Durometer). The Tissue Tonometer (Flinders Biomedical Engineering, Adelaide, Australia) is a weight-loaded device that exerts pressure directly on the area to be measured. The weight drives a blunt probe into the tissue with a tissue deformation as a result. This tissue deformation can be measured in millimeters, with a sensitivity of 0.01 mm. The readings are directly proportional to the firmness of the tissue being measured.

The Tissue Tonometer shows good intra-observer reliability, but a moderate correlation ($r = 0.44–0.46$) with the pliability score of a subjective scoring system (the VSS scale) is found. Additionally, the measurement requires a contralateral reference point, making it a relative measure [Lye 2006]. Another study, using a modified Tissue Tonometer, shows excellent interobserver reliability (ICC = 0.95) for healthy skin, accompanied by a low SEM of 0.025 mm [19]. A significant difference between scars and normal tissue was also demonstrated in the latter study. The Durometer (Rex Gauge Company, Inc., Glenview, Ill.) also shows good ICCs for the interobserver reliability (0.82–0.91) in one study, however, this is on sclerodermal skin [20].

Important to mention is that tonometers are influenced by the hardness of underlying tissue, which may limit the compression of the skin. This has to be taken into account when measuring locations where bone structures are situated directly under the area of interest. Possibly, measurements in these areas are not reflecting the condition of the skin/scar but instead of the underlying structure. Another shortcoming of tonometers include the need to place the device accurately, which must be within 5° of upright position to measure correctly.

17.4 Perfusion

Hypertrophic scars result from a wide array of derailed wound healing processes. It is suggested that new blood vessel formation, mainly apparent as angiogenic sprouting of preexisting blood vessels, is an essential process in the development of hypertrophic scars. Therefore, several treatment regimens (e.g., laser, pressure garments, and cryotherapy) work by destructing the microvasculature and/or reducing the blood flow. This may result in hypoxia that would lead to fibroblast degeneration and collagen degradation, both enhancing shrinkage of the hypertrophic scar tissue. As a result, it is of interest to measure scar blood flow (i.e., perfusion).

17.4.1 Laser Doppler Imaging

Laser Doppler imaging, a noninvasive flow measurement technique, can be used to quantify and visualize blood flow in scars [15, 21]. Laser Doppler imaging can be divided in the older technique, laser Doppler flowmetry (LDF), in which the fiber optic probe is in contact with the tissue, and the newer laser Doppler imaging (LDI) devices. The working mechanism is based on the Doppler principle. In LDF, a single-point measure of the cutaneous blood flow in a scar is obtained. LDF systems are therefore more limited compared to the other systems and unsuitable to use in larger heterogeneous scars. However, there are currently modern and high performance LDF systems such as the moorVMS-LDF (Moor Instruments Ltd., Axminster, United Kingdom) or the PeriFlux 5000 (Perimed AB, Järfälla, Sweden) that are ideal for laboratory or scientific use. In LDI, laser light directed at moving erythrocytes in sampled tissue exhibits a frequency change, which is photo detected and processed to generate a line-by-line color-coded map that is proportional to the amount of perfusion in the tissue. After completion of a LDI measurement, data can be analyzed offline using software to calculate the blood flow automatically, where after it is expressed in perfusion units (PU).

To assess blood flow in a scar, the moorLDI Imaging System (Moor Instruments Ltd., Axminster, United Kingdom) can be used. Previous studies show that hypertrophic scars sustain an elevated blood flow compared to normal skin [15, 22]. Another clinical study also presents a statistically significant increase in blood flow values of scars compared to healthy skin [5]. In more detail, the latter study shows increased LDI blood flow values in 29/32 included patients. Interestingly, this study also compares the association between the outcomes of LDI and colorimetry using the DSM II ColorMeter. The results indicate that blood flow and erythema values are not correlated. During measurements of 32 hypertrophic scars, a widespread in erythema values is observed, whereas the accompanying blood flow values are mostly beneath 300 PU and thereby low. These data are in agreement with a previous study, presenting that erythema (measured using the skin-colorimeter expressing L∗a∗b index values) is associated with blood flow, but this correlation is not consistent at different test moments [4]. As a result, it is concluded that LDI and colorimetry are non-interchangeable measurement tools.

LDI can be a valuable adjunct in the research setting, where it might be useful to monitor scar development and/or response to treatment that is directed at lowering blood flow. However, although new laser Doppler instruments became available over the last years, it is important to keep in mind that the tool has some limitations in terms of feasibility (e.g., high cost, long assessment time, and moderate ease of use). Therefore, LDI seems less suitable for the follow-up of scars in daily practice.

17.4.2 Laser Speckle Imaging

Laser speckle imaging (LSI) or laser speckle perfusion imaging (LSPI) are alternative perfusion monitoring techniques that generate high-resolution images of tissue in a shorter assessment time than LDI. In addition, these devices provide the possibility to zoom in with increased resolution of a smaller area of interest. The moorFLPI-2 blood flow imager (Moor Instruments Ltd., Axminster, United Kingdom) and the PeriCam PSI (Perimed AB, Järfälla, Sweden) both use the laser speckle contrast technique to deliver real-time high-resolution blood flow images. The latter system contains an invisible near infrared laser (785 nm), spreading the beam over the area of interest by a diffuser, creating a speckle pattern. Subsequently, blood perfusion is calculated by analyzing the variations (i.e., interference) in the speckle pattern. High values reflect high blood flow and should thereby indicate immature or hypertrophic scars.

A clinical study comparing the ability of LSPI with LDI in determining and monitoring hypertrophic scar perfusion shows a positive correlation ($r^2 = 0.86$) [23]. Moreover, in terms of feasibility, the LSPI device demonstrates a faster scan time and higher resolution, which may be an advantage for usage in clinical practice. Also, reactions to mechanical or pharmacological interventions can be studied nearly real time, allowing a dynamic way of studying scars. Perfusion rates within keloids are also assessed by LSI, showing significantly higher perfu-

sion in keloids and adjacent skin compared with nonadjacent healthy skin [24]. However, a thorough clinimetric evaluation of LSI in scars is currently not available.

17.5 Conclusion

Color, elasticity, and perfusion are scar characteristics with a high clinical relevance. Two features, erythema and pigmentation, determine the color of the scar. Erythema is a complex characteristic that may be defined as the level of oxygenated hemoglobin measured at 660 nm. Pigmentation is often referred to as the level of melanin, which can be excessively present (hyperpigmentation) or underrepresented (hypopigmentation). Reflectance spectroscopy is the most widely used measurement technique to assess scar color. Perfusion of vascularization and scar color are often bracketed together but both represent totally different features. The mixture of terms can also be found in literature where vascularization is described as scar color, blood flow, the presence of microvessels, as well as the amount of redness [9, 12, 15, 25]. Conform definitions in several dictionaries and physiology textbooks, we would like to propose that vascularization is defined as the formation of blood vessels and capillaries in living tissue, which reflects a process. The presence of microvessels is a physical result of this process, and blood flow fulfils the functional role of perfusion. Scar redness is likely to be a derivative of all features that is assessed subjectively. For the purpose of clarity, it would be beneficial to provide a detailed description of every feature when assessed in research as well as in clinical practice, as we feel that the various scar features cannot be generalized into the umbrella term "vascularization." The term elasticity is most probably related to the lack of elastin in the dermal layer of scar tissue, but can also be considered as an umbrella term including extensibility, pliability, or suppleness of the scar. The most reliable assessment technique here measures vertical elasticity or extensibility by means of suction.

All tools are able to differentiate between scar tissue and healthy skin; however, this can also easily be determined by subjective evaluation. Objective tools should be able to monitor an individual patient in clinical practice, thereby distinguishing small scar changes. Thus, the measurement error of the tool must be smaller than the desired scar change to be measured. Taking into account reliability, patient friendliness, and feasibility in terms of cost and portability, a recommended panel of devices for the assessment of color, elasticity, and perfusion of scars consists of the DSM III ColorMeter for scar color, the Cutometer for scar elasticity and laser speckle imaging to assess scar perfusion.

Take-Home Messages

- A range of handheld tools is available to objectively assess physical scar parameters.
- When using a tool in clinical practice or for scientific use, take the clinimetric properties into account.
- To monitor scars in an individual patient, it is of paramount importance that the minimally important change (MIC) is smaller than the measurement error of the tool.
- It is showed that erythema and blood flow are not directly related to each other and therefore seem two different scar parameters (i.e., constructs).
- It is essential to provide a precise description of which scar parameter is aimed to assess.
- To assess scar color, the most widely used tool is the DSM III ColorMeter, offering read-out of erythema and melanin index values as well as CIE L∗a∗b values.
- Elasticity can be best measured using the Cutometer, reflecting absolute and relative parameters of which Uf and Ue are recommended.
- To assess scar perfusion, laser Doppler imaging and laser Speckle imaging are available.

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Objective Assessment Techniques: Physiological Parameters in Scar Assessment

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_18

18.1 Background

With advances in medicine, we are able to modulate wound healing and scarring. In order to assess new and often costly treatments, the need for objective scar measurement tools has become increasingly important. A combination of subjective and objective measures should be the aim of every researcher. In daily practice, time is a limiting factor, and the choice for objective measurements should always incorporate feasibility and cost. Objective assessments provide a quantitative measurement of the scar. Quantitative assessment of scars requires devices to measure their physical and physiological properties. These properties include, but are not limited to, the following:

Physical parameters:
- Color
- Thickness
- Elasticity or pliability
- Texture
- Surface
- Tissue anisotropy

Physiological parameters:
- Skin hydration
- Transcutaneous oxygen level
- Tactile sensitivity

In this chapter, an overview of the assessment tools to evaluate physiological scar parameters will be given. Physiological scar parameters are scar characteristics relevant to pathological scarring which cannot be seen with the bare eye. This also means that they can only be assessed with objective assessment tools. This overview lacks skin characteristics which are measured with digital imaging systems. These assessment tools will be discussed in a separate chapter.

18.2 Skin Hydration

Skin hydration is defined as the water content of the epidermis and the dermis. Approximately 20% of water present in our body is accumulated in the skin. Of this amount, 60–70% is located in the dermis, and 15–30% is retained in the stratum corneum (SC). Functionally, the amount of water in the skin can be divided into free and bound water. In healthy skin, most of the water are bound to macromolecules. The ability of the skin to retain water is primarily related to the SC, which plays the role of the outer skin barrier, protecting the skin from water loss. The SC consists of cells called corneocytes and various lipids (fats) between them. The retention of water in the SC is dependent mainly on the presence of natural hygroscopic agents within the corneocytes and the SC intercellular lipids orderly arranged to form a barrier to trans-epidermal water loss [1]. The corneocytes are often compared to bricks and the intercellular lipids to mortar, an appropriate metaphor for a layer of skin that serves as a barrier. The corneocytes are dead cells without nuclei. They contain various substances that hold water. For our skin to feel smooth and supple, the SC has to be at least 10% water; ideally, it is 20–30%. The SC can absorb as much as five to six times its own weight and increase its volume threefold when soaked in water. But it is not simply the water content that matters. Water has an effect on the enzymes that control orderly shedding of corneocytes, a process dermatologists call desquamation. Without water, the corneocytes accumulate, so the skin becomes flaky instead of peeling off nicely, and the SC gets disorganized and full of cracks instead of being tightly packed.

The glycosaminoglycan (GAG) polymer hyaluronan (HA, hyaluronic acid) forms a scaffold on which proteoglycans and matrix proteins are organized. These supramolecular structures are able to entrap water and ions to provide the skin with hydration. HA occurs in both the dermis and epidermis, with the dermis containing the greater proportion. HA present in the epidermis may play a role in a epidermal barrier function and SC hydration [1]. The lack of interaction between water and surrounding molecules contributes to dry appearance of the skin. Water content can vary depending on varying factors as skin site, skin depth, body mass index, age, sex, diurnal hour, seasons, and climates.

18.2.1 Skin Hydration in the Epidermis

The epidermal thickness is variable. It had been reported to be between 40 and 240 μm thick, depending on the measuring area and method used. Water originates in the deeper epidermal layers and moves upward to hydrate cells in the outermost skin layer, the stratum corneum (SC). Aquaporins (AQPs), cell membrane-bound water channels present in the epidermis, are essential hydration-regulating elements controlling cellular water and glycerol transport. Glycerol, thus present in the outer epidermal layers, binds and holds water, important for maintaining optimal skin hydration. The epidermis contains two different levels of water, separated by the interface between the stratum granulosum (SG) and the SC. The largest gradient of water in the epidermis occurs in the underlying layers of the SG (viable epidermis), while the SC water content is 4–5 times lower [2]. This gradient isolates the SC from the body, helping to conserve important solutes and water within the viable epidermis. The presence of a water gradient at

the deeper part of the SC triggers important keratinocyte functions such as the production of natural moisturizing factors (NMF). Dehydration of the upper skin layers increases when the SC water is lost more quickly than that which is received from the lower layers of the skin (viable epidermis and dermis), thus affecting the natural flow of water. Water originates in the deeper epidermal layers and moves upward to hydrate cells in the SC, eventually being lost to evaporation. Then, an evaporation barrier is needed to maintain body water homeostasis. The SC functions as the main evaporation barrier [2, 3].

18.2.2 Dermal Water Content

The dermis is between 1 and 4 mm thick, and it consists mainly of connective tissue. Dermis thickens as it binds more water. In the dermis, the collagen fibers, the interstitial space GAGs, and the proteoglycans can absorb large quantities of water, which leads to youthful skin. With skin fibrosis, the collagen fiber network is stretched by external mechanical forces, reduces its absorption capacity and water retention, and can lead to prolonged inflammation. Dermal hydration is highly related to the content and distribution of GAGs. The GAGs most often present in the human skin are hyaluronic acid (not attached to a protein core) and the proteoglycan family of chondroitin sulfates (GAGs attached to a protein core). GAGs bind up to 1000 times their volume in water [4]. GAGs in photodamaged or scarred skin are abnormally deposited in the papillary dermis, rather than diffusely scattered as in young skin. This aberrant localization interferes with normal water binding by GAGs, despite their increased quantity [4].

18.2.3 How to Measure Skin Hydration?

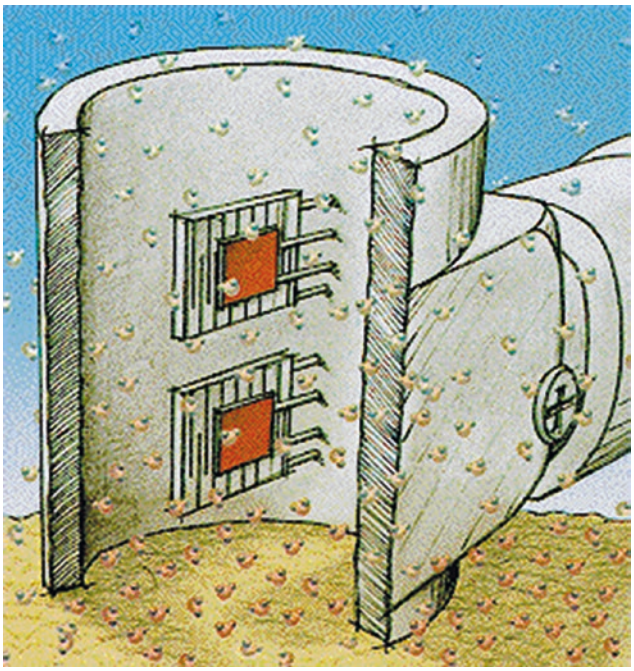
Many approaches exist to measure skin water content. One single method is often not enough to capture all the relevant information. Trans-epidermal water loss, stratum corneum water content, and dermal water content are equally important and related to each other.

The skin acts as a barrier against the water evaporation from the internal tissue. The water content in the skin preserves the softness and the smoothness of the skin surface. Diffusion of condensed water through the stratum corneum (SC) occurs and is highly elevated in pathological situations such as scaring; this can be measured by trans-epidermal water loss (TEWL). The results of these measurements are a good indicator of the recovery of the skin barrier and are a useful indicator of the scar maturation process [5]. TEWL is strongly related with the moisture content of the skin and can be measured with open- or closed-chamber systems [6]. The open chambers are the oldest but still most widely used.

18.2.3.1 Trans-Epidermal Water Loss: Measuring Principle

Trans-epidermal water loss represents the outward permeation of condensed water through the stratum corneum by means of diffusion [7]. TEWL can be measured by using an open-chamber method or closed-chamber method. Open chambers are open to the surrounding atmosphere and are therefore easily influenced by external air convection and turbulence. Closed-chamber methods have been designed more recently, the measuring chamber is enclosed from the surrounding atmosphere, and measurements are therefore not influenced by external air convection and turbulence.

TEWL can be calculated by measuring the water vapor pressure (VP) gradient at the skin surface. In the open-chamber method, the VP gradient is calculated by measuring the difference in VP between two distinct points aligned perpendicularly to the skin surface (see ◘ Fig. 18.1). VP is calculated as the product of relative humidity (RH) and saturated VP; this is dependent on temperature. RH is measured using capacitive sensors; temperature is measured with fast thermistors located in the cylindrical measuring chamber with open ends [7–11].



◘ **Fig. 18.1** TEWL measured by using an open-chamber method. Reused with permission from Courage + Khazaka electronic GmbH.

18.2.3.2 Open-Chamber Method

To date, the open-chamber method is still considered the most reliable method to measure water evaporation in scarred skin. Open-chamber systems measure water evaporation rate based on diffusion principles [9, 11]. The vapor density gradient is measured indirectly by two pairs of sensors (temperature and relative humidity) inside a hollow cylinder [7, 11]. The resulting data are analyzed by a microprocessor. Measurement values are given in g/m^2/h. The physiological water vapor mantle surrounding the human skin is a gradient of water with a thickness of about 10 mm. The two sensors of the evaporimeter probe are typically placed 3 and 6 mm above the skin surface. Open-chamber evaporimeters have limitations in practical use and should ideally be used in a climatized room with control of convection, temperature, and humidity [9, 10]. Used outside a climatized room, special attention should be given to air convection, room temperature, and ambient humidity [9].

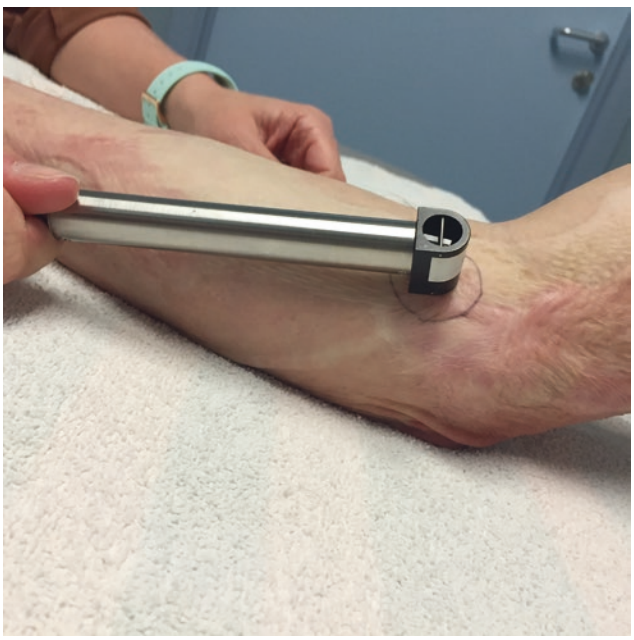
The most widely used systems are the Tewameter® TM300 (Courage+Khazaka, Cologne, Germany) and the DermaLab® (Cortex, Hadsund, Denmark). Both are available as stand-alone devices or as a probe attached to a Multi Probe Adapter System like the Scarbase Duo™ (Courage+Khazaka, Cologne, Germany) and the DermaLab Combo® (Cortex, Hadsund, Denmark).

Both the Tewameter® (◘ Fig. 18.2) and the DermaLab USB® TEWL (◘ Fig. 18.3) showed good to excellent reliability and validity with rather high minimal clinically important difference (MCID) [12, 13]. The MCID is the smallest change in an outcome that a patient or a clinician would identify as important. An overview of the results is set out in ◘ Table 18.1.

18.2.3.3 Semi-Open-Chamber Method

Recordings with open-chamber evaporimeters are not intrusive to the 10 mm physiological water vapor mantle over the skin and due to its specificity sensitive to ambient airflow. Open-chamber instruments perform best under standardized ambient conditions with an air protection shield or box controlling the ambient air conditions, as described in standards [9, 10]. Closed-chamber methods are insensitive to ambient air but, unfortunately, directly intrusive to the water vapor mantle. Accumulation of water vapor in the chamber during the measurement instantly and directly influences the diffusion of water out of the skin. Thus, closed chambers interfere with the physiological skin barrier and thus cannot record physiological TEWL directly. For the same reason, measurements may only be made as an initial estimate and not continuously. In the DermaLab system (Cortex Technology, Hadsund, Denmark), a special grid serving as a semi-open windshield has been incorporated directly in the top of the open probe of this instrument. This grid is open and allows evaporation of water out of the probe chamber and at the same time protects the sensors in the probe against ambient

◘ **Fig. 18.2** The probe of the Tewameter® TM300. Reused with permission from Oscare. © All rights reserved



◘ **Fig. 18.3** DermaLab® USB TEWL-probe. Reused with permission from Oscare. © All rights reserved

Table 18.1 Comparison of reliability, validity, and MCID for trans-epidermal water loss assessment on scars

Device	Intrarater reliability (ICC)	Interrater reliability (ICC)	Validity	MCID
Tewameter® [13]	0.95	0.96	Good correlation with DermaLab® TEWL ($r = 0.93$)[b]	12%
DermaLab® TEWL [12]	0.86–0.88	0.78–0.93	DermaLab® TEWL is able to distinguish normal skin from spontaneously healed scars ($p = 0.036$)	17%

air convections. The system can be considered respectful to the water vapor mantle.

18.2.3.4 Closed-Chamber Method

Two types of closed-chamber methods are available – a condenser chamber method and an unventilated-closed-chamber method. With the unventilated-chamber method, the measuring cylinder is closed off at the top. When placed on the skin, water vapor from the skin collects in the chamber, and with time, the humidity in the chamber increases slowly at first, and thereafter linearly. Flux density (amount of water diffusing through the SC per unit distance and time) is calculated from the change in RH and temperature over time. Due to the accumulation of water vapor and humidity in the chamber, these instruments cannot be used for continuous measurements. Overall, the measurement time of unventilated-closed-chamber instruments is very short (<10 seconds). Various skin barrier impairment studies revealed that the open-chamber devices are more sensitive or discriminative and are able to detect significantly smaller differences than the closed-chamber devices [14]. The VapoMeter (Delfin Technologies Ltd., Kuopio, Finland) is an example of a unventilated-closed-chamber system [15]. The VapoMeter is simple in principle; a humidity sensor in the closed chamber measures the gradual buildup of humidity. On its commercialization, it was postulated that TEWL measurements were not affected by ambient or body-induced airflows.

18.2.3.5 Stratum Corneum Hydration Level: Measuring Principle

Hydration of the skin surface is a good indicator of epidermal function. Hydration is directly proportional to retention of electrical charge and is therefore often measured by dielectric capacitance or the conductance of the superficial skin layers [11]. Technical aspects such as type of probe surface, degree of direct galvanic contact with the skin, distance between the electrodes, and depth of measurement all vary when comparing the different technologies. Due to the higher TEWL, scar sites are dryer than control sites and seem to become dryer as they mature. Water content is very important in the evaluation of biophysical properties of scars. Evidence suggests that a sufficient amount of water in the stratum corneum (SC) keeps the skin soft and flexible and ensures that the skin appears smooth and healthy. The water holding capacity of the SC also influences its barrier function and mechanical properties [16]. Measurements of hydration are often influenced by environmental factors [7].

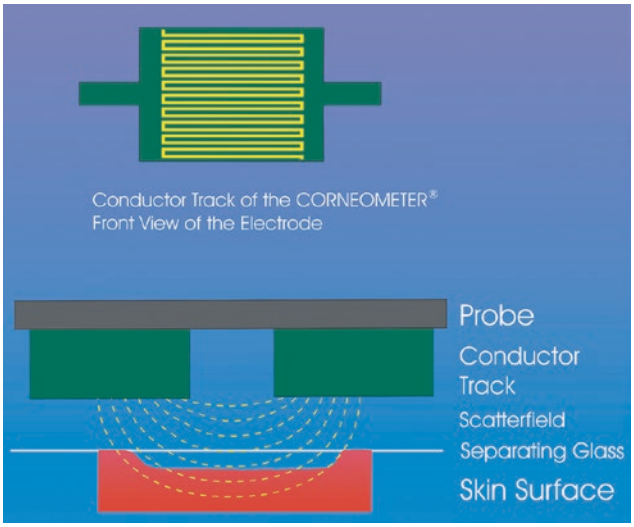


Fig. 18.4 The measurement principle of the Corneometer® CM825 is based on the capacitance method. Reused with permission from Courage + Khazaka electronic GmbH. © All rights reserved

The Corneometer CM 825® (Courage+Khazaka, Cologne, Germany) is based on the capacitance method. It is a well-known and efficient instrument in measuring hydration of the SC. In the past, the measuring probe of the Corneometer used an analog signal, but now, digital technology is used, resulting in higher stability and less interferences [17].

The Skicon instruments (I.B.S. Co., Hamama-T), based on the conductance method, are also widely used. A modern version of the Skicon (Skicon-200EX®) has been developed with a new concentric interdigital probe.

18.2.3.6 Corneometer CM825®

The measuring principle is based on the capacitance method (see Fig. 18.4). Technical description of this type of instrument and its use has been published by

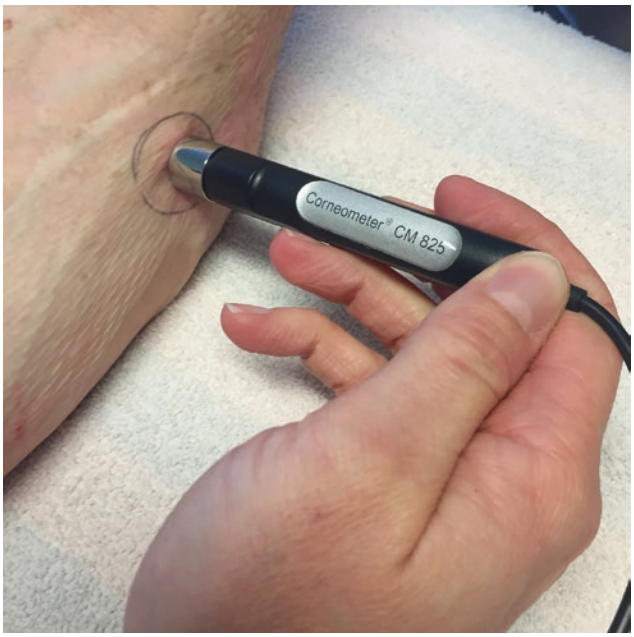


Fig. 18.5 Probe of the Corneometer® CM825 device. (©Oscare)

many authors. Both probes (analog and digital) contain an interdigital grid of gold electrodes, covered by a low dielectric vitrified material (see Fig. 18.5). A resonating system in the instrument detects the frequency shift of the oscillating system related to the capacitance (and hence hydration) of the biomaterial in contact with the probe. Unlike the Skicon instruments, there is no direct galvanic contact between the electrodes of the Corneometer and the skin surface. To enable a constant pressure of the probe on the skin surface, a spring system is incorporated. According to the manufacturer, the pressure of the old analog probe is in the range of 1.1–1.8 N; the new digital probe operates at a lower pressure (about 1 N or less). The Corneometer is factory calibrated using an in vitro method. Corneometer® results obtained with different instruments in different laboratories can be pooled if a pretest validation demonstrates concordance between instrument.

Anthonissen et al. investigated the reliability of the Corneometer and concluded that the instrument can be used in clinical trials but only under very strict conditions with standardized test protocol, preferably in combination with the evaluation of other physiological parameters [18]. The results revealed excellent ICC values (ICCintra = 0.985; ICCinter = 0.984) with relatively low within-subject coefficient of variation (WSCV) (WSCVintra = 6.3%; WSCVinter = 10.6%) for, respectively, intra- and inter-observer reliability. However, the Bland–Altman plot showed that more than 5% of differences were expected to exceed 4 a.u., the limit of what has been defined as a clinically acceptable difference. Results for day-by-day variability showed good ICC value (ICCday-by-day = 0.849) and higher WSCV (WSCVday-by-day = 20.5%).

18.2.3.7 Skicon-200EX

The Skicon instruments manufactured by I.B.S. Co. are based on the conductance principle. These instruments measure the conductance (μS) of a single high-frequency current at 3.5 MHz. The measuring probe consists of 75 μm large concentric interdigital electrodes with a gap of 200 μm between the electrodes. The total probe surface is 0.8 cm^2. The probe makes use of a spring system ensuring a constant pressure force of 0.78 N when applied to the skin. The electrode makes direct galvanic contact with the skin surface. The device is calibrated in vitro using various external calibration standards in the range of 2–2000 μS conductance [19].

18.2.3.8 General Recommendations for Skin Hydration Measurements

The applied probe pressure has a large influence on hydration measurements. Despite the existence of a spring to ensure constant probe pressure, Clarys et al. have demonstrated that the measured hydration levels increase with higher probe pressures. This phenomenon is exacerbated on dryer skin (e.g., scar tissue). It is therefore advisable to use complete compression of the spring when applying the probe on the skin surface. Use a precision balance to practice obtaining more or less identical values. Finally, try to transpose this to the in vivo application of the probe on the skin surface [20].

Digital capacitance probes are very sensitive for evaluating dry/very dry skin conditions (e.g., scars), while digital conductance probes are more suited for evaluating very high levels of hydration [17].

Skin hydration has a positive correlation with ambient temperature and humidity; it is strongly affected by these two environmental parameters [7].

Results of TEWL or skin hydration measurements should be reported as differences or percent change rather than absolute values. This approach partially eliminates influencing factors.

In order to obtain reliable results for skin hydration, it is advisable to minimize, as far as possible, the influences of endogenous, exogenous, environmental, and instrument or measurement-related factors [7].

For the Corneometer®, the MCID is 7% on healthy skin and 4% on scars [18].

18.2.4 Dermal Water Content Measurement

18.2.4.1 Confocal Raman Spectroscopy

Raman spectroscopy is a spectroscopic technique used to observe vibrational, rotational, and other low-frequency modes in a system. Raman spectroscopy is

commonly used in chemistry to provide a structural fingerprint by which molecules can be identified. Confocal Raman spectroscopy can directly measure the water content from the skin surface down to the upper epidermis with high depth resolution (5 μm) [21]. Moreover, it produces a more absolute measurement value than other methods. Using confocal Raman spectroscopy, the water content is calculated from the ratio of integrated Raman signals for water and protein. The proportionality constant is estimated from the Raman spectra of various solutions of proteins in the water. Nakagawa et al. concluded that in vivo measurement of the dermal water content with confocal Raman spectroscopy was highly reliable [22]. The benefit of using confocal Raman spectroscopy is that the depth increment between measurement points can be freely adjusted. The most widely used depth resolution of the confocal Raman spectroscopy is 5 μm. With confocal Raman spectroscopy, the smaller the region of interest, the higher the depth resolution.

18.2.4.2 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a spectroscopic method that uses the near-infrared region of the electromagnetic spectrum (from 780 nm to 2500 nm). NIRS is based on molecular overtone and combination vibrations. One advantage is that NIRS can typically penetrate much further into a sample than mid-infrared radiation. NIRS is not a particularly sensitive technique, but it can be very useful in probing bulk material with little or no sample preparation [23].

The molecular overtone and combination bands seen in the near-IR are typically very broad, leading to complex spectra; it can be difficult to assign specific features to specific chemical components. Multivariate calibration techniques (e.g., principal components analysis, partial least squares, or artificial neural networks) are often employed to extract the desired chemical information. Careful development of a set of calibration samples and application of multivariate calibration techniques is essential for near-infrared analytical methods. NIRS can measure overall skin water content as well as of the various components constituting the skin, i.e., the stratum corneum, epidermis, and dermis. This technique has the ability to directly determine the changes in the various types of water (free, bulk, and protein-bound water), which are present in the various skin layers.

Another interesting advantage is that this technique does not require direct contact with the skin and can easily be integrated in smartphones. This technique also allows to determine the thickness of separate skin layers [24]. However, its lack of sensitivity and frequent integration of algorithms raises doubts about its reliability, which still needs to be investigated in scar tissue.

18.3 Transcutaneous Oxygen Tension

Scar maturation has been related to transcutaneous oxygen tension that can be measured with electrodes on the skin. Heat is induced to the electrode and causes oxygen and CO2 to diffuse through the skin. In hypertrophic scar, PO2 is lower than in healthy skin. An increase over time was correlated with clinical improvement. Upregulated levels of transcutaneous oxygen tension in treated scars correlated well with a downregulation of scar thickness assessed both clinically and by ultrasound. It is hypothesized that low levels of transcutaneous oxygen pressure (tcpO2) in evolving scars result from low oxygen diffusibility through scar tissue rather than from rapid metabolic consumption of oxygen by scar tissue [25].

18.4 Tactile Sensitivity

Tactile sensitivity of the skin can be divided in two parts. Discriminative touch is a sensory modality that allows a subject to sense and localize touch. Non-discriminative touch is a sensory modality that allows the subject to sense that something has touched them, without being able to localize where they were touched. Scars are frequently accompanied with sensory deficits often remaining present months or even years after injury.

Tactile sensitivity of the skin can be measured by esthesiometers. There are different types of esthesiometers depending on their particular function. The simplest is a manual tool with adjustable points similar to a caliper. It can determine how short a distance between two impressions on the skin can be distinguished.

Another type of manual esthesiometer is used to test lower thresholds of touch or pain. The tool uses nylon monofilaments with varying calibrated diameters (see ◘ Fig. 18.6). The force needed to cause the monofilament to "buckle" determines the tactile reading (see ◘ Fig. 18.7). The filaments are calibrated by force applied, rather than by gram/mm^2 pressure ratings because sensation follows force (when the stimulated area is small).

The most commonly used is the Semmes-Weinstein Aesthesiometer and its variant the Weinstein Enhanced Sensory Test (WEST) that determines the touch perception threshold (TPT). Meirte et al. concluded that the Semmes-Weinstein monofilament test is a feasible and reliable outcome measure to evaluate TPT in burn scars, showing excellent intrarater and interrater reliability (ICC >0.90) [26].

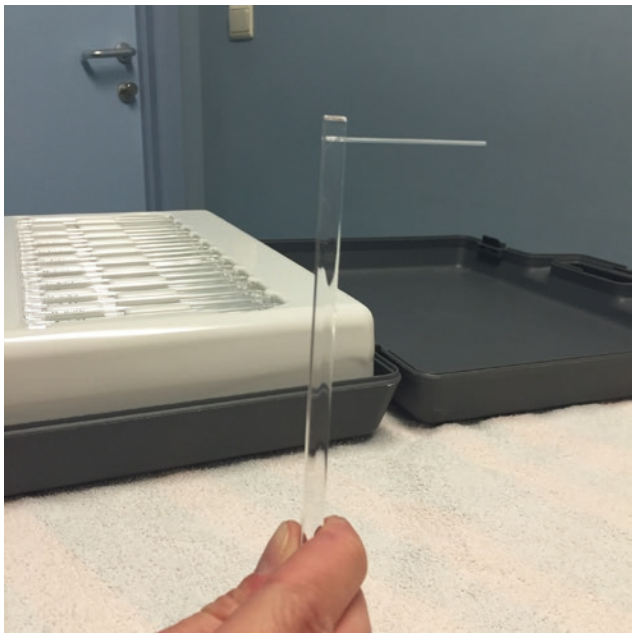


Fig. 18.6 The Semmes-Weinstein Aesthesiometer® uses nylon monofilaments. (©Oscare)

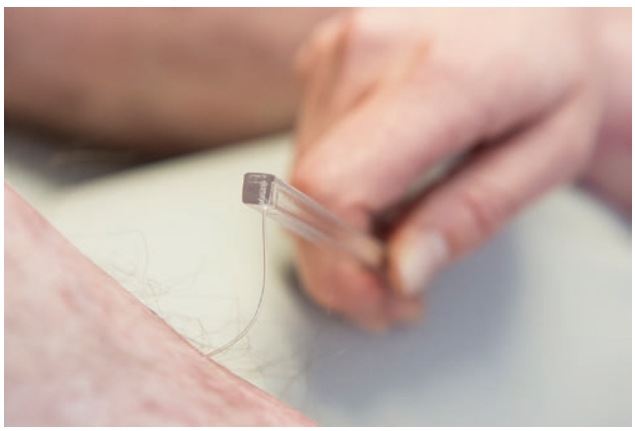


Fig. 18.7 The force needed to cause the monofilament to "buckle" determines the tactile reading. (©Oscare)

18

Take-Home Messages

- The stratum corneum acts as an evaporation barrier to maintain body water homeostasis.
- In the epidermis, water originates from the deeper layers.
- In scars, the absorption capacity and water retention are reduced and may contribute to prolonged inflammation.
- In scars, TEWL is higher than in normal skin.
- One single method to measure skin water content is not enough to capture all the relevant information.
- The open-chamber method is the most widely used to measure TEWL.
- The dielectric capacitance method is the most reliable method to measure SC hydration level in scars.
- Confocal Raman spectroscopy is a reliable technique to measure dermal water content.
- The Semmes-Weinstein Aesthesiometer is a reliable tool to assess tactile sensitivity in scars.

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Structural Assessment of Scars Using Optical Techniques

L. van Haasterecht, Paul P. M. van Zuijlen, and ML. Groot

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_19

19.1 Introduction

The skin, the largest organ of the body, consists of an epidermal layer and a dermal layer underneath. The thin epidermal layer functions as a barrier to the outer world. The dermis is much thicker, and its structural organization is responsible for the functional qualities of the human skin. It consists for almost 80% of collagen, elastin, and different types of cells, which render the skin strong and at the same time remarkably pliable. In scar tissue, visual aspects (discoloration and texture [1]), functional aspects (stiffness [1] and moisture retention [2]), and sensory functions [3] of the skin differ significantly from those of healthy skin.

In clinical practice, objective assessment of cutaneous scars remains a challenging task. The use of scar assessment tools has increased significantly in the last decade. The clinical follow-up of scar treatment necessitates precise measurement of thickness, surface area, and relief. Further, a better visualization of the precise 3D microstructural organization is crucial in understanding the etiology of pathological scarring. As most aspects of clinical scar assessment scales are based on the visual appearance, the potential for optical techniques as an objective assessment tool is high. With a so-called optical biopsy, it is possible to assess the microstructure below the surface of the skin with optical methods, negating invasive physical biopsies. Furthermore, a range of extensions for these techniques allow simultaneous structural, mechanical, and even chemical characterization.

This chapter aims to describe current progress in objective imaging techniques used in the clinical follow-up of scar progression on the one hand and some of the most powerful techniques for basic structural research of scar microstructures on the other hand. For the sake of brevity, we limit our discussion to techniques and devices that have been shown to be valid and reliable. For a complete overview of available devices, we refer the reader to an extensive review by Lee et al. [4].

19.1.1 Volumetric Analyses

The number of devices that measure scar volume has seen a rapid growth in the last decade, partly advanced by increased attention to wound and burn research.

Volumetric aspects of scars discussed here are surface area, thickness, and surface topology. Although there exists significant overlap between these aspects and some devices measure multiple aspects (surface roughness can be considered as fluctuations in scar height/thickness; newer analysis methods of surface area are often intrinsically three dimensional and therefore include information on surface topology), we discuss them separately as the reliability (the consistency of the measurements) and validity (whether the device measures what it intends to measure) of individual aspects of a device aren't necessarily similar.

Volumetric assessment has gone from manual paper tracing to high-tech 3D cameras.

Although manual tracing of scar surface area is reliable in the case of linear postoperative scars [5], for scars with irregular boundaries, the reliability decreases with scar size [6]. The LifeViz 3D camera (Quantificare SA, Valbonne, France) has been extensively tested in both the surface area and volumetric analysis mode by Stekelenburg et al., who reported it to be a reliable and valid tool [7, 8]. The LifeViz 3D works by comparing two photos from different angles, from a predefined distance. The Vectra 3D is a speckle pattern-based system that utilizes six cameras to construct a 3D image. Its interrater reliability was found to be excellent in a trial on raised scars [9]. A device with a similar working mechanism, MAVIS III (Photometrix, Pontypridd, United Kingdom), was assessed in a study on burn scars. The authors note that poorly delineated scars on curved surfaces pose a challenge in the boundary selection and subsequent analysis [10].

Rashaan et al. tested another stereophotogrammetry device, the Artec MHT (Artec 3D, San Diego, CA, USA), and found it to be highly reliable and valid in burn scars [11].

Other strategies that include laser scanning cameras and structured light scanners need additional clinical evaluation.

19.1.2 Surface Topology

Roughness, or surface irregularity, has a significant impact on a patient's perception of scars [12]. Furthermore, the predictive validity of long-term scar quality was found to be significantly influenced by the "relief" item on the POSAS observer scale [13] (see ▶ Chap. 16 for more on scar assessment scales). Most scar assessment scales include such a texture item, and even though subjective analysis isn't necessarily inferior to objective analysis, quantification of these aspect remains challenging.

Early attempts at quantitative evaluation of roughness entailed the casting of a positive or negative mold of the scar surface and its subsequent optical or mechanical analysis [14]. This process, although accurate, is overly cumbersome and time-consuming. Current contactless techniques use a combination of illumination and analysis of disturbance patterns. The most frequently used device, the Phaseshift Rapid In Vivo Measurement of the Skin (PRIMOS, Canfield Scienitifc, Inc., Parsippany, USA), has been shown to reliably mea-

sure scar topology [15, 16]. PRIMOS projects patterns of light onto the skin surface. Fluctuations in the surface profile cause disruptions in these patterns that are subsequently analyzed.

Antera 3D (Miravex, Dublin, Ireland) is based on photometric stereo, in which light from different angles produces shade based on surface topology. The reflected light is analyzed to form a surface reconstruction. Similarly, LifeViz Micro (Quantificare SA, Valbonne, France) is one of the devices in the LifeViz series mentioned earlier. Although they have been described in the context of clinical scar assessment [17, 18], their clinimetric properties have not been analyzed for the surface roughness aspect.

The Visioscan VC 98 uses software analysis of gray-scale values in UVA-illuminated photographs (Visioscan VC 98). Reliability in healthy skin relies heavily on the chosen outcome measure of the "surface evaluation of living skin" method [16].

The analysis of relief can be considered a structural analysis of scar volume. Indeed, most devices offer some volumetric analysis. Furthermore, the Antera 3D offers additional colorimetric analysis. The abovementioned devices show great heterogeneity in measured parameters, resolution, and field of view, and thus, it is difficult to make a qualitative comparison. In the future, further cross-pollination between techniques can be expected. Askaruly et al. showed the potential of optical coherence tomography (OCT) to measure relief [19]. Although their study was not on scar tissue, the possibility of combining 3D surface analysis with structural analysis looks promising.

19.1.3 Thickness

Follow-up of scar thickness is especially important in both hypertrophic and keloid scars, where the aberrant deposition of ECM proteins leads to significant expansion. Therapies are mostly focused on reducing the scar's prominence over the surrounding tissue, and correctly analyzing the thickness of cutaneous scar is paramount.

Although not an optical technique, we discuss high-frequency ultrasound here as it's by far the most commonly used technique. Its inferior resolution compared to optical equivalents is mitigated by its superior penetration depth allowing thickness analysis, even in severe scar thickening. The working mechanism is based on reflection of sound waves of structures with different acoustic impedances and the analysis of the reflection time to determine the depth of the structure. The penetration depth ranges from the upper dermal layers to full-thickness skin and subcutaneous structures, depending on the employed frequency.

Numerous ultrasound systems exist that are marketed for dermatological applications; we succinctly limit our discussion to systems that have been applied to scars. The frequency used by these systems ranges from 5 to 50 MHz and forms the most important limitation in scars, as this limits the penetration depth. For example, the most frequently described device, the Dermascan C (Cortex Technology ApS), utilizes a frequency of 20 MHz which has a penetration depth described as inadequate in up to a third of burn scars in a study by Gankande et al. [20] (using the DermaLab Combo).

Reliability of these instruments has been tested in several studies and shows excellent inter-observer [20–23] and intra-observer reliability [20, 21, 23–25].

From a validity standpoint, it is of interest to note that a golden standard does not currently exist. Comparison with scar assessment scales has yielded inconsistent results, possibly due to heterogeneity in scar scales and ultrasound frequency [23, 26]. Histology has several drawbacks that include deformation during the biopsy process dependent on resting skin tension, manipulation during fixation, and slicing [27]. Agabalyan et al. found poor correlation between 20Mhz ultrasound analysis and histological analysis of skin graft scars in a small group of patients [26]. Andrew et al. found biopsies to be significantly thicker after excision, advising the use of pinning during formaldehyde fixation to mitigate this effect [27]. Li et al. compared ultrasound measurements with the use of a micrometer [24], theoretically bypassing the negative effects of sample preparation for histology. Although they achieve a high correlation, sonographic analysis was performed on porcine excised tissue in which it is conceivably easier to recognize the skin's boundaries.

Scar height can be measured using volumetric analyses like the 3D camera LifeViz 3D (Quantificare SA, Valbonne, France), although studies comparing this device with ultrasound measurements have favored the latter [23, 28]. It seems that the reliability is suboptimal due to the device having difficulty scanning over curved surfaces.

19.2 Experimental Techniques

Scarring involves the aberrant deposition of matrix molecules. The collagen content of scars, especially, differs from healthy skin in terms of amount, type, and, importantly, organization. In the past decades, quantification of the extracellular matrix (ECM) organization was mostly limited to two-dimensional images from fixated and stained tissue. Depending on the orientation of histological slices relative to the skin surface, analysis of orientation will yield different results. For example, Verhaegen et al. found significantly different supramolecular organization depending on which cross section was imaged (e.g., perpendicular to the surface or in the

parallel plain) [29]. Gaining a better three-dimensional perspective of ECM organization is paramount in elucidating the etiology of pathological scars.

As the goal is not only to assess scar tissue based on texture, volume, and color but also to perform microstructural analysis, more advanced microscopic tools are required. An ideal optical scar assessment technique would have a resolution with which microstructural changes can be clearly identified, even in the deeper parts of the dermis. However, in optics, there exists a common trade-off between spatial resolution and penetration depth, and the marked thickening of hypertrophic and keloids scar complicates this trade-off. In this sense, a "perfect technique" does not exist. A technique's suitability depends merely on whether the application matches its strength. In the following, we will discuss several microscopic techniques and their applications in scar assessment and research.

19.2.1 Optical Coherence Tomography

Colloquially known as "Ultrasound based on light," OCT is a promising technique based on low-coherence interferometry. In short, light with a broad bandwidth is split into a sample arm and a reference arm. The interference pattern that arises from the combination of the reference arm and the sample arm, containing reflected light from different depth layers of the sample, creates a depth profile of the sample. Combining a lateral series of these profiles creates a cross-sectional image (B scan) or a three-dimensional reconstruction when a stack of B scans is combined. Scanning approaches with full-field illumination allow the acquisition of stacks of "en face" scans. Typically, penetration depths of 1–2 mm can be reached, at a resolution of 4–10 μm [30].

The capability of OCT to create high-resolution tomography first piqued the interest of the ophthalmological community, where it is now a staple technique in retinal assessment. Naturally, attributes like fast acquisition time, high-resolution images, noninvasiveness, and multifaceted structural assessment make OCT an interesting technique for dermatology. Moreover, OCT devices are often manageable handheld scanners, increasing their usability in the clinic.

Polarization-sensitive OCT (PS-OCT) has been described as a quantification tool for collagen density and alignment by means of tissue birefringence [31]. Jaspers et al. compared burn scars and healthy skin using a volume-based birefringence method, which showed strong correlation to histologically determined collagen content [32]. By applying speckle decorrelation, Liew et al. visualized the microvasculature of burn scars in three dimensions [33]. A similar strategy was used in the clinical follow-up of burn scars undergoing laser ablation [34], allowing the authors to distinguish mature and immature scars [35]. Comparable strategies have been applied to lymph vessels [36]. Combined vascularity, lymph vessels, and birefringence analyses were used by Park et al. to longitudinally follow wound healing in a mouse model, showing angiogenetic changes and realignment of birefringent signals [37].

Simultaneous mechanical testing allows the correlation of local structural changes to variations in stiffness. Es'haghian et al. showed that combining a handheld OCT probe with a mechanical loading device permits concurrent imaging of the in vivo scars and stiffness mapping [38, 39]. Vibrational perturbation of the skin and the analysis of resonance frequencies while imaging the layers of the skin have also received some attention recently for bulk measurements of mechanical properties [40, 41].

OCT has been described as a tool for measuring thickness of individual skin layers. Because the limited penetration depth makes full thickness imaging impossible, its application is limited to the epidermal thickness [42, 43].

19.2.2 Confocal Microscopy

Higher-resolution images to assess structures with submicron resolution in 3D can be obtained using various microscopic techniques. In confocal fluorescence microscopy, the addition of a set of pinholes to a traditional fluorescence microscope allows for the selection and detection of a small focal volume. Selective labeling with a fluorophore allows for the imaging of a particular substance of interest by excitation of the fluorophore by a lamp or laser and detection of the fluorescence emission signals. Images are obtained by scanning the laser or the sample, yielding images with a resolution of $0.4\,\lambda/NA$ where λ is the wavelenght of the emitted light and NA is the numerical aperture of the objective, which is an improvement of ~30% compared to traditional fluorescence microscopy. Another advantage over widefield microscopy is that the labeling with fluorophores can be sparser, allowing for a fairer comparison of relative quantities of structures.

Confocal microscopy has been used to determine the ratios of collagen of different scar types [44], cell-signaling molecules [45] or innervation [46] of different scar types and as an ex vivo tool in evaluation of microneedling penetration depth [47]. Furthermore, the superior resolution allows for quantitative collagen orientation analysis [29, 48]. Devices like the VivaScope (MAVIG, Munich, Germany) [49] are based on reflectance confocal microscopy (RCM), in which backscattered light from unlabeled structures is analyzed, based on changes in refractive index. The in vivo applications of RCM lie predominantly in the diagnosis of various

skin cancers [50], as its penetration depth is limited to the epidermis and upper part of the dermis. However, attempts to analyze collagen production after microneedling of acne scars have been described in vivo with a combination of dermoscopy and RCM [51]. The limited penetration depth seems a significant hurdle in scar research; however, combining the device with an OCT arm allowed Iftimia et al. to analyze both structural and birefringence properties in burn scars [52].

19.2.3 Nonlinear Optical Microscopy

19.2.3.1 Introduction

As discussed above, confocal microscopy allows for three-dimensional imaging; however in this technique, samples require specific staining and sometimes also fixation and slicing, which may affect ECM structure and organization. Nonlinear optical (NLO) microscopy involves label-free imaging of unfixed tissue in three dimensions and has strong potential in the visualization of the scar microstructure. Here, we discuss several types of NLO microscopy, namely, higher harmonic generation microscopy (HHG) and multiphoton excited autofluorescence (MEA), and explain their strengths in label-free imaging of scars.

Nonlinear microscopy can be described as the conversion of multiple photons into a single photon, based on the specific nonlinear behavior of certain molecules or structures. This process occurs only when the intensity of the incident light is sufficiently high. To keep the average laser power on the sample sufficiently low, short-pulsed lasers are used (generally femtosecond lasers) [53].

MEA involves the absorption of two or more photons by an intrinsic fluorophore and the recording of the subsequent fluorescence emission, which is then at a wavelength shorter than of the excitation light. Alternatively, external fluorophores can be applied to the sample to label specific structures. In contrast to single-photon fluorescence, excitation wavelengths typically lie in the infrared region, allowing deeper tissue penetration of up to 1.6 mm [54].

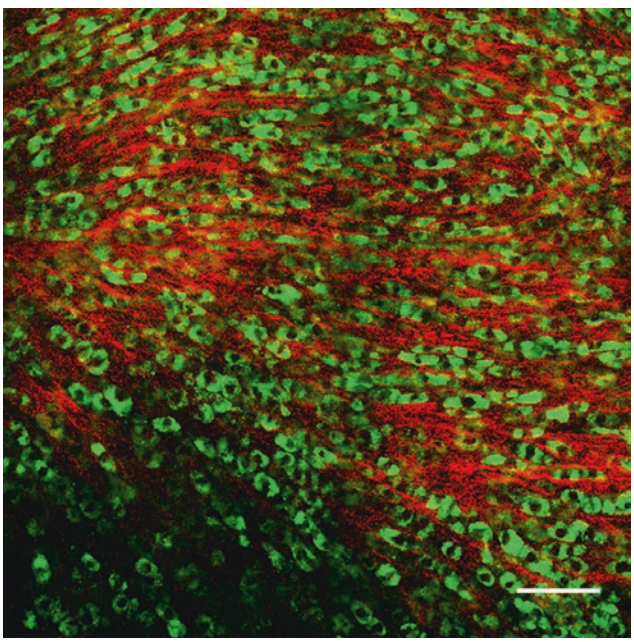
Comparably, in the HHG processes, two or three photons are converted into a single photon. No energy transfer takes place however, and the emitted photons have exactly half (second harmonic generation, SHG) or a third (third harmonic generation, THG) of the wavelength of the incident photons and exactly double or triple the energy, respectively. This allows the detection of the specific signal using narrow-banded filters, improving contrast between structures. Simultaneous registration of these signals using one system allows for label-free visualization of the most important structural proteins of the ECM.

19.2.3.2 Two-Photon Excited Autofluorescence (2PEF)

MEP involves two or three photons being absorbed by a fluorophore and the subsequent emission of a single photon of a shorter wavelength. Two-photon excited autofluorescence (2PEF) has been described extensively in skin research.

2PEF is applicable to fluorophores used in single-photon fluorescence. As this is a fundamentally different process, excitation wavelengths will not equate to exactly double the wavelength of the single-photon excitation. The emission spectrum however will be identical. Fluorophores naturally present in biological tissue have well-described excitation and emission spectra, and extrapolation to the two-photon excitation wavelength is usually warranted. Although penetration depths more than one millimeter have been described in the context of brain tissue [54], the density of the skin and the relevant excitation wavelengths do not permit such deep penetration. Imaging systems are conventionally limited to several hundred micrometers in depth.

Both collagen and elastin, the most important structural proteins of the extracellular matrix (ECM), have convenient 2PEF profiles [55]. On the cellular level, the abundantly present cytoplasmic metabolites NADH and FAD are prolific emitters in their reduced and oxidized states, respectively. An example of 2PEF imaging of dermal fibroblasts can be seen in ◘ Fig. 19.1.



◘ **Fig. 19.1** Combined two-photon excited fluorescence image (2PEF, green) and second harmonic generation image (SHG, red) of cultured human dermal cells and their derived collagen matrix, respectively. Collagen fibers induce a bright SHG signal, whereas intrinsic fluorophores in the cytoplasm of the dermal cells outline the cells. In vitro images were acquired using a previously described setup [87]. Scale bar: 500 μm

Simultaneous recording allows a redox ratio to be calculated. The feasibility of this strategy was shown in an in vivo mouse model by Quinn et al. [56], visualizing metabolic changes during wound healing. Another in vivo study used the same concept to investigate the depth-dependent metabolism of keratinocytes [57]. Melanin content has been used as an in vivo marker for several dermatological disorders [58].

19.2.3.3 Second Harmonic Generation (SHG) Microscopy

The introduction of SHG microscopy has sparked a slew of research in dermatology. Also known as frequency doubling, it involves the interaction of two photons of the same wavelength with a nonlinear material and the subsequent creation of a single photon with double the frequency and energy. The ability of a material for second harmonic generation, described by the nonlinear susceptibility coefficient $\chi(2)$, depends on the non-centrosymmetric structure. Biologically significant harmonophores include collagen [59], myosin [60], and microtubules [61].

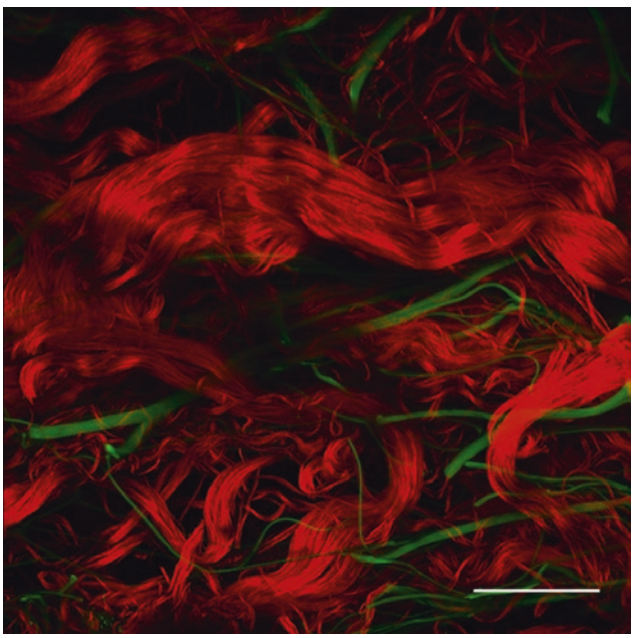
In the case of fibrillar collagen, the repeating dipoles of peptide bonds and the structural alignment on all levels of the molecular and supramolecular structure (parallel peptide bonds are assembled into parallel fibrils; fibrils are aligned into fibers) result in coherent amplification of the emitted second harmonic signal refs. This also means that the structural alignment of collagen fibers influences the SHG signal intensity [62]. As this is not the case for non-fibrillar collagen types, SHG microscopy is specific for type I and II collagens and forms a highly specific tool for 3D imaging of unprocessed skin samples as showed in ◘ Fig. 19.2 Abnormal ratios of collagen I:III have been described in multiple fibrotic processes [63]. Although collagen type III, often deposited alongside type I, is a fibrillar collagen, it produces only weak SHG signals [64]. As the SHG signal is dependent on phase-matching conditions, most of the signal forwardly propagated. The thin scattered fibers of collagen type III and their associated reduction in phase matching appear to be distinguishable from type I by comparing forward- and backward-scattered SHG images [65, 66]. The opacity of collagenous tissues however makes the detection of this signal impractical, rendering this technique possible only in thin specimens.

Multiple strategies to distinguish scar types using SHG images have been described. Most of these focus on software-based analysis of collagen fiber orientation and density [67–69]. Matrix organization and orientation have been described as abnormal in scars [29]. Non-software-based approaches rely on the dependence of the nonlinear susceptibility of collagen on the polarization of the incident light. Polarization-sensitive SHG (PS-SHG) probes the organization of collagen fibers by sequentially rotating the polarization relative to the optical axis and probing the SHG response. By analyzing the SHG intensity at different angles of polarization, orientation vectors can be reconstructed [70, 71]. Note that because of the strong dependence of SHG on polarization, software-based analyses should be performed on images from circularly polarized light sources.

Using unstained tissue allows simultaneous biomechanical testing during imaging. For example, Rosin et al. assessed the scarring capacity of healing split-thickness skin grafts by microstructural SHG imaging of collagen and biaxial stretch testing [72]. The authors correlate the loss of waviness patterns to increased stiffness.

The reduced phototoxicity (as no external fluorophores are used) from these optical processes allows in vitro and even in vivo imaging, for example, skin equivalents [73], lab-grown wound models [74], and antifibrotic treatments [75].

Several research groups have made attempts to include SHG in clinical decision-making. Predominately applied to neoplastic lesions, consecutive follow-up of



◘ **Fig. 19.2** Combined 2PEF (green) and SHG (red) image of elastin and collagen fibers, respectively. Unprocessed ex vivo human skin, specifically the reticular dermis, was imaged using the setup described in [87]. A stack of 35 images was acquired in the Z-axis. Image processing in ImageJ resulted in the 3D projection seen here [88]. Scale bar: 500 μm

scars and topical therapies has also been described. Commercial translation has already resulted in multiple devices marketed for in vivo dermatological applications. The Dermaspect (JenLab GmbH, Berlin, Germany) device entails a multimodal (2PEF, CARS, SHG) microscope with an adjustable scan head for in vivo skin imaging [76]. Innovations in laser technology allow for increasingly smaller and cheaper devices [77, 78].

19.2.3.4 Third Harmonic Generation (THG) Microscopy

The propensity of a material for third harmonic generation depends not only on its nonlinear susceptibility coefficient $\chi(3)$ but also on whether partial phase matching can be achieved by a small inhomogeneity at the focus, making THG an interface-sensitive technique [79]. THG is less specific than SHG, increasing the number of possible applications. By setting the focal volume of the incident laser beam to several times the size of a typical tissue structure, a geometry can be created where the phase-matching conditions enable efficient THG. As the THG contrast comes from inhomogeneities and tissue interfaces with a high $\chi(3)$, cell membranes and cell nuclei are clearly displayed with THG microscopy, since they contain lipids which are known to have a high $\chi(3)$ [80]. Not surprisingly, the multilayered structure of the epidermis provides excellent contrast. ◘ Figure 19.3 shows a THG cross section of the epidermis in a drug penetration experiment. To illustrate the potential in dermatology, THG was shown to be a viable imaging technique for label-free tracking of melanoma cells [81]. The THG contrast from melanin and structural features allowed differentiation of skin cancers [82].

In the context of scar tissue, the surface of elastin fibers is an adequate THG emitter [83]; thus, combining SHG and THG potentially allows for three-dimensional imaging of unstained, unfixed, and unsliced tissue.

Although an analysis of scar tissue has not been described yet, THG has strong potential as a label-free imaging technique because of reduced phototoxicity. Indeed, several articles describe the in vivo "optical biopsy" technique in the skin [78, 84].

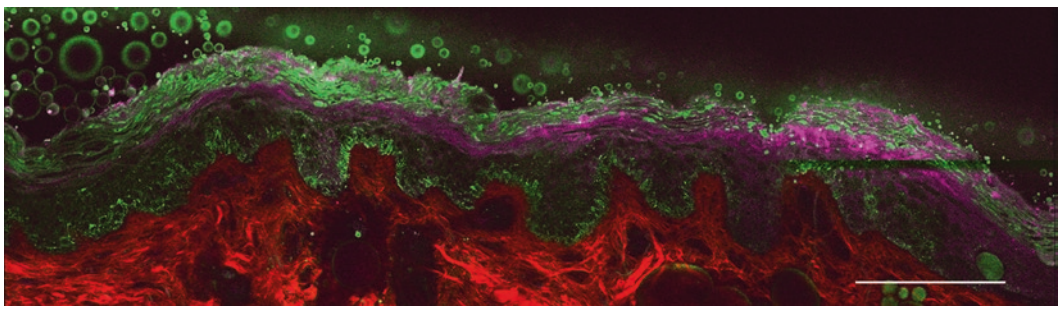
19.2.3.5 Coherent Anti-Stokes Raman Spectroscopy (CARS)

The structural information provided by SHG and THG can be supplemented by chemical information using another nonlinear process, Coherent anti-Stokes Raman Spectroscopy (CARS). Here, two lasers with different frequencies are focused on the sample, to probe the vibrational fingerprint of the molecules in the focal point. The CH2 content of lipids provides excellent contrast when imaging phospholipid-rich cell membranes and adipocytes. The OH signal from water molecules makes this technique especially applicable for research into transepidermal water loss [76, 85].

19.3 Future Perspectives

The enormous increase in available devices for volumetric analysis is indicative for the increased attention for quantification tools in scar research. Technological advances and the need for point of care solutions have already resulted in smaller and manageable devices suitable for bedside use. This trend can be expected to continue with smartphone-based solutions already being investigated in wound evaluation [86]. Both researcher and clinicians should however be mindful of the fact that most devices are not adequately tested on their clinimetric properties.

This trend is also applicable to experimental techniques. As image acquisition times decrease and devices get smaller, we can expect integration of different imaging techniques, each bringing their own strengths in elucidating the multifaceted issue of pathological scarring.



◘ **Fig. 19.3** Nonlinear microscopy image of a cross section of ex vivo skin. The THG signal (green) depicts the layers of the epidermis; collagen fibers in the papillary dermis give rise to the SHG signal in red. In this experiment, fluorescently labeled (magenta) hyaluronic acid (250 kDa) was applied to the skin's surface to quantify epidermal skin penetration. Scale bar: 500 μm

Take Home Messages

- Technological advances will increase the number of devices for scar assessment, while reducing their size.
- The integration of multiple techniques has the potential to improve scar assessment.
- For most devices, the clinimetric properties are insufficiently determined.
- SHG microscopy is a valuable tool for experimental research into scar pathophysiology and potential therapeutics.

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Ethical Considerations: Scar Management

Clarisse Ganier and Sonia Gaucher

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_20

The purpose of this chapter is to provide an overview and potential answers to the ethical considerations of the clinical management of patient scars. We will focus on two main aspects of this subject:

1. Is there truly a need to invoke ethics when the clinician is faced with managing a patient's scar?
2. What are the dilemmas that a clinician will confront in their daily practice when managing a patient's scar?

20.1 Is there Truly a Need to Invoke Ethics When the Clinician Is Faced with Managing a Patient's Scar?

The motivation for the clinical management of a patient's scar from both the patient's perspective and the clinician's perspective is clear: first, to improve the appearance of the scar and, second, if needed, to improve any functional impairment that the scar may have caused. If successful, these goals will enhance the beauty and function of the patient's skin and improve the patient's quality of life. Therefore, like all therapies or procedures in medicine, the ethical considerations of scar management are based upon balancing the risks and benefits of any treatment.

There are multiple causes of scars – scars generated by unintended accidents, iatrogenic scars from surgical procedures, and even self-inflected voluntary scars created by the patient. The constant among these, regardless of the reason(s) of the scar, is that the skin has been injured and has undergone the known phases of wound healing – clotting with platelet aggregation and activation, inflammation, reepithelialization, fibroplasia, neovascularization, granulation tissue formation, and then a long period of tissue remodeling with fibrosis and scarring. The scar is actually a witness to these events of "reparative" wound healing, rather than "regenerative" non-scarring wound healing that is seen in newts and lower animals.

Each cultural group has its own concept of beauty and of what it considers to be normal or aberrant. Moreover, the judgment of what is normal or not may be interpreted differently, not only by the society but also by the individuals. That is why when a patient bears a scar, it may take on different meanings, depending upon the societal and individual context of the scar.

Sometimes, a skin scar can carry a highly positive message. For example, the scar could be proudly exhibited as a testimony of some glorious actions such as the mark of a successful warrior exploit or survival from a savage assault. A voluntarily induced scar could also represent a ritualistic marking that symbolizes both social allegiance and beauty. Examples include scarifications and tattoos.

Conversely, a skin scar could represent an echo of an emotional scar. In these situations, the meaning of the scar is well beyond a simple previous threat to the integrity of the body envelope. Rather, the scar becomes a permanent remembrance a traumatic event. The scar may represent and even support the revival of the patient's spirit after a painful traumatic episode. The possibility of recognizing an aesthetic prejudice, which could be temporary and/or permanent, in the context of a judicial expertise, testifies to this aspect.

On the other hand, for patients whom are strictly compliant to societal standards and societal points of view of beauty, a scar in a visible location on the patient's body may cause loss of self-esteem and self-confidence, regardless of its origin.

Another potential context of scar management would be a patient who generates and accumulates self-inflicted scars and psychologically believes that the healed scars form sort of protective bandage.

Therefore, there is no single approach to the management of these various complex situations, except for the underlying understanding that patients who are scarred require attention, and a physician who listens to them assesses the proper context of the scar and considers carefully what the patient desires.

20.2 What Are the Dilemmas that a Clinician Will Confront in Their Daily Practice When Managing a Patient's Scar?

At the same time, the surgeon may be pleased to observe a minimal scar as the result from his/her surgical procedure and may be faced with the disappointed patient who wants the scar to disappear completely.

In many cases – and especially after surgery – scars can make the physician feels uncomfortable, because the scar is an obvious evidence of the physician's work and reminds the physician of his or her limitations and shortcomings. Totally scarless surgery is not possible. Beyond the disease that the patient would like to forget and beyond the pain and suffering that the patient went through, the physician needs to understand the disappointment and distress of the patient when he/she learns that the scar is permanent and cannot be erased.

Experience has taught us that objective criteria (surface area, surface texture, color, thickness, degree of fibrosis etc.) are not always sufficient to assess adequately a scar and its functional and psychological repercussions. A too fast clinical examination and judgment may lead to the conclusion that the patient's request for scar revision is superfluous, unnecessary, or even unreasonable. To avoid misunderstanding of the patient's feeling and desire for scar revision, the physician must look beyond the simple appearance of the scar and has to harken back to the patient's own history including his or her trauma

and the context of the scar. A large discrepancy between the perspective of the patient and the perspective of the physician might be an early indication of psychological difficulties and a call for further clinical attention [1].

When the patient adamantly demands scar revision by surgical intervention, it often comes from the patient's point of view (and/or experience) that less invasive solutions (topical steroids, silicone membranes, laser treatment, etc.) are not satisfactory.

The origin of surgical ethics is uncertain [2, 3]. Reviews and studies on skin scar ethics are scarce [4]. Most of the articles involve issues related to the ethics of burn scars [5], the ethics in plastic surgery [6], or the ethics in major surgery [7]. Nevertheless, some reviews highlight the current problems associated with emerging approaches for scar management such as the use of fetal cells in skin regeneration [8].

According to Miles Little publications [9, 10], surgical ethics have generally been framed as general medical ethics applied to surgical situations. There are five categories of experience and relationship, which are especially important in surgery field. These include (i) rescue, (ii) proximity, (iii) ordeal, (iv) aftermath, and (v) presence. The sense of rescue and of relational proximity, the ordeal, and aftermath of surgery are things that the patient experiences. Understanding these feelings allow surgeons to know what may be asked of them in an ethical point of view. Recognition of the reality and validity of each category in the surgical process highlights the importance of presence that is the acts by which the surgeon demonstrates that he is present to the patient throughout the surgical process and its consequences. While communication skill trainings may never completely compensate for insensitivity, the ideal of presence as a virtue and as a duty can be taught by precept and by mentors.

As Albert Einstein said "If you always do what you always did, you will always get what you always got." Because each scar, each patient, and each context are unique, the search for an adequate and appropriate surgical solution constantly forces us to innovate. Innovation in surgery has contributed to progress in medicine and has enhanced the overall patient's quality of life. Nevertheless, surgical innovation itself also raises numerous ethical issues, such as patient safety, informed consent, the proper use of healthcare resources, and conflicts of interest – especially in the case of developing new devices by an industry-physician partnership. None of these challenges are specific to surgery field, nor to scars, but there are features about surgery and scars that complicates the identification and resolution of these issues [11, 12]. Therefore, it is important, from an ethical point of view, to consider that innovation is not only the key to progress but also the greatest challenge to our professionalism [13].

Take Home Message

Given that scar treatment needs to balance risks and benefits for the patient, it's impossible to define a skin scar by its physical appearance only.

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Treatment of Immature Scars: Evidence-Based Considerations

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Ideal Wound Closure Methods for Minimizing Scarring After Surgery

Rei Ogawa

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_21

21.1 Background

The healing of open cutaneous wounds involves the generation of vascularized granulation tissue that closes the gap in the skin. Thereafter, an effective epidermal barrier is created over the granulation tissue. Wounds in which sutures have approximated the edges also undergo granulation, albeit less than in open wounds that must heal by secondary intention. In both cases, the adherence of the wound edges becomes stronger over time: in general, wounded skin acquires 80% of the dermal strength of the surrounding normal skin by 3 months post-wounding [1].

21.2 Cutaneous Wound Healing and Mechanobiology

These wound-healing phenomena are the result of a cascade of complex biochemical events that can be categorized into four general overlapping phases: coagulation, inflammation, proliferation, and remodeling. Significantly, all four phases of wound healing are influenced by both intrinsic and extrinsic mechanical forces. For example, the formation of granulation tissue in the proliferating phase is driven by intrinsic and extrinsic mechanical stimulation of the fibroblasts, myofibroblasts, endothelial cells, and epithelial cells that are in and near the wound. Similarly, myofibroblasts contract the wound in the proliferative phase by mechanical forces that are themselves shaped by many extrinsic forces, including the natural tension in the skin. The remodeling phase can also be influenced by extrinsic mechanical forces [2]. During this phase, fibroblasts secrete collagen and fibronectin, which are key components of the extracellular matrix (ECM). These cells then regulate the volume of the ECM by secreting collagenase. This repeated synthesis and enzymatic breakdown of ECM proteins remodels the three-dimensional structure of the ECM. For proper remodeling, the synthesis and degradation processes must be carefully balanced: if there is too much ECM synthesis, scars can become hypertrophic. Conversely, if there is excessive ECM degradation, the scar can become atrophic. Multiple lines of evidence show that this ECM remodeling process can become deranged by extrinsic forces on the ECM [3]. For example, wounds on the major joints tend to develop hypertrophic scars because the joint movements place strong cyclical tension on the wound. This tension provokes chronic inflammation of the dermis, namely, the unceasing influx and activation of inflammatory cells, the persistent generation of blood vessels and nerve fibers, and the constant production of collagen by the activated fibroblasts. This chronic inflammation blocks the conversion of the granulation tissue into dermis-like tissue by the remodeling process and results in an immature hypertrophic scar that is red, elevated, hard, and painful.

These observations suggest that, to prevent pathological scarring after surgery, it is necessary to ensure that the sutures cause the wound edges to adhere to each other without any tension, even when strong extrinsic forces are placed on the wound. This will allow the granulation tissue to convert smoothly into dermis-like tissue, thereby yielding minimal scarring.

21.3 Surgical Techniques that Can Minimize Dermal Tension

The risk of pathological scarring can be greatly reduced by using subcutaneous/fascial tensile reduction sutures [4]. This is because dermal sutures do not effectively reduce tension on the dermis: rather, to achieve this, we must access much deeper structures, namely, the superficial and deep fascia, and suture them. This type of suturing will elevate the wound edges smoothly while placing minimal tension on the dermis. In other words, it will cause the wound edges to attach naturally to each. Only then should dermal and superficial sutures be used. It is very important to realize that dermal sutures on their own cannot reduce the tension on the dermis: this concept is the key to preventing the formation of pathological scars after surgery.

Thus, in the case of benign tumor excision or scar revision surgery in high-tension areas such as the chest wall, the cutaneous mass should be completely excised along with a minimum of normal skin margin and all fatty tissues under the mass. Hence, all tissues above the deep fascia of the muscle are removed. The wound edges are then undermined under the deep fascia, and the deep fascia is sutured with 0 polydioxanone sutures such as PDS®II (Ethicon, Inc., Somerville, New Jersey). Thereafter, the fibrous membrane in the fatty tissues, namely, the superficial fascia, is sutured using 2–0 and 3–0 PDS®II. This approach causes the wound edges to adhere naturally to each other. Our previous study

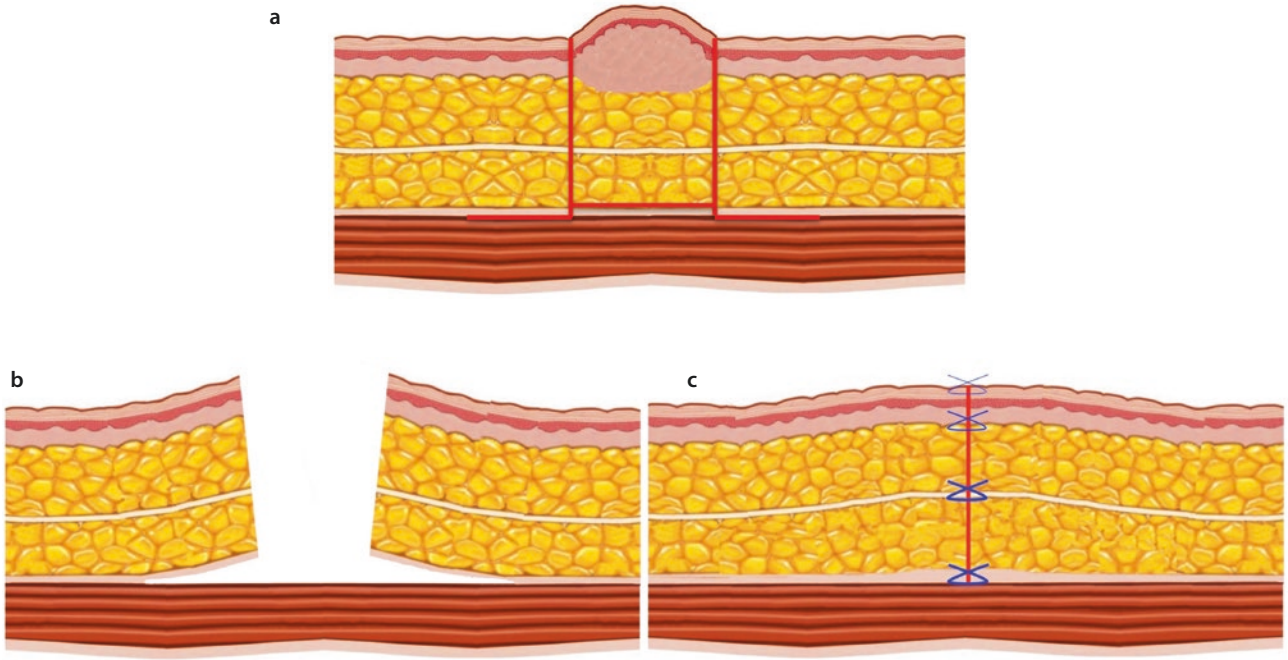

Fig. 21.1 The ideal closure method for minimizing the tension on the dermis. **a** The fatty tissues are removed along with the scar or tumor. **b** Undermining between the deep fascia and the muscle is performed. **c** The deep and superficial fasciae are then sutured to release the tension on the dermis. The red lines in **a** indicate where the tissue is incised and undermined. Dermal sutures themselves do not effectively reduce tension on the dermis. To achieve this, we must access much deeper structures, namely, the superficial and deep fasciae, and suture them

showed that deep fascia suturing reduced about 90% of the tension on the wound edge, while superficial fascia suturing reduced the remaining 10% [5]. After fascial suturing, dermal sutures using 4–0 PDS®II are started. This is followed by superficial sutures with 6–0 polypropylene or nylon sutures such as Proline® or Ethilon® (Ethicon, Inc., Somerville, New Jersey) (Figs. 21.1, 21.2, and 21.3).

21.4 Z-Plasty

Another way to prevent pathological scar formation in high-tension areas is to use zigzag suturing techniques such as the Z-plasty [5]. This is particularly suitable for joint or limb surgery because the fatty tissue layers in these areas are thin: this means that it is difficult to find the superficial fascia and apply the subcutaneous/fascial tensile reduction sutures. Zigzag suturing is also good for long suture wounds because it effectively disrupts the tension on the resulting scar. As a result, zigzag suturing is an effective approach for releasing linear scar contractures. Another major benefit of Z-plasties is that segmented scars mature faster than long linear scars. Thus, if a scar or wound crosses a joint, zigzag incision and suturing will significantly reduce the risk of pathological scar recurrence or development (Fig. 21.4).

In terms of Z-plasty design, the sides of each triangular flap should be 7–10 mm long and the pitch between each z-plasty should be 2–4 cm, depending on the total length of the wound [5]. In our experience, this pitch yields the most satisfactory results (personal observations). Dermal sutures can be started after confirming that the triangular flaps are fully elevated and can be transposed with each other.

It should be noted that, because keloids have much stronger inflammation than hypertrophic scars, it is best to use both tension reduction sutures and Z-plasties during keloid revision surgery [5]. This significantly reduces the risk of recurrence (Fig. 21.5). This risk is also strongly ameliorated by postoperative radiotherapy.

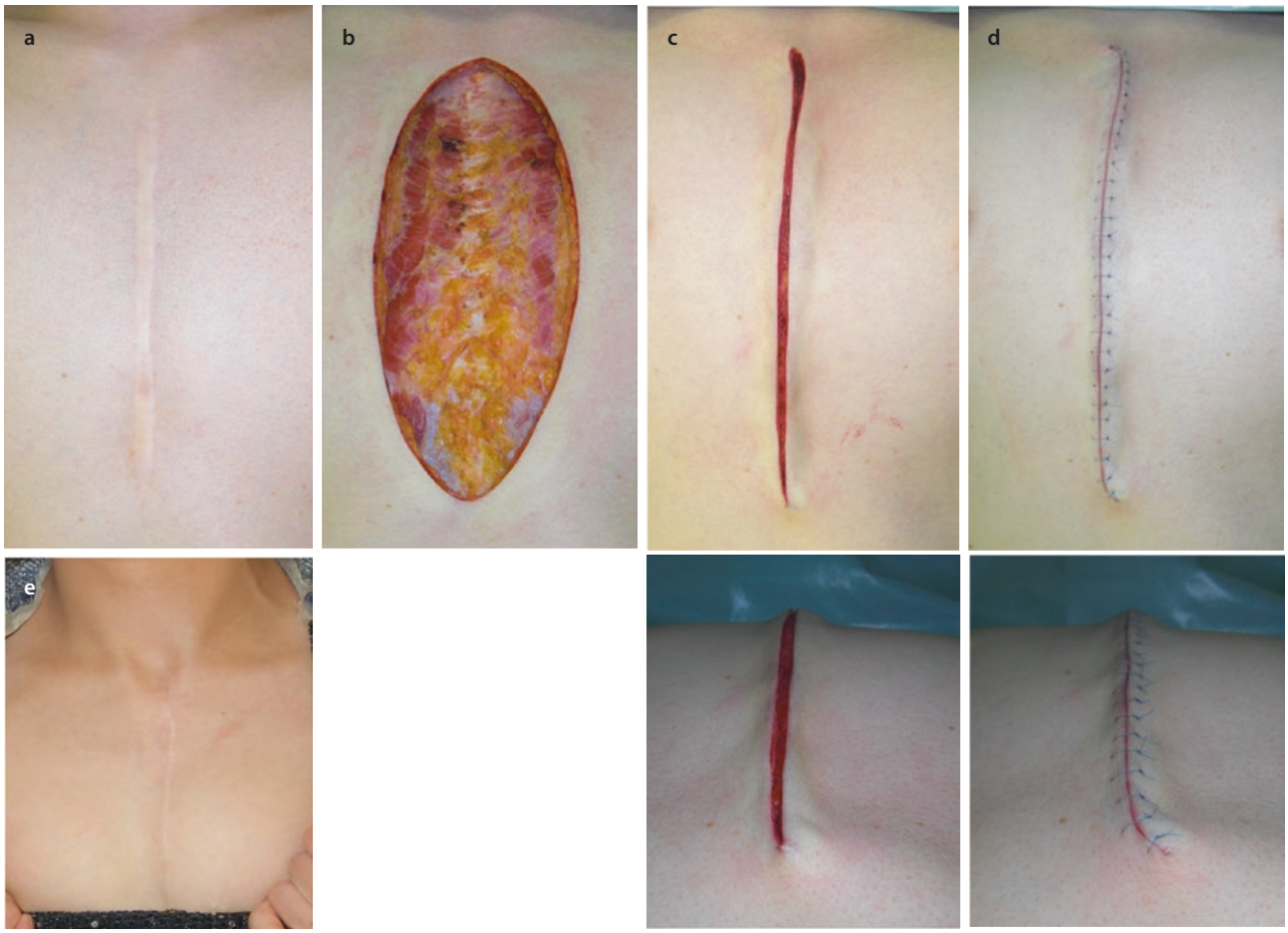

Fig. 21.2 Chest wall scar revision. **a** Preoperative appearance of the scar. **b** View after the scar and fatty tissues were removed. **c** View after the deep and superficial fasciae of the pectoralis major muscle were sutured. **d** View immediately after the dermal sutures and superficial sutures were placed. **e** View 2 years after surgery. The wound edges were undermined under the deep fascia, after which the deep fascia was strongly sutured. These deep sutures absorb 90% of the tension on the wound

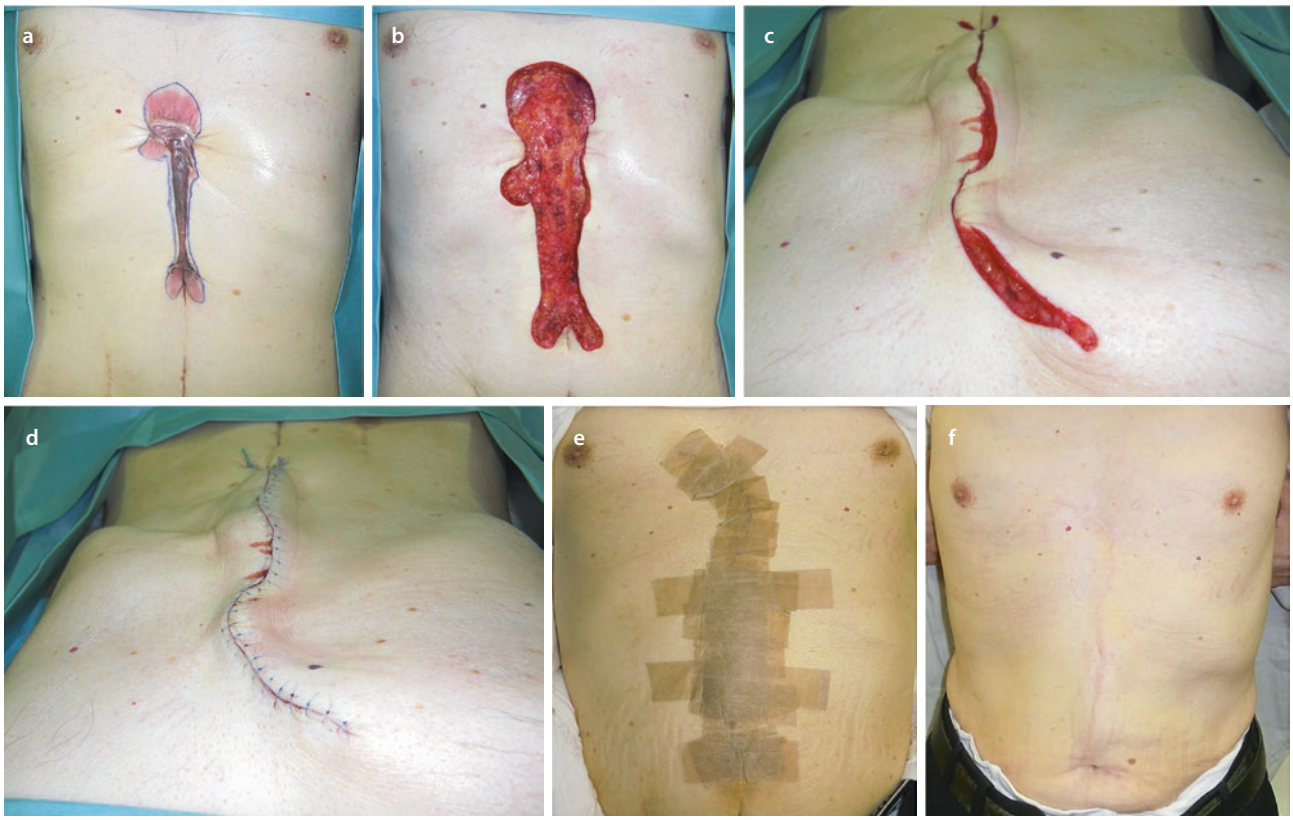

Fig. 21.3 Abdominal wall scar revision. **a** Preoperative appearance of the scar and the design of the incisions. **b** View after the scar and fatty tissues were removed. **c** View after the deep and superficial fasciae were sutured. **d** View immediately after dermal sutures and superficial sutures were placed. **e** View of the postoperative taping fixation that was used to stabilize the wound and protect it from extrinsic mechanical forces. **f** View 2 years after surgery. The anterior sheath of the rectus abdominis muscle was strongly sutured. The wound edges were smoothly elevated so that they attached naturally to each other. Dermal sutures could then be placed

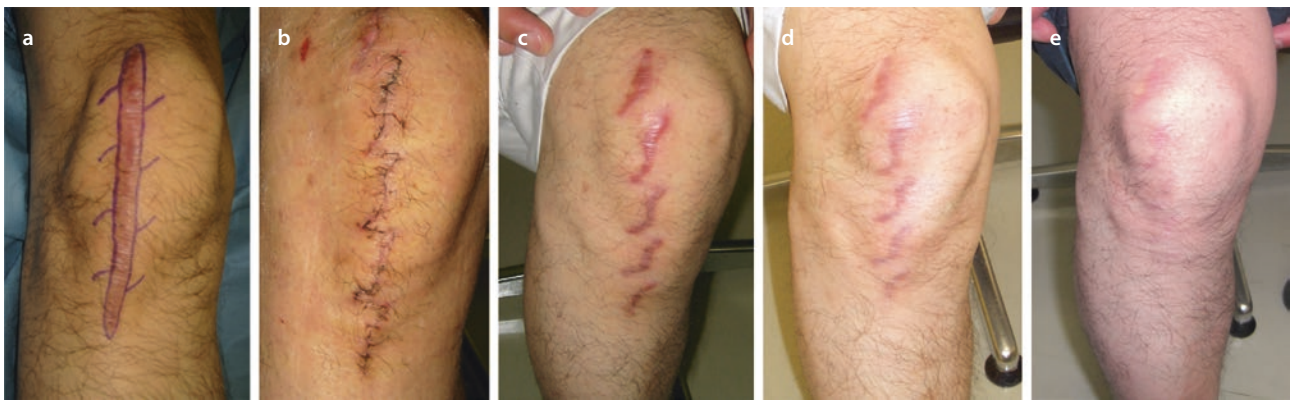

Fig. 21.4 Knee joint scar revision. **a** Preoperative appearance of the scar and the design of the incisions and Z-plasties. **b** View immediately after the operation. **c** View 3 months after surgery. **d** View 6 months after surgery. **e** View 1 year after surgery. In the case of limb surgery, it is difficult to place deep tissue sutures. Therefore, it is necessary to dissipate the tension on the wound by using zigzag line suturing methods such as the Z-plasty: this approach segments the scar and thereby releases its tension. This in turn causes the chronic tension-induced inflammation that is driving pathological scar growth to wane over time

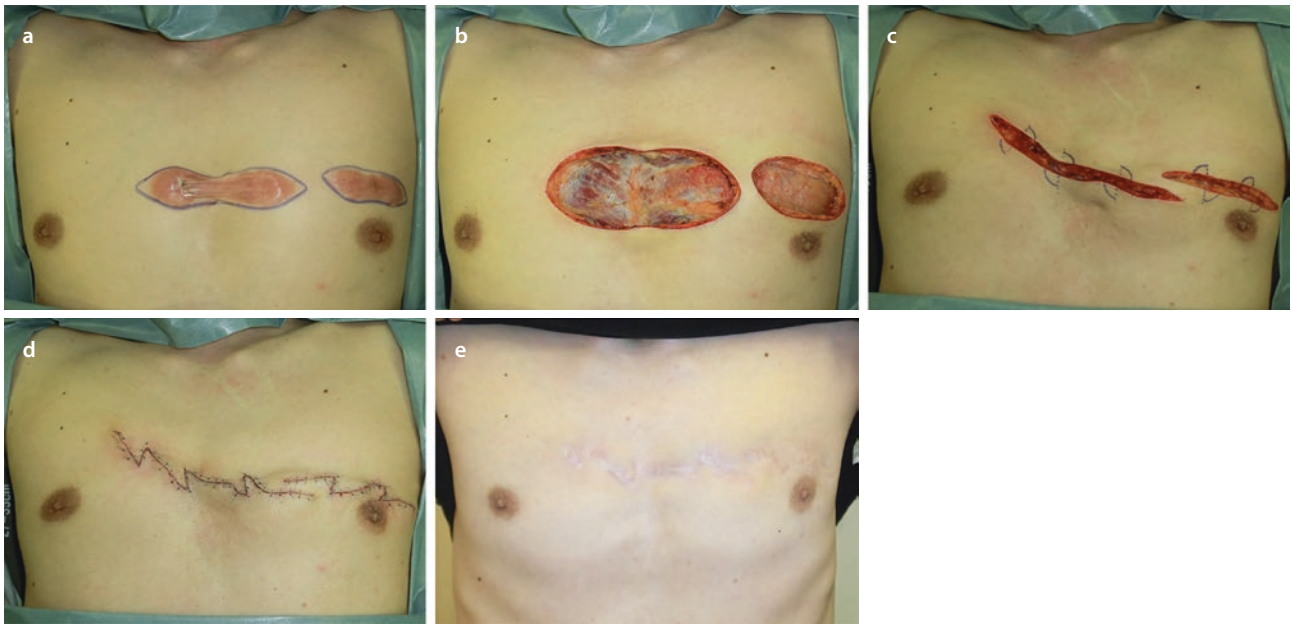

Fig. 21.5 Anterior chest keloid treatment using tension reduction sutures, Z-plasties, and postoperative radiotherapy. **a** Preoperative appearance of the keloid and the design of the incisions. **b** View after the scar and fatty tissues were removed. **c** View immediately after the deep and superficial fascial sutures were placed and the Z-plasties were designed. **d** View immediately after the dermal sutures and superficial sutures were placed. **e** View 2 years after surgery. In cases of keloid revision surgery, great care is needed to decrease the powerful chronic inflammation that is driving the growth of the scar. A combination of tension reduction sutures, Z-plasty, and postoperative radiotherapy can effectively prevent keloid recurrence after revision surgery

21.5 Conclusion

All four phases of wound healing are influenced by mechanical forces. These mechanical forces provoke chronic inflammation of the dermis and cause pathological scars. Dermal sutures do not effectively reduce tension on the dermis: rather, to achieve this, we must access much deeper structures, namely, the superficial and deep fascia, and suture them. Another way to prevent pathological scar formation in high-tension areas is to use zigzag suturing techniques such as the Z-plasty.

Take-Home Messages

- The risk of pathological scarring can be greatly reduced by using subcutaneous/fascial tensile reduction sutures.
- Dermal sutures do not effectively reduce tension on the dermis: rather, to achieve this, we must access much deeper structures, namely, the superficial and deep fascia, and suture them.
- A study showed that deep fascia suturing reduced about 90% of the tension on the wound edge, while superficial fascia suturing reduced the remaining 10%.
- Z-plasty is particularly suitable for joint or limb surgery because the fatty tissues layers in these areas are thin: this means that it is difficult to find the superficial fascia and apply the subcutaneous/fascial tensile reduction sutures.

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Treatment of Immature Scars: Evidence-Based Techniques and Treatments

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Background

Effective scar treatment has come a long way in recent years. Classifications allow us to differentiate between individual types of scars and allow us to propose scientifically proven therapeutic regimes to improve even severe pathological scarring. This has helped not only in improving functional and aesthetic results in the affected patients but also to ameliorate their oftentimes severely impaired quality of life.

However, efforts have long been underway to prevent pathological scarring altogether. Hopes are that through early intervention in fresh scars, excessive scarring can be limited or prevented altogether.

The use of compression garments or silicone gel sheeting has long been established to steer the scar maturation process away from excessive and proliferative scarring disorders. Flavonoids, too, have proven a promising option for the prevention of excessive scarring in recent years.

Through the advent of newer techniques for the treatment of hypertrophic scars and keloids and fresh insights into the pathophysiology of excessive scarring, new methods for scar prevention are currently making their way into routine practice.

Since fractional photothermolysis has shown its potential in mitigating proliferative scarring and aiding scar remodeling in mature scars, more and more researchers are attempting to alter these ongoing processes in fresh scars to prevent excessive scarring.

This chapter explores the different modalities for scar prevention (see Table 22.1), their mode of action, and the evidence supporting their use.

Table 22.1 Treatment modalities for immature scars, their indications, and recommendations for treatment

Treatment modality	Indication	Treatment paradigm
Pressure therapy	Gold standard for burn injuries after skin grafting or after deeper second-degree burns that have healed without surgery	Begin treatment as soon as the skin grafts are stable enough or after reepithelialization in wounds that have healed without surgery
		Garments should be worn for as close to 24 hours per day as possible for 6 to 12 months, depending on the level of scar activity
		Garments should be replaced regularly, at least every 3 months so as to ensure sufficiency
	As an adjunct after earlobe keloid excision	Pressure earrings should be worn for as close to 24 hours per day as possible after surgery to minimize the risk of keloid resurgence, starting on the day of suture removal
	Children with linear hypertrophic scarring or keloids, where intralesional treatment is not an option	Same treatment paradigm as in burn scarring. Especially in younger children, sudden growth can require frequent garment replacement
Silicone-based products	First-line therapy for linear and widespread hypertrophic scarring as well as minor keloids and first option for the prevention of hypertrophic scarring	Sheets or patches should be applied to the desired area for 12 to 24 hours per day. Treatment times can vary depending on scar activity, but 3 to 6 months of treatment should be performed
		Gels should be applied to the scarred area two to three times per day. They are better suited for mobile areas close to joints
Onion extract	Can be considered for the treatment of hypertrophic scarring or scar prevention	Treatment recommendations vary depending on the manufacturer
		Patches are commonly applied for 6 to 12 hours overnight for 3 to 6 months
Pulsed dye laser (PDL)	Can be considered for the treatment of erythematous and pruritic postsurgical scars	No clear recommendations or fixed treatment paradigms exist; however, studies indicate that up to three treatment sessions are required for favorable results

Table 22.1 (Continued)

Treatment modality	Indication	Treatment paradigm
		In most studies, treatment is begun at the date of suture removal or shortly thereafter
Fractional ablative CO_2 laser	Should be considered in patients where excessive scarring is expected (after severe burns/trauma)	Expert committees recommend starting treatment one to three months after the original injury to modulate the scarring process
		Again, no carefully researched treatment paradigms exist; however, based on the data available, low-density, high-energy treatment of the deep dermis in combination with careful superficial smoothening seems favorable
	Experimentally, the laser has been used intraoperatively for scar improvement	To aid with the wound healing, this laser has been used to treat the wound margins intraoperatively before placing the sutures. One to two passes of low-density, high-energy laser treatment were performed on the wound margins
		Thus far, this research was mostly empiric and uncontrolled; thus, no recommendations regarding its use can be made, and caution should be used when considering it
Fractional nonablative Er:Glass laser	Indications for this laser are similar to those of the CO_2 laser	Treatment with the Er:Glass laser has less side effects than with the CO_2 laser; however, its treatment effects are reduced as well, thus requiring more sessions for similar results
		As with the CO_2 laser, little research on the potential for immature scar treatment has been performed, so no clear recommendations can be made

22.1 Techniques for the Treatment of Immature Scars

22.1.1 Pressure Therapy

Upon the discovery of the clinical effects of pressure garments on hypertrophic burn scarring by Silverstein and Larson in the late 1960s, the results of further research on the topic performed at Shriners Burns Institute in Galveston, Texas, were published in the early 1970s. This led to the onset of pressure garment therapy use to prevent hypertrophic scar formation in burn patients. Ever since, this method has become the gold standard for scar prevention in burn patients in many countries around the world. While the exact mode of action has not been fully understood, pressure garment therapy supposedly decreases capillary perfusion in the affected tissue, thus leading to localized tissue hypoxia which in turn increases the rate of fibroblast apoptosis, thus leading to a reduced production of collagen. A recent preclinical study by DeBruler et al. investigated the effects of early pressure garment application after skin grafting in burned Duroc pigs and found an increased level of matrix metalloprotease-1 (MMP1) in pigs that received pressure garment treatment within 1 week of grafting [1]. While further research on the matter is required and influences on the levels of collagen I and III or transforming growth factor 1 could not be proven, increased levels of MMP1 which is a known contributor in scar remodeling might help to explain the effects of pressure garment therapy.

Pressure garments come in the form of stockings, pants, sleeves, suits, bandages, girdles, and clip-on earrings, and for locations that are hard to reach through circularly applied pressure, special pelottes can routinely be fitted to allow for effective treatment of nearly every anatomic location. Garments should be worn for as close to 24 hours per day as possible and are usually recommended for at least 6–12 months. In patients showing scar activity after 12 months, treatment is often pro-

longed for up to 18 months. Being worn for such long times takes a significant toll on the garments which loosen drastically over time, thus requiring regular replacement to ensure sufficient pressure. In our experience, garment replacement is necessary at least every 3 months. To allow patients to wash their compression garments regularly, at least two complete sets should be available at any given time. In patients with physically demanding jobs, wear times might be reduced even further, and more pairs for regular changing might be required.

Pressure garment therapy is very taxing on the patient and compliance is often lacking. Especially during the summer, patients experience sweating and skin maceration, as well as strong odor. In countries without comprehensive health insurance, treatment cost is another important factor. Even in patients where only small areas of the body are affected, treatment over the course of a year will easily cost between one and two thousand euros for a small pressure garment like a glove (◘ Fig. 22.1) or a sleeve alone, whereas larger pieces or even suits for the whole body will cost low to medium five-figure sums, especially when combined with other treatment modalities.

The current consensus on the pressure applied through garments recommends between 20 and 25 mmHg, as studies have shown a higher efficacy when compared to lower-pressure garments (10–15 mmHg).

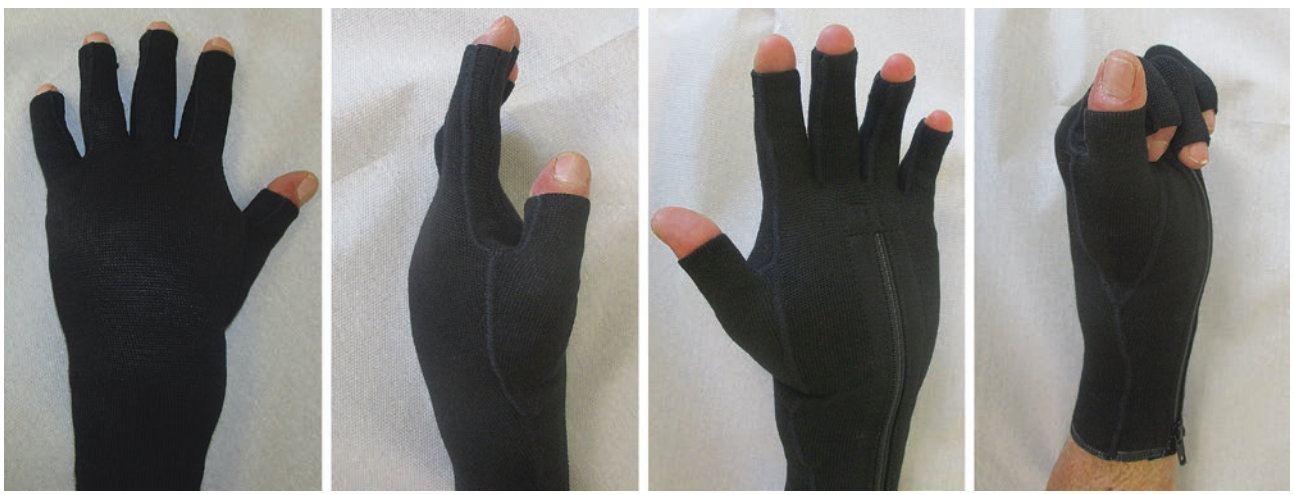
Even though pressure garment therapy has now been in clinical use for over 40 years, hard clinical data on its efficacy is largely missing, and the existing literature is quite heterogenous.

Early adopters of the technique like Larson, Kischer, and Tolhurst reported favorable results on the reduction of hypertrophic scar formation. More recently, Van den Kerckhove et al. reported positive effects on scar thickness when treating patients with garments with at least 15 mmHg of pressure, and Engrav et al. demonstrated that scars under compression were noticeably softer and thinner in their clinical study in 2010 aided by objective measuring devices. However, a large meta-analysis by Anzarut et al. in 2009 was unable to discern differences in scars treated with pressure garments and untreated scars [2]. In 2013, Atiyeh et al. came to a similar conclusion and questioned the widespread use and recommendation, especially in the light of the often poor patient compliance and the resultant cost-effectiveness of this course of treatment. Especially in burn patients, this course of treatment, however, has become the accepted standard. This makes randomized controlled trials with an untreated patient population nearly impossible on ethical grounds, thus limiting the designs of further studies investigating this treatment method.

Thus far, based upon many different studies indicating the clinical efficacy of pressure garment therapy, current guidelines for the treatment and prevention of pathological scarring recommend its use while noting the less than robust level of evidence.

Furthermore, pressure garment therapy can be considered in children with linear hypertrophic scarring or keloids, where intralesional treatment is abandoned because of side effects or the associated risk of the treatment and pressure garment therapy has empirically shown greater efficacy than in adults.

In patients that received surgical treatment for earlobe keloids, pressure earrings have been shown to greatly reduce the risk of keloid recurrence and are thus regularly recommended as an adjunct. Pressure earrings are readily available from specialized orthopedic technicians, and if keloids are excised elsewhere on the ear, like on the helix, tragus, or other parts of the ear, special splints can be custom-made.



◘ **Fig. 22.1** Patient with severe burn scarring of the left hand wearing a compression glove. The glove allows full function (full finger flexion and extension) while providing full coverage

22.1.2 Silicone-Based Products

Silicone-based products come in a variety of forms. They are available as creams, oils, gels, or, most commonly, patches or sheets that can be applied to the affected areas. Their mode of action regarding the treatment and prevention of excessive scarring has not yet been fully understood, but it is stipulated that the occlusive effect of the silicone inhibits the transepidermal loss of water (TEWL), thus ensuring sufficient hydration of the skin. Thus far, no properties of silicone, which directly influence the process of scarring, have been discovered.

Treatment with silicone-based products can be started after complete reepithelialization of the wounds. Sheets or patches should be applied for 12–24 hours per day throughout 3–6 months. Gel- or cream-based silicone products are better suited for areas that are subject to constant motion (i.e., large joints) where wound dressings might prove unsuitable. To achieve the desired effect, applying the gel two to three times daily is recommended.

Patches and sheets come in many different forms and thicknesses. Commonly, thicker sheets last longer than thinner ones. Larger sheets can be cut into the desired size. They should be cleaned with water and special cleaning solutions that come with the product regularly and can be put back on their carrier foil for storing in between applications. Reusing a single sheet is usually possible for 6–8 weeks, before the silicone disintegrates and becomes gelatinous in its structure, whereupon a fresh sheet should be used.

Side effects or allergies to silicone-based products are rarely observed. Skin maceration through the occlusive effect is possible, whereupon patients can reduce the application time of the silicone.

Silicone has been used in the treatment of immature scars since the early 1980s, where it was first used in the Adelaide Children's Hospital for the treatment of burn scars. Ever since, it has become one of the pillars for early scar intervention. Different prevention and treatment studies have reported outcomes documenting the efficacy of silicone for preventing scar hypertrophy. Cruz-Korchin compared patients after bilateral mammoplasty, after which the scars on one breast were dressed with silicone sheets for 12 hours a day for 2 months while the other remained without preventative treatment. Results demonstrated scar hypertrophy in 60% of the untreated breasts after 2 months, whereas only 25% of the scars in the treatment group showed hypertrophy. Ahn et al., in 1991, could demonstrate that surgical incisions treated with silicone gel bandages showed less proclivity for hypertrophy than an untreated control.

In 2001, Gold et al. showed that patients suffering from abnormal scarring showed significantly less hypertrophic scarring when treated with silicone gel sheeting after skin surgery compared to an untreated group of patients.

However, a variety of studies have failed to document significant effects regarding scar prevention of treatment through silicone-based products. In 1998, Niessen et al. failed to show positive effects regarding scar prevention through silicone gel sheeting and even reported a higher rate of hypertrophic scar development than in their control group treated with nonocclusive micropore in their breast reduction scar model.

Cochrane Reviews in 2006 and 2013 noted the generally poor quality of prevention and treatment studies analyzing the effects of silicone regarding pathological scarring [3]. While seemingly reducing the risk of abnormal scarring in high-risk patients and improving scar parameters such as color and softness in existing scars, significant bias was a main critique point in most studies.

Nevertheless, silicone gel sheeting is recommended as a first-line therapy for linear and widespread hypertrophic scarring, as well as minor keloids in national and international guidelines on the management of pathological scarring, and has furthermore been noted as an important option for the prevention of excessive scarring.

22.1.3 Onion Extract

Products that contain onion extract have seen increasing popularity for the treatment of immature scars in recent years. They are available as creams or patches and commonly include adjuncts such as allantoin or heparin. Onion extract contains quercetin, a flavonoid that has anti-oxidative and anti-inflammatory properties. Experimental research has suggested that quercetin influences transforming growth factor beta 1 and 2 and SMAD signaling pathways, thus inhibiting fibroblast proliferation and collagen synthesis. In cell cultures, it has also been shown to induce matrix metalloproteinase-1 expression, thus influencing extracellular matrix remodeling.

Scar treatment is begun after complete reepithelialization of the wound is complete. Onion extract patches are commonly used overnight, where they are applied for 6–12 hours over the course of 12–24 weeks, though no clear recommendations regarding the length of treatment exist to date. Gels are often applied multiple times throughout the day for weeks or months, according to manufacturer recommendations, though there is a variance between different formulations and manufacturers.

Regarding the efficacy of onion-extract-based products, different studies documented significant potential regarding the prevention of pathological scarring. Draelos et al. reported a significantly improved appearance of fresh surgical scars treated with onion extract gel when compared with a control group in two different studies in 2008 and 2012. Parameters positively influenced through the treatment included scar softness, redness, texture, and global appearance. In 2006, Ho et al. evaluated the effects of onion extract gel on scarring after Q-switched Nd:YAG laser tattoo removal in a Chinese patient population and reported significantly less scarring in the treatment group than in the control group.

In 2018, a randomized controlled study by Prager et al. on 125 subjects with fresh postsurgical scars that were treated with an overnight patch containing onion extract, allantoin, and heparin demonstrated significantly better rated scars by both patients and investigators after 12 and 24 weeks of treatment when compared to the control group [4]. Overall treatment comfort was good, and no safety concerns were identified.

Some studies have, however, come up with less positive conclusions. Chung et al. investigated the effects of an onion extract gel when compared with a petrolatum emollient on fresh surgical scars and found no difference between the treatments. Ocampo-Candini et al. published a randomized controlled trial documenting the development of Pfannenstiel scars after cesarean section under treatment with onion extract gel and found no significant improvement over their untreated control group when comparing POSAS scores.

Overall, this relatively new treatment option requires further intense scientific evaluation to improve the level of evidence regarding its efficacy. Due to the promising data that has been collected thus far, current guidelines support the consideration of onion-extract-based formulations for the treatment of hypertrophic scarring as well as the prevention of excessive scarring after surgery.

22.1.4 Pulsed Dye Laser (PDL)

The pulsed dye laser is a nonablative laser with a wavelength of 585 or 595 nm. Its target chromophore is oxygenized hemoglobin, and application of the laser will therefore lead to coagulation of capillaries, thus inducing tissue hypoxemia. In scar tissue, this effect will induce a reduction of profibrotic processes and stimulate scar remodeling.

Alster et al. reported significant therapeutic benefits of the PDL for the treatment of keloids in 1995; however, other research groups failed to replicate their findings with some even showing high numbers of recurrence. Further clinical research, however, has established the laser potential for the treatment of erythematous and pruritic scars, for which it is routinely considered. Recently, however, more and more authors have started treating fresh postsurgical scars with the PDL to elucidate whether this can favorably alter the process of scar maturation. McGraw et al. were the first to publish a study on the prevention of hypertrophic scarring with the PDL in 1999. They found that early treatment within the first few weeks after trauma or surgery resulted in a faster resolution of scar stiffness and erythema, as well as a decreased frequency of hypertrophic scarring. Furthermore, they noted an improved scar quality due to the good color match with the healthy skin. In 2003, Nouri et al. published similar findings. In their study, they included 11 patients with 12 postoperative linear scars that were divided into a treated and an untreated half. Overall, three sessions of 585 nm PDL treatment at monthly intervals were performed, whereupon the cosmetic appearance of the treated scars was reportedly significantly better, when analyzed by a blinded examiner using the Vancouver Scar Scale. In 2006, however, Alam et al. found no significant difference in their randomized controlled trial, where fresh postsurgical scars were treated with one pass of PDL treatment upon suture removal. They noted that 6 weeks after treatment, both groups had improved while the result of neither group was superior. In 2011, Kim et al. examined the effect of three sessions of PDL treatment followed by three sessions of fractional ablative erbium:YAG laser treatment on fresh thyroidectomy scars and noticed favorable effects after PDL treatment with 83% of patients expressing satisfaction with the result. Er:YAG treatment further improved the observed results [5].

To date, further studies on the potential of the PDL as an option in the treatment of fresh postsurgical scars to quicken scar maturation and to prevent scar hypertrophy exist. However, most studies lack a long-term follow-up that encompasses the entirety of the natural length of scar maturation (12–18 months), thus inhibiting judgment about whether the final results are superior to an untreated control or simply accelerate the process. Therefore, so far, no clear recommendations on the use of the PDL for scar prevention can be made, while the current literature indicates that positive results at the cost of low rates of side effects can be achieved.

22.1.5 Fractional Ablative Carbon Dioxide (CO_2) Laser

While the 10,800 nm carbon dioxide (CO_2) laser has been around for decades, the recent development of fractional lasers has led to a significant expansion of its therapeutic range.

In fractional units, the laser beam is divided into an array of smaller columns, leaving untreated skin islets in between. The divided laser columns ablate tissue and can reach depths of up to 4 mm newer models, with maybe their most important effects taking place in the dermis. Through the heating of the surrounding tissue, fractional CO_2 laser treatment activates heat-shock proteins which in turn stimulate antifibrotic factors such as transforming growth factor beta 3 (TGF-β3) and matrix metalloproteinases, thus stimulating scar remodeling. Additionally, through classic tissue ablation, scar surface irregularities can effectively be smoothened through use of the CO_2 laser.

After the discovery of these effects through experimental research, different clinical studies have since used the fractional CO_2 laser to treat mature burn scars. Recent studies found that a single treatment can improve scar softness and surface irregularities by up to 30% all the while positively influencing patient quality of life. While further research is warranted, current guidelines for the treatment of excessive scarring are recommending the CO_2 laser for treatment in severe widespread hypertrophic scarring.

Side effects of the treatment commonly include swelling and oozing of the wounds throughout the first days after treatment, as well as erythema, which commonly recede within 1–2 weeks after treatment. In the author's experience, when treating severe scarring with higher fluences, posttreatment hyperpigmentation often occurs but tapers off after 4–6 months after treatment.

Since the fractional CO2 laser has seen great success in the treatment of mature widespread scarring and experimental studies suggest that this laser is able to normalize the oftentimes greatly disturbed architecture of the dermal matrix, research is under way to establish the CO2 laser's abilities regarding excessive scar prevention through the treatment of immature scars.

In 2011, Ozog et al. examined the intraoperative use of the fractional CO_2 laser. Before wound closure, one-half of the wound margins were treated with one to two passes of Active FX (Lumenis Ultrapulse, Santa Clara, California, USA), before the wound was closed. Upon the final evaluation of the scars after 2–3 months post surgery, both patients and examiners rated the laser-treated scar halves superior to the untreated halves [6]. Jung et al., also in 2011, treated immature thyroidectomy scars 2–3 weeks after surgery with a fractional CO_2 laser. Patients were treated with two passes, 50 mJ of energy and 100 microbeams/cm^2 with a coverage of 12.7%. Analysis of the treatment effect after 3 months revealed significantly improved Vancouver Scar Scale scores, as well as significantly improved values measured with a skin durometer [7]. However, no comparison with an untreated control group was performed. In 2013, Lee et al. performed a split-scar study on 15 three-week-old scars. Two laser passes were delivered at 80 mJ with a density of 100 microbeams/cm^2 achieving a total coverage of 15.6%. During the final observation, 3 months after treatment, a significant improvement of Vancouver Scar Scale values superior to those made in the control group was found. Especially, scar pliability and thickness improvements were larger than those in the control group, while vascularity and pigmentation did not differ considerably.

Overall, more research on the fractional CO_2 laser's abilities regarding scar prevention is required. While initial research shows promising results and the molecular defects thus far discovered suggest that early intervention could lead to a normalization of the dermal architecture in scar tissue, many issues remain to be elucidated. To exclude natural scar regression, which is an important factor in hypertrophic scarring, as a factor, long-term follow-up of over 12–18 months is required, as well as including a control group.

Nevertheless, expert committees suggest that early treatment, 1–3 months after the original injury, should be considered, especially when excessive scarring is expected. Thus far, no study researching early laser intervention found evidence of increased scarring or other severe side effects, thus supporting the safety the laser is known for in mature scar treatment.

22.1.6 Nonablative Erbium Glass (Er:Glass) Laser

The 1550 nm erbium glass (Er:Glass) laser is a nonablative fractional laser. It does not remove tissue but merely applies heat in a controlled way and leaves the epidermis intact. Through the application of heat in the dermis, its effect there is similar to those of the carbon dioxide laser, albeit at a reduced rate of side effects. Since treatment with the Er:Glass laser does not leave wounds, downtime is greatly reduced. Patients commonly experience light swelling and posttreatment erythema for a few days.

Regarding its efficacy for early scar intervention, thus far, few studies exist. Tierney et al. compared PDL and Er:Glass laser treatment in 2-month-old scars after Mohs surgery in 2009. The study was performed in a split-scar fashion, and patients were blinded as to what side was being treated with which laser. Every scar received four treatment sessions at four-week intervals, and follow-up was performed 1 month after the last treatment session. Overall, patients preferred the results of the Er:Glass-laser-treated scars (83% of patients). Regarding the scar parameters, pigmentation, scar thickness, and overall aesthetic outcome were all superior in the Er:Glass group [8].

In 2014, Ha et al. compared the effects of PDL treatment to Er:Glass laser treatment in a split-scar study on 2–3-week-old thyroidectomy scars. Overall, both groups saw significantly improved scar ratings 6 months after treatment. Patients reported that they found the PDL treated scars less apparent; however, pliability appeared superior in the Er:Glass-laser-treated scars [9]. In their 2014 study, Shin et al. performed another split-scar study, this time comparing ablative fractional CO_2 laser treatment to Er:Glass laser treatment. After three treatment sessions in 2-month intervals, follow-up examinations 3 months after the last laser session revealed significant improvement of the scarring in both groups without statistically significant differences between the groups overall. However, the CO_2 laser group showed greater improvement of scar hardness, while the Er:Glass-laser-treated scars proved superior regarding their color [10].

Overall, current research has shown promise regarding the Er:Glass laser's efficacy for early scar intervention. However, thus far, few clinical studies are available, thus requiring further research on the matter. As with other laser modalities for the treatment of immature scars, further studies should focus on longer follow-up times as well as larger group samples to further improve the level of evidence.

22.2 Conclusion

Efforts to prevent pathological scarring have been underway for many decades. One of the most established methods is pressure garment therapy, which has been used in the prevention of widespread hypertrophic burn scarring since the early 1970s. Years of use have seen this modality become the gold standard, and thus, pressure garments are routinely prescribed for most burn patients in the developed world. However, upon further inspection of the evidence, hard clinical data on the efficacy of pressure garment therapy is only scarcely available. Furthermore, patient discomfort is often high, leading to infrequent treatment compliance. Other options for the treatment of immature scarring are tolerated better. Silicone gel sheeting is often applied throughout the night, and its continued use has been shown to improve scar pliability and height in connection with little to no side effects. Clinical evidence, however, is not as explicit as frequent mentions in national and international guidelines for the treatment and prevention of pathological scarring might infer. Similar in their application to silicone-based products, onion-extract-based gels, creams, and patches have appeared on the market in recent years. Often combined with further active ingredients like allantoin and heparin, they are specifically marketed for use in fresh scars, where they show promise in alleviating scar redness and firmness as well as improving further scar parameters. While additional research will determine the future role of this treatment modality, the low side-effect profile and the appearance of natural ingredients appeal to many patients. In the treatment of mature scars, and increasingly so in the treatment of fresh scars, lasers cannot be ignored. While PDL treatment has been around for years and its use in immature scars to alleviate pruritus and erythema has been well researched and documented, researchers are more and more focusing on fractional lasers. Their effects on dermal matrix remodeling through the stimulation of heat-shock proteins and the resultant effects on transforming growth factor beta isotypes and the concentration of matrix metalloproteases have resulted in researchers trying to employ these effects to modulate the active scar process in favor of remodeling rather than excessive fibrosis. While initial research, both for the ablative CO_2 laser and for the nonablative Er:Glass laser, has shown promising results, most recent studies lack sufficient follow-up observation time. To assess whether clinically measured effects are caused through treatment and not through natural scar regression over time, scar maturation must be waited for to make a final conclusion. To date, this presents the largest problems with most research on immature scars. Overall, however, patients today can rely on a variety of promising options for the prevention of excessive scarring. While not every patient requires a robust prevention regimen after surgical intervention, care should be taken to identify patients at risk for excessive scarring and to tailor a treatment algorithm according to their needs. After all, preventing a hypertrophic scar or keloid from forming saves patients from months or years of strenuous symptoms and treatment. Furthermore, today, most algorithms for the prevention of excessive scarring are well tolerated and go along with minimal treatment discomfort and side effects.

Take-Home Messages

- Pressure garment therapy is the gold standard for the prevention of widespread scarring, e.g., after burns. Even though it has been in use since the early 1970s, evidence for its efficacy is largely empiric. Additionally, side effects of pressure garment therapy often lead to low compliance which affects the treatment efficacy.
- Silicone gel sheeting has proven effective in softening scars, and its use shows little to no side effects. Its mode of action, however, remains largely unknown, and recent meta-analyses question its efficacy.

- Onion-extract-based products are available as creams and patches. Early research has shown promise regarding the prevention of pathological scarring, but further research is needed to further elucidate its role in the treatment of immature scars.
- PDL treatment has been found to improve pruritus, erythema, and stiffness in fresh postsurgical scars; however, the overall level of evidence for immature scar treatment is low.
- Fractional CO_2 laser treatment has been shown to affect dermal matrix remodeling and is therefore increasingly used to modulate immature scars. While initial studies show promise and scar pliability and height seem to improve through treatment, long-term follow-up is crucial in future studies to further strengthen the clinical evidence for this therapeutic option.
- Fractional nonablative Er:Glass laser treatment employs a similar mode of action, much like the CO_2 laser, but does not ablate tissue. Thus, downtime and side effects are greatly reduced.
- Scar prevention is imperative in patients with a history of pathological scarring to avoid severe functional, aesthetic, and psychosocial impairments.
- Most modern methods for scar prevention have a minimal likelihood of severe side effects, and treatment discomfort is commonly very low.

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Silicone Gel for Scar Prevention

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_23

23.1 History

Silicone gel was first discovered to be useful in the treatment of scars by Perkins in Australia and New Zealand when observations were made empirically that scars improved when silicone was used as part of a dressing. The observations although anecdotal were impressive enough that use spread to the UK, and at the University of Strathclyde in Glasgow, Scotland, a biomedical engineering student, Karen Quinn, undertook a series of studies for her PhD thesis to determine the mechanism of action and published a paper in burns [1]. She determined that neither heat nor pressure nor silicone absorption or chemical effects were responsible for its effects in studies done together with surgeon from the Plastic Surgery Unit at Canniesburn (Professor Reid). By chance, I was visiting the Canniesburn Hospital for 2 weeks and had the opportunity to observe the use of silicone gel, which was made by Dow Corning. They were already sponsoring some of my studies at Washington University School of Medicine, and I suggested a controlled clinical study which had not yet been done. The effects on immature hypertrophic scars were in some cases dramatic with each patient serving as their own control. We subsequently did a follow-up study on using silicone on very early scars to prevent hypertrophy with equally encouraging results. Although there was some skepticism, in part due to a lack of a clear mechanism of action, subsequent studies by several other investigators confirmed the efficacy. I will detail some of these studies later in this chapter.

23.2 The Role of the Epithelium in Scar Formation

Hypertrophic scars are due to an excess of collagen deposition which is almost entirely from fibroblasts. The role of excess inflammation, myofibroblasts, and other fibroblasts phenotypically that produce excess collagen, tension, and genetic factors all play a role in hypertrophic scar formation. Given that silicone is not absorbed into the skin and covers intact epithelium, the beneficial effects must be indirect through effects on the epithelium.

The epithelium serves an important barrier function. Water loss through the epithelium is limited by a functional stratum corneum, and disturbances in barrier function are associated in many dermatologic conditions with increased inflammation instigated by inflammatory growth factors and other inflammatory mediators produced by epidermal cells. Epithelial mesenchymal cell cross talk is well known.

23.2.1 Delay in Epithelization

When barrier function is disrupted by tissue injury, restoration of the stratum corneum lags behind epithelization which is initially only one cell layer thick as epithelium rapidly migrates over an open wound, followed by stratification, followed eventually by a multilayered stratum corneum. However, there is evidence that the immature stratum corneum does not become fully functional as a water barrier for weeks to months. During that time, there is a stimulus to restore homeostatic barrier function by increased epithelial proliferation, as manifested by increases in thickness, alterations in differentiation markers in the immature differentiating epithelium, and increased inflammatory mediator synthesis [2].

In cell culture, prevention of water loss by a liquid or high-humidity environment results in a reduction in soluble inflammatory mediators and consequently a reduction in collagen synthesis in a coculture setup with fibroblasts [3, 4]. In vivo, in models in rabbits, rats, and mice, prevention of water loss from an epithelium with an immature, deficient stratum corneum results in increase in inflammatory mediators similar to those utilizing human cells in an in vitro system [5]. There are multiple highly upregulated factors including IL-1, IL-8, and Cox-2. In total, over 1000 genes are either upregulated or downregulated in an environment where transepidermal water loss (TEWL) is limited by a semiocclusive dressing versus no covering [6].

Humans are almost unique in their tendency to heal with excessive or hypertrophic scarring. In part this is due to the "tight-skinned" characteristic of the human skin which is tightly adherent to the underlying muscle layer due to the lack of a panniculus carnosus. Thus, human wounds heal only part by wound contracture, with both a delay in epithelization and also tension forces due to the constraints on skin contraction by adherence to the underlying deeper tissues. The rabbit ear [7] mimics human skin in being firmly adherent to the underlying cartilage which splints the wound and minimizes contracture. Healing is almost entirely due to epithelization, and with wounds larger than 6 mm in diameter, healing is delayed beyond 2 weeks which in humans is the critical delay in healing sufficient to increase the risk of hypertrophic scars. In addition, during the healing process, the fibroblasts in the granulation tissue are under tension because the contractile forces generated by the myofibroblasts are counteracted by the resistance to contraction by the stiff underlying cartilage. Wounds on the rabbit ear heal with scar elevation (◘ Fig. 23.1) which both from gross visual appearance, and also histologically closely mimic human hypertrophic scars. Larger wounds with epithelization delayed beyond 2 weeks have

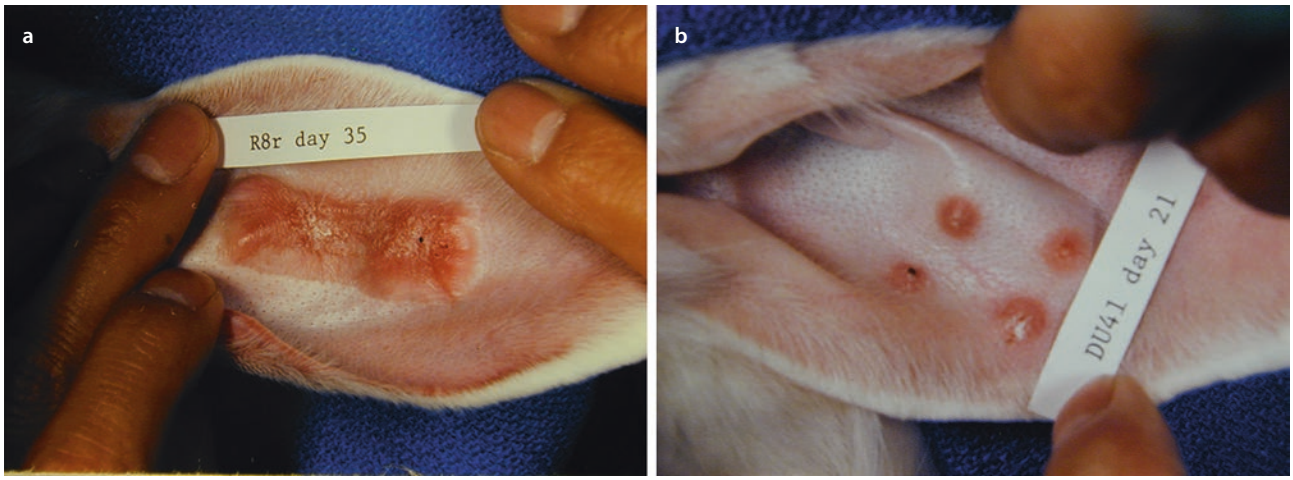

Fig. 23.1 **a** A large scar in the rabbit ear created by full-thickness removal of the skin followed by healing without dressings. **b** By creating small 6–8 mm in diameter full-thickness wounds with a circular punch, healing is complete in about 2 weeks and the scar is elevated allowing quantification. This rabbit ear model has been used for all of our experimental studies

greater scar elevation, and like humans, older rabbits heal with flatter scars. The scars respond to interventions like local steroid and injections and blockers of fibrosis including TGFB antibodies and antisense to CTGF, in which both growth factors induce collagen synthesis and are upregulated in fibrotic processes. Silicone gel sheets and silicone cream both reduce scarring, and other semi-occlusive agents such as paper tape, polyurethane films, cyanoacrylates, or stoma adhesive are also effective which implicates occlusion as the working mechanism of silicone gel, when combined with negative data ruling out absorption (chemical process) or heat or pressure.

We have used this model to investigate the working mechanism of silicone gel or other occlusive dressings in a series of experiments. In our model, silicone gel resulted in decreased inflammatory cytokines including IL-1, TNF, IL-8, and Cox-2 among others. The net effect of increased hydration is a decrease in osmolarity and several extracellular fluid ions including calcium, sodium, and chloride. By controlling otherwise for potential ions and osmolarity, we found that Na concentration was the critical factor controlling signaling for the inflammatory cytokines affected by hydration. We also found that changes in extracellular Na concentration resulted in changes in transmembrane Na flux which is mediated chiefly by the Na channel ENaC. Briefly, an increase in Na concentration due to increased TEWL caused by a deficient epithelial barrier results in activation of ENaC which controls levels of COX-2 resulting in increased prostaglandins [3].

The question remained of how increases in Na concentration are sensed resulting in activation of ENaC. We looked for changes in all of the candidate Na channels in epitheilia cells that could conceivably respond to changes in Na concentration and found only one channel, Nax, had a significant response. Nax is a member of the voltage-gated Na channels but lacks the extracellular domain responsive for voltage gating. It's function previously has been unclear. NaX has been found to be Na concentration sensor in the central nervous system, but its function and presence in other organs and cell types had not been extensively studied. With a series of knockdown experiments in vitro, we established that NaX controls the entire signal transduction signaling seen with changes in Na concentration and hydration in vitro in epithelial cells and also skin explants. Utilizing our model of hypertrophic scarring in the rabbit ear, we found treatment with antisense to NaX results in a very significant reduction in scarring, similar or greater to the effects of silicone gel. Furthermore blocking downstream signals including Cox-2, IL-B, and the S-100 proteins also reduced scarring. Blocking ENaC with a clinically used pharmacologic agent, amiloride, also resulted in decreased scarring. Experiments to elucidate the signal transduction pathways further have established that NaX responds or senses high salt with activation of a serine protease, prostasin, which activates ENaC. The importance of NaX in controlling changes in the epithelium includes profound changes in epithelial differentiation, cell migration, and cell proliferation in knockdown experiments in vitro [4].

In summary the application of silicone gel to an acute scar with a deficient epithelial water barrier due to an immature stratum corneum results in decreased water loss (TEWL). This prevents the increase in Na concentration which otherwise results in an NaX-mediated complex signal transduction pathway which includes downstream activation of ENaC as well as hundreds of other genes, mirroring the kind of broad changes in gene expression found to be controlled by many cyto-

kines such as TGFB. Other occlusive treatments are also effective, but the degree of occlusion is important (complete occlusion results in excessive hydration with impacts on surface bacterial levels as well as undesirable physical changes in the epithelium).

23.2.2 Clinical Studies

The first controlled clinical study to demonstrate efficacy of silicone gel utilized silicone gel sheets applied to portions of immature hypertrophic scars due to burns, trauma, or surgery, in an effort to treat immature hypertrophic scars (Fig. 23.2). Treatment went on for 3 months with application of the gel for 12 hours. We found that 24-hour treatment led to maceration and was poorly tolerated. One of the challenges was to quantify the improvement in scarring. Although photographic evidence is essential, rating scar severity remains challenging and is ultimately nonquantitative. In an effort to have a completely objective and quantitative method of measuring scar severity, we turned to measuring the scar stiffness. Scars are stiffer (less elastic) than normal skin, and as scars improve they become more pliable or more elastic. Utilizing an extensometer which measures the amount of stretch when the skin is subjected to a given force, we were able to calculate Young's modulus and get an objective measure of scar stiffness. We first used an extensometer to measure the stiffness of burn scars and found that older scars were more elastic and there was a very good correlation with age of burn scar to stiffness of the scar over several years [8]. In our scar study, we found a highly statistically significant reduction in stiffness that reached closed to its maximum after 2 months of treatment, with only minor changes by extending treatment for 3 months [9]. Furthermore, the improvement was sustained after treatment was terminated. At the same time, there were a substantial reduction in scar erythema and flattening of the scar clinically which was obvious on photographs. We saw no response in a keloid and much more impressive results in immature scars, with minor effects or no effect on mature scars (scars older than 1 year without erythema).

In a follow-up study (Fig. 23.3), we wanted to see if we could prevent the development of hypertrophic scars by beginning treatment early on surgical incisional scars. Again, a portion of the incision was treated with an adjacent area untreated [10]. We again utilized photography but wanted to quantify the scar volumes for an objective quantitative measure. Dental alginate was used to make a negative impression which was then converted to a positive impression using dental plaster in similar fashion to the way dentists take dental impressions for models used in a variety of dental and oral surgical procedures. The positive molds there then burred down to a totally flat surface and volumes calculated by measuring the difference in weights. Treated areas of the scars were found to have significantly less volumes as long as the untreated scar developed some hypertrophy. Not surprisingly, in scars that healed favorably, minimal or no differences were seen.

Initially, although these studies received considerable attention, even in the popular press, there was some skepticism by many clinicians, due in part to the lack of mechanism. Over the subsequent years, many studies have confirmed the observations we made relying on subjective evaluation of scar severity using a variety of scar severity scales such as the Vancouver Scar Scale and Patient and Observer Scar Assessment Scale (POSAS). In 2002, an international group developed an evidence-based analysis to develop guidelines for treatment [11] and found that there was strong evidence for the use of

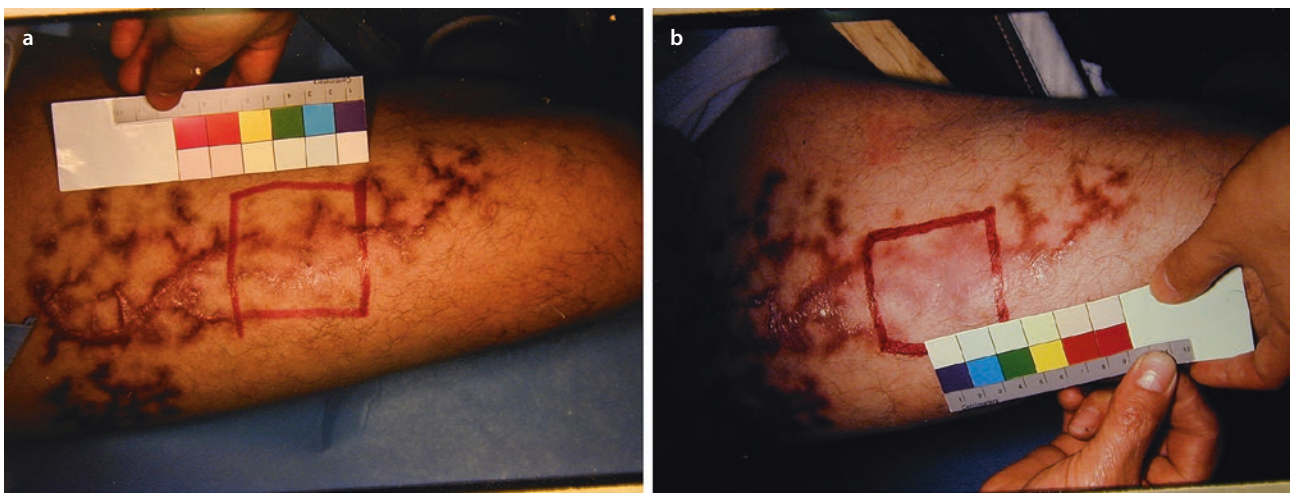

Fig. 23.2 **a** Partial-thickness immature hypertrophic burn scar. The square marks the planned treatment area with silicone gel. **b** After 2 months of treatment, the treated area is flatter, more pliable, and less pink

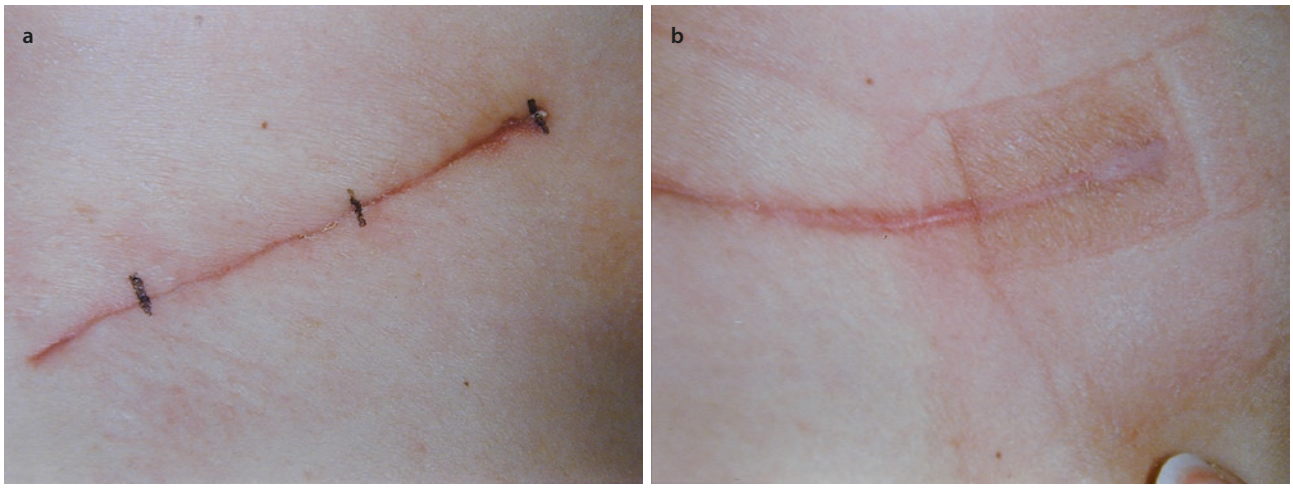

Fig. 23.3 **a** A fresh surgical incision prior to treatment. One area of the scar is going to be treated preventively with the other portion of the scar serving as comparison. **b** After 2 months, the untreated scar is slightly elevated and pink in color. The area of the scar treated with silicone gel sheeting is flatter and less pink in color

silicone gel both for the treatment and prevention of hypertrophic scars.

Since 2002, many more studies have been published on silicone gel with supportive data. Most of these studies were not prospective randomized trials and by the nature of the treatment virtually impossible to blind. The Cochrane group did an analysis and noted the deficiencies of the studies and made the conclusion that solid evidence for silicone gel was lacking but failed to recognize the strengths of our early studies in which the patients served as their own control and quantitative objective data was collected.

23.2.3 Sheets Versus Creams

There are some limitations to silicone gel sheets. They are not completely self-adhering with some attachment method such as a covering bandage, although clothing can be used in some situations (such as a bra) to aid in fixation. In tropical climates with high humidity, the scar can develop a "heat" rash due to excessive moisture underneath the gel. The gel sheeting can pick up dirt and perspiration which makes cleaning or using new sheets essential. As a practical matter, patients have difficulty wearing the sheets 24 hours/day. Our original studies suggested that using the sheets to cover the scars needed to be utilized at least 12 hours/day to be effective.

Silicone gel creams have been alternative products that address many of the limitations of silicone gel sheeting. They can be used in tropical climates more easily, do not require any additional adherence methodology, and are easier to apply 24 hours/day with twice-daily applications. The question arises whether they are as effective. One potential limitation is the chance that the cream will be rubbed off. Some silicone creams dry in place and are less likely to rub off.

We have addressed the question of efficacy of silicone gel creams in our rabbit ear animal model of hypertrophic scarring and have found the cream to be as effective as sheeting in multiple studies. All of our studies investigating the mechanism of silicone gel that we referred to earlier utilized silicone gel cream because of its ease of use.

Multiple well-done clinical studies have been done over the last 15 years that have confirmed efficacy of silicone gel. In Asian patients who are particularly high risk for hypertrophic scars, Chan [12] performed a randomized, double-blind controlled study in 50 Asian patients with a sternotomy wound following coronary bypass surgery or cardiac valvular surgery. They found that silicone gel significantly reduced multiple scar attributes including visual parameter pigmentation, vascularity, pliability, height, as well as symptoms of pain and itchiness compared with control wounds ($p \leq 0.02$ for all). No treatment-related adverse effects were reported. To date, no comparison studies have directly compared the efficacy of sheeting to silicone gel cream. Due to the very thin film formed by silicone gel cream and the uncertainty of how effectively it remains in place when subjected to rubbing by clothing or movement, it is quite possible or even likely that sheeting might be more effective, but in practice this may be offset by the ease in 24 hours/day use.

Recently a meta-analysis of all prospective randomized controlled trials as well as additional controlled studies between 1990 and 2014 found a total of 11 studies that qualified involving 864 patient scars in which the silicone gel was used to prevent scars. They found a highly positive result from silicone gel or silicone gel sheeting particularly in patients at high risk, but even

when all patient were included, the results were statistically significant ($p < 0.02$) [13].

In summary, silicone gel sheeting has an almost 40-year history, with widespread clinical use for 20 years. Our laboratory and others have found a compelling mechanism based on the semiocclusive properties of silicone gel, which normalize transepidermal water loss in scars with a deficient stratum corneum barrier function, and via the Na channels ENaC and Nax regulated.

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Onion Extract

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_24

24

Background

Multiple studies on hypertrophic scar and keloid formation have led to a multitude of therapeutic strategies in order to prevent or attenuate keloid and hypertrophic scar formation. Until today preventing pathologic scarring remains undoubtedly more effective than treating it later on. Thus, avoiding all unnecessary wounds in any patient, whether keloid/hypertrophic scar-prone or not, remains an obvious but imperfect solution. Since delayed epithelialization beyond 10 to 14 days increases the incidence of hypertrophic scarring dramatically [1], achieving rapid epithelialization is mandatory for avoiding excessive scar formation. Particularly, wounds subjected to tension due to motion, body location, or loss of tissue are at increased risk of scar hypertrophy and spreading [2]. Thus, in case of any cutaneous injury, the goal for rapid primary closure of wounds under little to no tension cannot be overstated. In addition to gentle surgical techniques and suitable suture material, careful hemostasis, and intraoperative tissue treatment, the prevention of wound infections and delayed wound healing are extremely important for good scar healing. The incision should be made along the "Langer" lines of the skin and take esthetic subunits (especially in the face) into account. The patient himself or herself should expose fresh scars to little traction, pressure, and stretching, consistently protect them from the sun, and return early to the treating physician as growth increases. If there is a known tendency to formation of keloids and hypertrophic scars, early intralesional injection of triamcinolone acetonide into the fresh surgical wound after surgery may be considered. According to various studies, next to pressure garments, early and regular application of silicone-based products seems to lead to an improvement in scar quality and an accelerated reduction in redness. Current guidelines emphasize the importance of silicone gels and patches for preventive treatment (at the earliest from the 14th postoperative day for at least 2 months) to avoid excessive scars in high-risk patients.

Topical gels containing onion (*Extractum cepae*) extract have been available for more than 60 years treating, preventing, and reducing dermatologic scars and keloids [3]. *Extractum cepae* is reported to have anti-inflammatory, antimicrobial, antiproliferative, and regenerative activities [4]. Several clinical trials have indicated that *Extractum cepae* may prevent pathologic scarring and improves preexisting scars. It has been introduced as a preventional approach for unpleasant hypertrophic scars in current German scar guidelines in 2012 and in current international scar guidelines in 2014.

24.1 Onion Extract

Extractum cepae acts in an anti-inflammatory manner and is bactericidal. It is currently believed that the flavonoids (quercetin and kaempferol) in onion extract play the main role in reducing scar formation through inhibition of fibroblast proliferation and collagen production. A study by Phan and others suggested that these inhibitory effects may be mediated through inhibition of transforming growth factor-β (TGF-β1, −2) and SMAD proteins by quercetin [5, 6]. Specifically, the authors demonstrated that basal expression and activation of several key proteins in the IGF (insulin-like growth factor)-1 signal pathways were significantly reduced when keloid fibroblast cells were exposed to quercetin. The authors also analyzed keloid fibroblast cells treated with quercetin by means of immunoblotting and electron microscopic approaches. Fibronectin expression was suppressed by quercetin suggesting a strong inhibitory effect of this compound on production of fibronectin. Transmission electron microscopy was performed on keloid fibroblasts with and without quercetin. Keloid fibroblasts without quercetin showed markedly higher density of ECM fibers in a homogenous ECM, but no ECM deposition was seen in the fibroblasts treated with quercetin, indicating a strong effect of quercetin in the suppression of ECM production and deposition by keloid fibroblasts. In a follow-up study, Phan et al. treated keloid fibroblast cells with quercetin at different concentrations, and cells were then harvested and subjected to immunoblotting analysis. In the pathogenesis of keloids, both IGF-1 and transforming growth factor-β (TGF-β) signaling systems are usually overactive, stimulating fibroblast overproliferation and production of collagen and ECM. The data of Phan and colleagues suggested that quercetin could potentially have an anti-scarring effect by inhibiting the signaling pathway of IGF-1 and TGF-β systems.

It has been further demonstrated that several flavonoids inhibit the antigen-induced histamine release from human basophils, which may be of certain importance since there is evidence to the effect that histamine may accelerate collagen formation.

Today, an increasing body of literature and clinical experience are available testing the ultimate clinical benefit of onion extract-containing scar creams as monotherapy (Fig. 24.1) or in combination with other measures (Fig. 24.2). Study data on the efficacy of *Extractum cepae* for prevention and treatment of hypertrophic scars or keloids, however, remains inconsistent, and the quality of the studies is relatively poor.

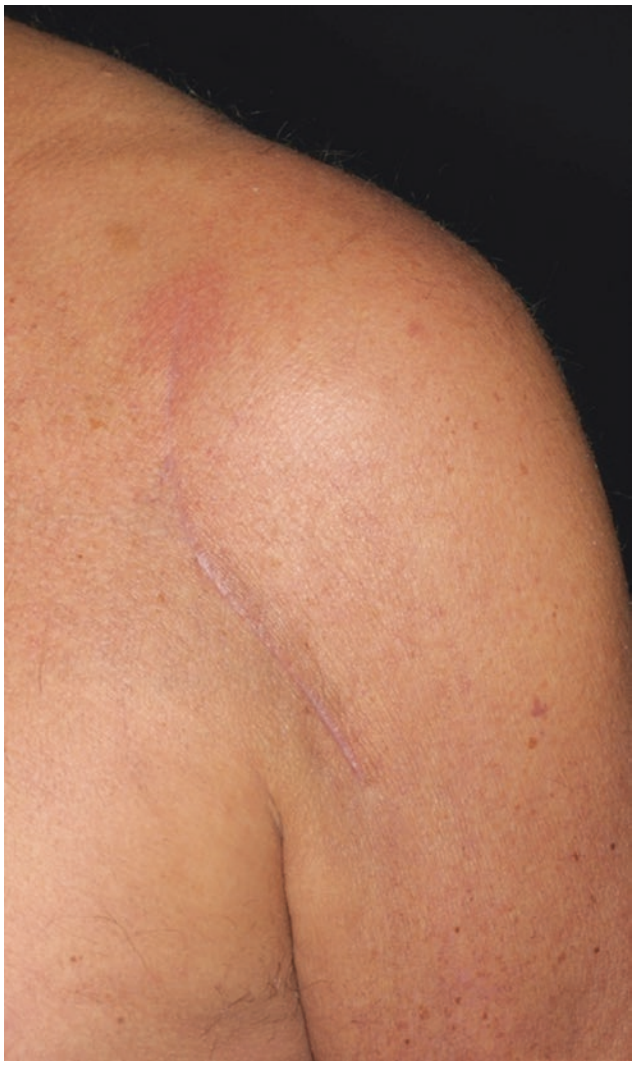

Fig. 24.1 Upper half of the scar has been treated twice daily for 3 months with onion extract gel

Currently several onion extract-containing scar gel preparations do exists that are mainly based on combinations with either allantoin alone or allantoin and heparin.

Willital et al. evaluated the efficacy of *Extractum cepae* in combination with allantoin and heparin on early scars in an uncontrolled, multicenter, prospective observational study in 1268 subjects. In this study, the scar gel was used at least twice daily. The observational period was 4 to 5 months [7]. Data was recorded at start of treatment, after 2–3 months, and after 4–5 months. Even though the authors were able to show some benefit of regular application of an onion extract-containing gel and a considerably high patient satisfaction, the study was completely uncontrolled; did not use any consistent, recognized scar scale; and was thus highly susceptible to bias. For prevention of hypertrophic scars and keloids, a prospective, randomized, controlled non-blinded study on children with surgery on the thorax after 6-month use of a scar gel containing onion extract, allantoin, and heparin observed a less frequent development of excessive scars than in the untreated comparison group [8]. The therapy in the comparative group, however, remained largely unclear with the statement "normal wound therapy." This is of particular significance, as in a further comparative study on improving scar quality (erythema, pruritus, burning, pain, hypertrophy) between scar gels containing onion extract and a topical agent based on petrolatum, a specific effect of the ingredients could not be proven [9]. It must be considered, however, that the patient number in this study was low, the operations were not performed on specific predilection sites such as the thorax, and thus statistically significant results could have been expected only with very high patient numbers. For treatment of hypertrophic

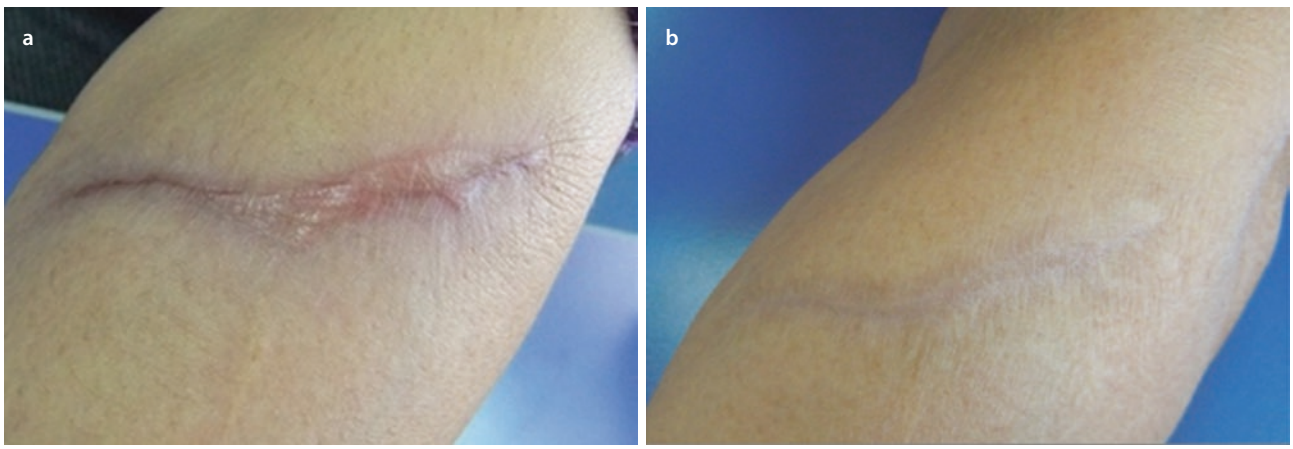

Fig. 24.2 Before (**a**) and after (**b**) three sessions of fractional CO_2 every 4 weeks, in between onion extract-containing scar gel twice daily

scars and keloids, the benefit of a combination of intralesional triamcinolone and an onion extract combinational gel was reported as positive, with both monotherapy with triamcinolone alone and the combination with an additional topical agent containing onion skin extract resulting in statistically significant improvement. A calculation of statistical significance with respect to the differences of the therapy concepts was, nonetheless, not performed in the study [10].

In a prospective randomized controlled trial conducted in China, the use of onion extract was investigated in the prevention of scarring after laser removal of tattoos [11]. Local experience according to the authors found that nearly 25% of Chinese subjects with dark skin (Fitzpatrick types III–IV) developed scarring after laser removal of tattoos. A total of 120 subjects with 144 professional blue-black tattoos were randomized into the onion extract group or the control group. Subjects in the onion extract group applied onion extract to the treatment areas after reepithelialization twice daily in between laser treatment sessions, and subjects in the control group did not apply anything. A total of 52 subjects with 61 tattoos completed the study in the onion extract group. Seven tattoos (11.5%) in seven subjects developed scarring, four subjects (7.7%) had permanent hypopigmentation, and three (5.8%) had permanent hyperpigmentation. The control group comprised 55 subjects with 68 tattoos. Sixteen tattoos (23.5%) in 14 subjects developed scarring, 4 subjects (7.2%) had permanent hypopigmentation, and 5 (9%) had transient hyperpigmentation. According to this publication, the rate of scarring was statistically significantly lower in the onion extract group than in the control group.

It is currently recommended to apply the gel several times daily (usually two to three times a day) with mild massage of the scar tissue. In firm, mature scars use under occlusion or in combination with ultrasound may also be considered. In prophylactic postoperative use, treatment may be started shortly after removal of sutures. In the treatment of open wounds, scar prophylaxis using an onion extract gel should be delayed until complete epithelialization of the wound. Treatment usually continues over several weeks to months. While side effects are generally very low, treatment containing onion extract might be slightly irritating in facial areas, particularly in younger children.

Recently, an onion extract- and allantoin-containing patch has been introduced to the market. This product features an occlusive active release liner with an adhesive layer separated by a micro-air cushion seal. The so-called overnight intensive patch may be cut to size for small scars or placed side-by-side for larger scars. Its efficacy has been elucidated in an intraindividual randomized, observer-blind, controlled study in adults with post-dermatologic surgery scars [12]. Two scars per subject were randomized to no treatment or overnight treatment with the OIP for 12 to 24 weeks. Scar quality was assessed in a total of 125 subjects using the Patient and Observer Scar Assessment Scale (POSAS) and Global Aesthetic Improvement Scale. The authors found a decrease in observer-assessed POSAS from baseline, which was significantly greater for treated than untreated scars at week 6 and 24. The decrease in patient-assessed POSAS was further significantly greater for the treated scar than the untreated scar at week 12 and 24. Subject- and investigator-evaluated Global Aesthetic Improvement Scale scores were higher for the treated than the untreated scar at all visits. According to the manuscript, all subjects considered the global comfort of the OIP to be good or very good, and no safety concerns were identified. Also, no further studies have been published, testing this rather novel product, and current communications do confirm a high patient satisfaction due to the patient orientation application and a certain benefit for early scarring.

24.2 Conclusion

Scarring following surgery or trauma is difficult to predict, and both physicians and their patients are highly concerned with minimizing scar appearance and value even small improvements in scarring as clinically meaningful. Till to date, preventing pathologic scarring remains undoubtedly more effective than treating it. Next to specific surgical techniques and appropriate general aftercare of fresh wounds, a multitude of scar gels, creams, patches, and ointments are available and are being promoted for scarless wound healing. Next to silicone-based products, onion extract or cepalin has been highlighted as one potential anti-scarring agent over recent years. Although its underlying study data remains in part contradicting regarding its efficacy, onion extract-containing scar creams appear to positively influence scar texture, height, and associated symptoms compared to placebo or untreated control. Based on the recently published German guidelines on scarring, onion extract-containing scar creams may be considered as additional therapy for active hypertrophic scars and for postsurgical prophylaxis of excessive scarring.

Take-Home Messages

- Preventing pathologic scarring remains undoubtedly more effective than treating it.
- Next to silicone-based products, onion extract-containing creams have been shown to positively influence scar maturation if used shortly after wound healing.
- Data remains contradicting, but guidelines have incorporated onion extract in their recommendations on preventing unpleasant scarring.
- Onion extract-containing products are available as creams, ointments, gels, or patches.
- Therapy can be started after complete epithelialization of the wound and should continue for 12 to 24 weeks.
- Onion extract-containing products are safe, and side effects beyond irritation of the treated skin are extremely rare.

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Treatment of Immature Scars: Manual Massages

Docteur N. Frasson

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_25

25

25.1 Background

Scar massages are used to improve skin qualities in terms of flexibility, adhesions, pruritus, and pain. The specific techniques are not always mastered by all the therapists. Indeed pathological scars can appear following strong massage movements or too long sessions during the inflammation stage. The techniques must be controlled and take into account the inflammation, the appearance, and the localization of the scar.

25.2 Introduction

Care of the burn skin and scars requires specific treatments to reduce and control the inflammation stage and its consequences [1, 2]. Adapted rehabilitation technique restores flexibility and limits esthetic and functional sequelae. The treatment will progress and be adapted throughout the scar maturation process. Several specific manual massages are part of the treatment but have to be applied respecting the inflammation, the fragility, and the localization of the scar [3, 4, 5].

25.3 Indications of Manual Massages

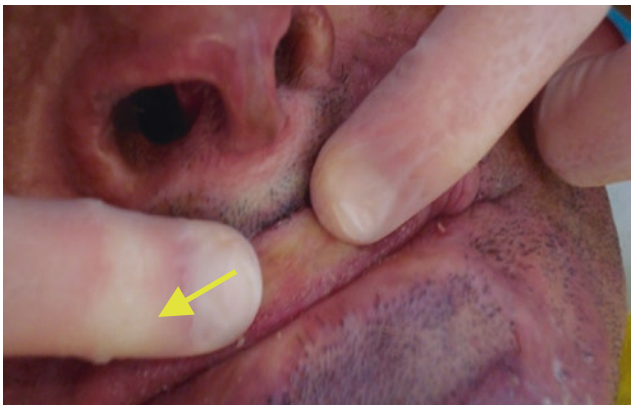
Manual massages allow to improve cutaneous mobility compared with the deep plan and its elasticity. They are indicated on burn scars but also in case of traumatic or surgical scars [6].

They can be started as soon as the scar tissue is epidermized and solid and allows to support specific manual techniques. The massages are contraindicated when the tissue is thin and hyper-inflammatory. When the skin is fragile and presents a vitropression test less than 1.2 seconds, the massages will be realized at first around the scar [7, 8].

25.4 Description of the Techniques

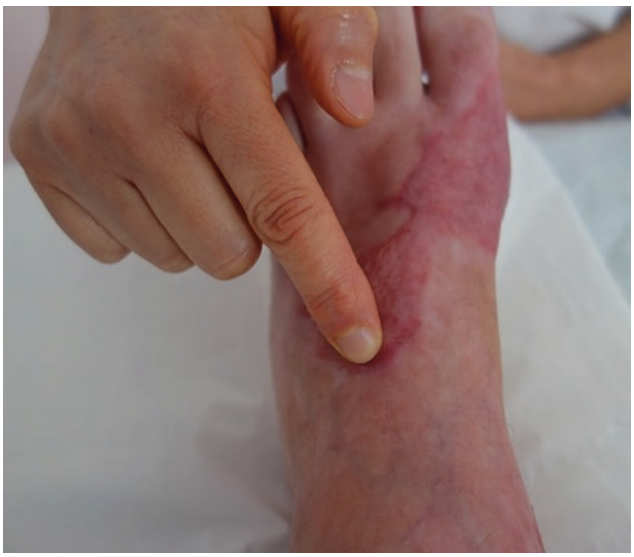
25.4.1 Morice Orthodermic Stretching

Orthodermic stretchings such as they were described by René Morice are compatible with an inflammatory skin. Indeed the technique can be summarized by a fixed pulpaire pressure associated with a moderated stretching supported in the inverse direction of the retraction. This kind of massages is frequently used on the face and dorsal side of the hand.



25.4.2 Punctual Crushing

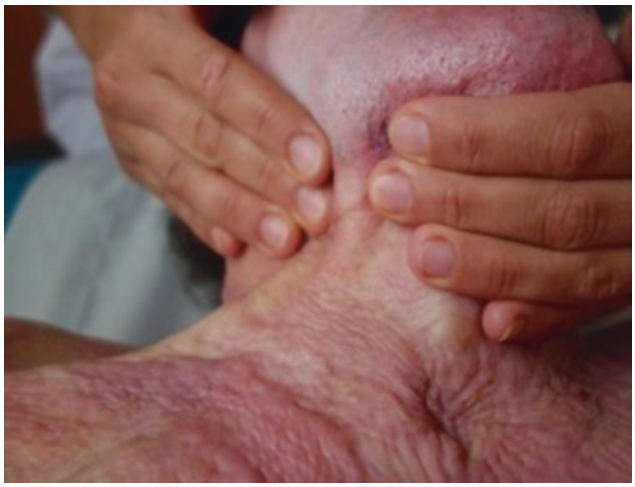
The punctual crushing is also used during the inflammatory stage and allows to crush the edges of grafts or hypertrophic scars. The pressure is moderated, vertical, and realized with the pulp of one or several fingers. The pressure can be circular but without practicing however of friction or lifting fingers.

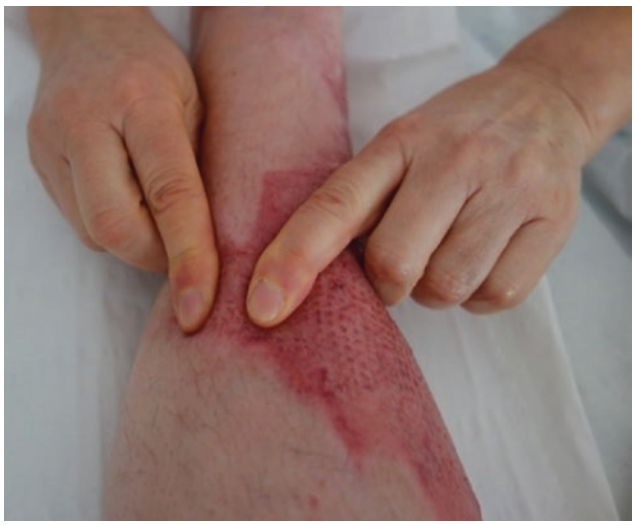


25.4.3 Static Fold

Statics folds are realized during the inflammation stage on a solid epidermis and when the vitropression test is close to 2 seconds. They improve various plans if sliding and have an action on the suppleness of the skin.

According to the surface or area to be treated, they are realized between two fingers or more globally between two hands. There are no movements of friction during this care.





25.4.4 Palpate-Rolling

When the vitropression test gets closer to 3 seconds, the static fold evolves in rolled fold. This also significantly softens the deep plans and fibrosis scars. Palpate-rolling has also an interest to raise adhesions. It is crucial to observe the scar tissue before, during, and after the massage treatment.

25.4.5 Efficacy

The massages are widely used within the care and rehabilitation of burns and scars.

The techniques have a role in the improvement of the characteristics and evolution of the scar.

25.5 Conclusion

Treatment of skin and scar following burn injuries must be performed with caution and requires the input of the whole multidisciplinary team. It is necessary to align the treatment according to the stage of scar maturation. The inflammation of the scar is the main factor to consider to guide the therapist's treatment [9].

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Treatment of Immature Scars with Botulinum Toxin

Alexandra Chambers

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26.1 Background

Botulinum toxin type A (BoNTA) and occasionally of serotype B has been used for treatment of conditions associated with muscle spasm, hyperhidrosis and improving appearance of static rhytides.

The same neuronal effects and a muscle tension reduction at the site of injury were initially attributed to the benefits of BoNTA in a scar formation. However, a more detailed research into effects of BoNTA on wound healing suggested a variety of biologic effects of the toxin. New possibilities emerged for using BoNTA to modify early tissue repair mechanisms to promote more favourable outcomes and less noticeable scars.

26.2 Chapter Introduction

The Botulinum toxin A (BoNTA), and to a lesser degree type B (BoNTB), is used in clinical practice for the treatment of conditions associated with muscle spasms. The therapeutic indications include cervical dystonia, blepharospasm, strabismus, chronic migraine, and severe axillary hyperhidrosis. BoNTA is also approved for esthetic use in the treatment of facial wrinkles such as "crow's feet" and frown lines. In addition, there are many unlicensed off-label uses of BoNTA for the treatment of various other conditions.

The demand for BoNTA products is rapidly expanding due to ever-increasing esthetic applications, and there is a plethora of BoNTA formulations available across global markets. This can make it difficult to identify an adequate product for any specific application.

The most popular and well-tested products are Botox (onabotulinumtoxinA) and Vistabel (specifically for esthetic applications) that are manufactured by Allergan (USA). Dysport (abobotulinumtoxinA), marketed as Azzalure for cosmetic applications, is made by Ipsen Ltd. (UK) and Galderma Laboratories (USA). Xeomin (incobotulinumtoxinA) and its esthetic brand, Bocouture, are made by Merz Pharmaceutical (Germany).

Less known preparations include Evosyal made by Puretox (USA) and Linurase made by Phiderma (Canada). BoNTB preparations such as Myobloc (rimabotulinumtoxinB) are marketed by Solstice Neurosciences (USA). Other BoNTA products are available in Asian and Russian markets.

Although normally injected into the skin layer, several products for the topical delivery of BoNTA have become available recently. Examples include ANT-1207 (Anterios/Allergan), CosmeTox (USA), and RT001 (Revance, USA).

Each BoNTA product has a Botulinum toxin combined with a variety of other complex proteins, and each manufacturer uses a different assay to determine the potency of their batches. These differences make it difficult to compare clinical responses across products.

Recent studies have shown that BoNTA improves the appearance of established scars and can also positively affect the early stages of tissue healing for a more favorable mature scar. This chapter examines evidence of the BoNTA effects on early stages of scar formation and describes how this can be employed for controlling scar development as it occurs. Practical guidance on optimal doses of injections and on treatment protocols is described and evaluated. Choices of the BoNTA preparations used for immature scar treatment are also discussed.

26.3 Botulinum Exotoxin, Structure, and Mechanism of Action

Botulinum neurotoxin (BoNT) is an exotoxin of *Clostridium Botulinum* bacteria, which has several serotypes. In clinical practice, the serotypes A (BoNTA) and B (BoNTB) are most used for therapeutic, experimental, and esthetic purposes; however, due to their superior longevity of action, preparations of BoNTA have become the most popular.

26.3.1 Structure of BoNTA

The BoNTA molecule is made of a heavy (100 kDa) and a light (50kDA) polypeptide chain, linked together by a disulfide bond. The neurotoxin complex also includes associated nontoxic proteins: three hemagglutinin (HA) proteins and one non-HA protein. These play a role in transporting and protecting the toxin core.

26.3.2 Neuronal Mechanism of Action of BoNTA and Effects on Immature Scars

BoNTA impairs release of acetylcholine by disabling a soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) protein. The latter facilitates acetylcholine release by mediating docking and fusion of synaptic vesicles with the inner surface of the axonal membrane at the sites of release.

BoNTA adheres by its heavy chain to cholinergic cell membrane surface structures such as ganglioside moieties, a vesicular protein (SV2) and synaptotag-

min. Its light chain enters the neuronal terminal and reaches the cytosol (vesicles). It cleaves SNARE proteins: synaptosomal-associated protein (SNAP)-25, syntaxin, and vesicle-associated membrane protein (VAMP) also known as synaptobrevin II. The acetylcholine release into the synaptic cleft is impaired and the cholinergic mediation of neurons is blocked. Furthermore, BoNTA has also been shown to impair release of other neurotransmitters, such as glutamate, substance P (SP), and calcitonin gene-related peptide (CGRP).

The absence of the necessary mediator leads to a "chemical denervation" and temporary atrophy of the neuromuscular junction with a subsequent block of muscle contraction or reduction of exocrine glandular secretion.

Several studies involving animal and human subjects have tried to determine how reducing muscle contractility in the immediate vicinity to a fresh wound improves the esthetic result in scars. To date, findings have been inconclusive.

Immobilization of underlying musculature, reducing tension of the wound and skin (similar to the use of a surgical Z-plasty), has resulted in more favorable scarring according to Ziade M et al. (2013). Patients in this research were injected within 3 days following facial surgery, and results were assessed using a visual analogue scale. However, no statistically significant differences were found between the two groups in this study when using other assessment methods [1].

In another example of effects of BoNTA on the early stages of wound healing, researchers Lee B-J et al. (2009) [2] used a rat wound model. In this study, each of 15 animals was its own control. The results showed significant differences in wound size between BoNT-treated and untreated control wounds. Also observed were less infiltration of inflammatory cells, fewer fibroblasts, and a lower expression of transforming growth factor (TGF)-β1 (as compared to the control wounds).

TGF-β1 is a cytokine that has multiple mediatory actions in tissue healing, and it is involved in the formation of fibrotic tissue and hypertrophic scars. The finding that BoNT-treated wounds show a lower amount of TGF-β1 may be the result of the chemoimmobilization of the muscle as well as of a direct effect of BoNTA on the expression of TGF-β1 in fibroblasts and fibroblast proliferation.

It is known that a muscle paralysis due to the inhibition of acetylcholine exocytosis is reversible by natural SNARE protein recovery. After application of BoNTA, it takes 2 weeks to 4 months for neurotransmission to recover. Therefore, its period of action is definitely within the timeframe of early scar formation. Nevertheless, the effects of BoNTA on tissues are more complex than just reducing tension and decreasing TGF-β1.

26.3.3 Nonneuronal Mechanisms of Action of BoNTA and Effects on Immature Scars

More research into Botulinum toxin demonstrates that its biological effects on various cells and tissues are much more complex than previously understood [3]. The BoNT receptors and intracellular targets are not unique for neurotransmission, as several of these receptors and targets have been found in neuronal and nonneuronal cells.

BoNTA, for example, can attach to some other cell-surface proteins and, through them, modulate the function of a variety of human cell types [3]. These proteins include E-cadherin, fibroblast growth factor receptor 3 (FGFR3), and vanilloid receptors. Indeed, epidermal keratinocytes, dermal fibroblasts, sebocytes and vascular endothelial cells, adipocyte-derived mesenchymal stem cells, and many other cells including macrophages and neutrophils have receptors capable of binding and cleaving the BoNTA molecule. Therefore, the effects of BoNTA at the nonneuronal level have an impact on inflammatory and immunological cascades, neurosensory signaling, cellular inhibition and proliferation, vascular and tissue differentiation, and growth (or atrophy). Familiarity with these effects is useful in understanding how BoNTA is helpful for tissue healing and scar development.

26.3.3.1 Effects of BoNTA on the Inflammatory Cascade

Both pro- and anti-inflammatory effects by BoNTA have been demonstrated in animal models and cell cultures. Those effects are expressed on additional binding sites for BoNTA and its carrier proteins. These have been identified at the RMS 13 receptor sites of skeletal muscle cells, TIB-152 of lymphoblasts, Detroit 551 of fibroblasts, and SH-SY5Y of neuronal cells. BoNTA alone does not induce inflammatory responses; it only does so in a complex with the Neurotoxin Associated Protein (NAP). The latter is responsible for the release of pro-inflammatory cytokines such as IL-6, IL-8, MCP-1, and TNF- α at these sites [4]. This last reference suggests that it is NAP that determines the pro-inflammatory effects of BoNTA at the time of the toxin application.

The inflammatory phase of a wound healing lasts approximately 2–4 days. It is marked by an abundant

release of cytokines, growth factors (such as platelet-derived growth factor (PDGF)), interleukin-1 and interleukin-8 (IL-1 and IL-8), chemokines, and hormones. These all work to sustain activation of the target cells and promote migration of the inflammatory cells.

PDGF and transforming growth factor-β (TGF-β) released by Alpha granules of platelets attract neutrophils and macrophages. The latter scavenges the wound site, and the former produces transforming growth factor (TGF), tissue growth factor-α (TGF-α), and epidermal growth factor (EGF). These give rise to fibroblast and keratinocyte migration, signaling the start of the proliferative phase of healing.

Once the heavy and light chains of BoNTA have reached their targets, inflammation starts downscaling. They reduce lymphocyte proliferation and migration and decrease cytokine expression. This is seen a few days after wounds have been treated with BoNTA [2, 3].

BoNTA has also demonstrated the ability to decrease inflammatory enzyme cyclooxigenase-2 (COX-2) and prostaglandin E2 receptors [5] in animal models and cell cultures. It also decreases the infiltration of monocytes and macrophages while blocking expression of interleukins-1B (IL-1β). Moreover, it is able to suppress nitric oxide and tumor necrosis factor-α (TNF-α) via inhibition of specialist receptors on macrophages [6].

Inflammation in tissues is often associated with pain and itching. BoNTA reduces pain by local muscle spasm relief and by blocking cholinergic and other neuropeptide sensory transmission. However, it is now known that BoNTA has effects at sites distant to the injection location, as well as at a central level. In addition to the local uptake of BoNTA in the synaptic terminal, a distinct retrograde transport pathway results in accumulation of BoNT toward the neuronal soma. This retrograde channeling facilitates remote action of BoNTA at the dorsal root ganglion and the spinal cord, and it is believed to explain the efficacy of BoNTA used for the control of pain [7]. In addition to neurons, the glial cells such as Swann's and astrocytes are also receptive to BoNTA, which suggests yet another pain modulation mechanism.

BoNTA also has been shown to reduce infiltration by cutaneous lymphocytes and decrease acanthosis, processes associated with intense itching (most commonly mediated by histamine). BoNTA affects chemotaxis of mast cells, affecting their migration and histamine release and IL-4 expression. The histamine acts as the main mediator of H1-H4 receptors, responsible for activation of the target molecules within the sensory neurons that code pruritic signals. BoNTA also downregulates transient receptor potential channel type V1 (TRPV1) and type A (TRPA1), responsible for histamine-mediated and non-histamine-dependent itch, respectively [8].

It is believed that the ability of BoNTA to moderate a florid inflammatory response and control itch and pain may explain its off-label use in treating scar hypertrophy and keloid formation. A recent double-blind randomized study concluded that BoNTA was as effective as steroids when injected into keloid scars, but patients additionally reported the alleviation of pain and itching after use of the former [9].

In experiments, BoNTA has demonstrated properties inhibiting the overgrowth of a variety of cells, including malignant proliferation in breast, prostate, and colon cancers. It has been theorized that this is the same mechanism as the one that provides its inhibitory effects on fibroblast proliferation. This has motivated the use of BoNTA on the unchecked growth of the cells leading to keloid deposition.

26.3.3.2 Effects of BoNTA on Fibroblasts and Keratinocytes

BoNTA has a direct effect on dermal cells such as fibroblasts and keratinocytes and through them can positively mediate dermal tissue remodeling. This is an important characteristic for reversing the effects of skin aging, assisting in wound epithelization, and reducing scar formations.

Fibroblasts and their differentiated subset, myofibroblasts, are the main components of the proliferation phase in wound healing. The transforming growth factor-beta 1(TGF-β1) prompts some of the fibroblasts to differentiate into myofibroblasts, possessing a retractile protein alpha-SM (α-SM), similar to those in smooth muscle cells. Myofibroblasts create bridging connections and promote the approximation and retraction of wounds. They do this by creating a matrix that further promotes the migration of additional fibroblasts and keratinocytes [10]. BoNTA seems to interrupt the differentiation of fibroblasts to myofibroblasts by blocking TGF-β1 signaling and in so doing reduces excessive wound retraction and scar thickening [11].

Fibroblasts are also responsible for angiogenesis in a healing wound. This is mediated by fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), both of which also promote epithelization and collagen synthesis. Epithelial growth will happen either from the basement membrane or from the edges of the wound by migrating keratinocytes. BoNTA acts to increase migration, proliferation, and differentiation of keratinocytes and the expression of epidermal growth factor (EGF). Collagen type III is mainly produced in this stage, actively promoted by IL4 mediators. Subsequently collagen type III degrades, and it is replaced by collagen type I with reorganized orientation of the fibers. This adds strength to the resulting scar.

BoNTA influences the ratio of collagen I to collagen III by increasing or inhibiting its degradation by matrix

metalloproteinases (MMPs) [12]. Excess of collagen synthesis by fibroblasts can determine scar hypertrophy and keloid formation, whereas lack of collagen matrix can predispose to a weak scar with atrophy [13].

26.3.3.3 Effects of BoNTA on Vascular Endothelium

BoNTA has been shown to have protective effects on dermal flap survival in animal models even with adverse conditions such as nicotine exposure, oxidative stress, or preexisting diabetes. BoNTA reduced accumulation of reactive oxygen species and prevented oxidative damage to endothelial cells. It increased the blood flow in dermal vasculature by dilating lumen of the blood vessels. The model skin flaps also had increased production of vascular endothelial growth factor (VEG) and expression of platelet endothelial cell adhesion molecules 1, CD31 and CD34 lymphocyte subsets, interleukin (IL)-1, and tumor necrosis factor (TNF) [14].

26.4 Clinical Application of BoNTA for Treatment of Scars

The time frames of the various stages of wound healing are not precise and can be overlapping. The vascular stage lasts for roughly 24 to 48 hours after trauma, and the inflammatory phase runs 2 to 4 days. The proliferative phase starts from roughly day 3, peaks around day 7, and finishes after 2 to 4 weeks. Finally, scar maturation (often referred to as remodeling) can take up to 12 months.

The usefulness of BoNTA in the management of immature scars (by definition, less than a year old) can be summarized as follows:

- Reduces local muscle contractility, allowing better approximation of the edges of healing wounds
- Moderates the inflammatory response at the site of the injury via suppression of inflammatory cytokines and neuropeptides
- Reduces pain and itching in healing wounds (these effects can be both peripheral at the site of the scar and central through a retrograde uptake of the toxin)
- Inhibits excessive proliferation of fibroblasts and their increased differentiation under TGF-β1 into myofibroblasts and so downgrades the over-proliferative scarring and retraction of the wound bed
- Mediates MMP enzymatic activity in controlling expression of collagen fibers, optimizing collagen I to III ratios, and preventing fibrosis and scar thickening

26.4.1 Timing of BoNTA Injections

The most efficacious timing of BoNTA application remains to be determined. For example, some researchers advocate injecting the toxin before surgery [15, 16] for better titration of BoNTA dose and improving local circulation via inhibition of norepinephrine. In other studies, BoNTA have been applied intraoperatively [17] at the time of wound closure or within the first 24 hours [2, 18–20]. Several clinicians have reported using the toxin after 72 hours [1], while others injected BoNTA at the time of suture removal (7 to10 days) [21]. In another study, BoNTA was only used at the time of a scar revision [22].

As can be seen, there are a wide variety of protocols proposed in the literature for the timing of BoNTA injections. That said, in the context of the discussion in Sect. 2, there are good reasons to prefer a single, early application of BoNTA from the onset of an injury. This timing is the one that has the best potential of benefitting from all the additional effects of BoNTA.

26.4.2 Choosing BoNTA Preparation

The majority of published studies have used BoNTA preparations, including ona-, abo-, and incobotulinumtoxinA. However, BoNTB had been reported to also have beneficial results in wounds healing in a study involving facial reconstruction surgery [17]. Most other published studies use BoNTA, namely, the brand preparations such as Botox, Dysport, and Xeomin. Quantitative reporting on conversions of BoNTA unit rate and levels of toxin spreading is mainly based on these three products. Given the availability of the data, it would seem prudent to continue using the well-tested products when planning a scar treatment.

26.4.3 Reconstituting BoNTA

Currently BoNTA preparations are manufactured in lyophilized powder form. There have been some attempts at creating liquid preparations; however, these are not widely available.

Normal saline is most commonly used for the reconstitution of the toxin. Gassner et al. (2000) [18] have recommended mixing BoNTA with lidocaine and epinephrine, the former for immediate efferent block and the latter for the reduction of toxin diffusion.

Preparing BoNTA with bacteriostatic normal saline (BNS) reduces the discomfort of injections. Various dilution proportions have been tried, but the most com-

mon volume of saline used per 100 U of BoNTA was 1.5 to 2.5 ml. For keloid and large surface scars, the volume of BNS can be doubled.

26

26.4.4 Dose of BoNTA for Scar Treatment

A dose titration for a novel application of any medicine is always a challenge, and the amount of BoNTA required for the treatment of scars seems to be much lower than traditional doses used for immobilizing muscles and treating wrinkles. The most popular BoNTA doses tried in various studies have been 5 U [21], 7 U [18, 19], and 10 U [2]. In the main, however, these studies do not provide a rationale for their choices.

One reference, however, performs a preliminary systematic study of BoNTA dosages to determine optimum outcomes. Quantities of 5 U, 15 U, and 25 U of BoNTA were used on the postoperative wounds of rhytidectomy patients [20]. For the specific approach of this study, the best results were obtained with the use of about 15 units of BoNTA. That said results might vary significantly if other parameters are adopted. Facets that could be investigated going forward could include modifying the injection protocol. For example, these results suggest that increasing the number of injection points might achieve a more uniform reduction in scar width.

This last study seems to correlate to in vitro experiments demonstrating the dose dependencies of keratinocytes and endothelial cell function when subjected to the effects of BoNTA [25]. Doses lower than 20 units were found to support proliferation of endothelial cells but higher than 20 units impaired keratinocyte and endothelial migration and growth, these being responsible for epithelization and angiogenesis, respectively.

26.4.5 BoNTA for Treatment of Keloid and Hypertrophic Scars

The treatment of pathologically healed wounds such as keloid and hypertrophic scars is a difficult and often fruitless task. BoNTA has demonstrated some promising results for reducing stiffness, hardness, and pain characteristic for these types of scars; see Figs. 26.1 and 26.2.

Studies based on repeated monthly application of BoNTA, involving multiple injections of the toxin covering the entire surface of a scar, have shown some effectiveness [23, 24]. In these cases, the maximum concentration of 35 U was diluted to enable full coverage of the scar area. The injection volume was reduced into a microdroplet to ensure distribution was mainly in the skin and the superficial muscle layer [24].

Fig. 26.1 A post-traumatic hypertrophic scar, restricting articulation of the patient

Fig. 26.2 The scar is reduced in size and more pliable following a single session of BoNTA injections

26.4.6 Summary of Practical Guidelines for the Application of BoNTA in the Treatment of Scars

In summary, a practical clinical approach for the treatment of scars is to administer BoNTA reconstituted in 1.5 to 2.5 ml of bacteriostatic normal saline (BNS). Injections should be made using a superficial intradermal technique. The expectation is that the toxin will travel in the vertical and horizontal plane, reaching superficial muscles and even distant central locations by retrograde uptake. Leaving a 1 cm margin from the freshly sutured wound (see Fig. 26.3) and 1 cm between injection points (see Fig. 26.4) would seem to be adequate based on reported BoNTA diffusion distances. The total dose of BoNTA should remain below 20 U. A one-off treatment is likely sufficient to promote better healing of the wound and to achieve more favorable scarring.

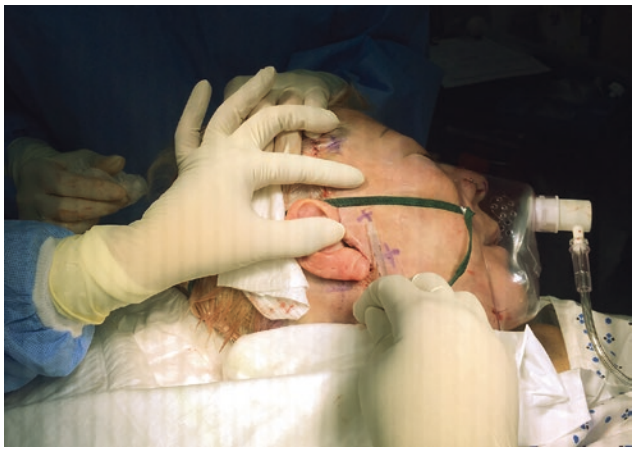

Fig. 26.3 BoNTA is injected immediately after closure of the facelift wound, about 1 cm anterior to the margin

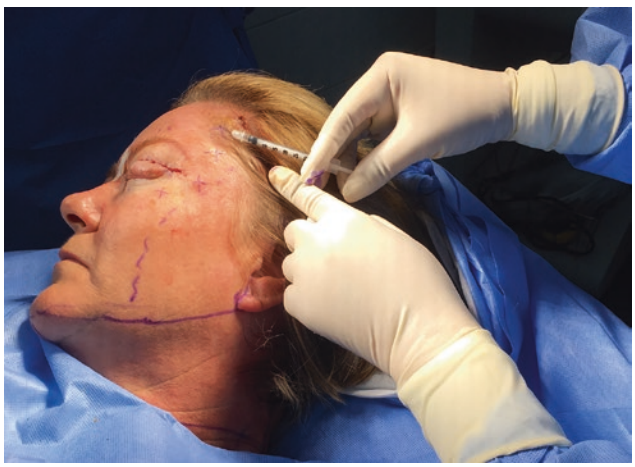

Fig. 26.4 BoNTA injections spaced evenly 1 cm apart after upper blepharoplasty and eyebrow lift surgery

For scars already displaying features of keloid or hypertrophic change, reconstituting 20 U of BoNTA in 3 to 5 ml of BNS is recommended. An example of this is shown in Fig. 26.5. Injections, delivered in microdroplets, should be applied to cover the whole surface of a pathological scar (similar to a mesotherapy technique). Monthly repeated treatments, consisting of three to eight sessions, are advised.

26.5 Conclusions

The scope of using of Botulinum toxin for various conditions is ever expanding, and the benefits it provides for tissue healing and immature scar management are gaining recognition and acceptance. Clearly, the complex effects of BoNTA on various cells and tissues are still not fully understood, and we continue to discover more about its full range of biological effects and useful applications. This chapter concludes with a description of practical approaches for the use of BoNTA in managing scarring in a clinical environment.

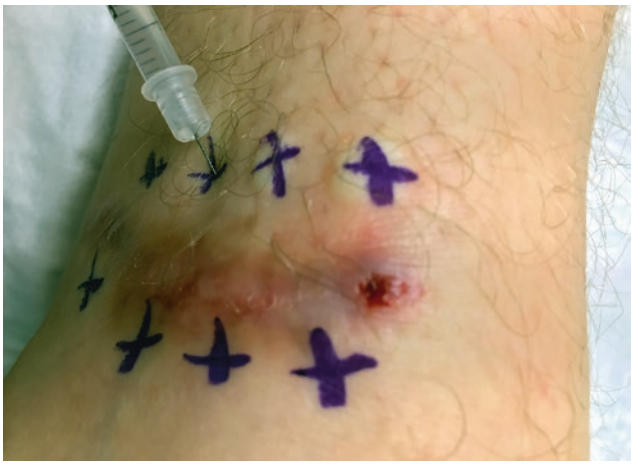

Fig. 26.5 BoNTA injections should cover the entire surface of the early keloid scar and the adjacent normal skin

Take Home Message

- Effects of BoNTA on wound healing are multifaceted and not restricted just to the underlying muscles relaxation and a wound tension reduction. The toxin exerts influence on various cells and tissues involved in tissue repair following an injury. BoNTA can alter inflammatory reactions, cellular proliferation, mediation and inhibition
- Early application of BoNTA, within 24–72 hours of initial injury seems to ensure a less conspicuous scar
- All well known commercially available BoNTA preparations seem to be effective for that purpose
- A dose of 15 -20 units of BoNTA demonstrated to be sufficient to benefit for a wound of a traditional rhytidectomy length (15–20 cm). The preparation injected in equal amounts of 1–5 U spaced evenly along the length of the wound 1cm from the border. Injection points can be spaced either along the both sides of the wound or a just unilaterally.
- Dilution of the BoNTA for wound treatment was 1.5 -2 ml of Bacteriostatic Normal Saline for 100 u of the Botox (or equivalent in case of other products). For larger surface wounds BoNTA could be diluted in a double amount of saline to provide a sufficient volume for coverage, as the dose of up to 20 u is still applicable in these cases

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Compression Therapy and Conservative Strategies in Scar Management After Burn Injury

Eric Van den Kerckhove and Mieke Anthonissen

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Background

Since a few decades, the focus of treatment of burn patients has shifted from survival to optimizing the rehabilitation outcome of patients with severe scars. This outcome can influence both physical as well as psychological well-being and quality of life of the patient. Therefore, the interest in the field of conservative scar management of these patients has risen drastically. In this regard, the golden standard in all medical or paramedical treatments is aiming for evidence-based interventions. Also in this rather new domain of scar rehabilitation, caregivers strive to use the most efficient therapies. Unfortunately, for most of the daily used interventions, the number of proper scientific clinical trials is still limited and therefore the evidence-based level of many of them is often low. As a consequence, the recommended therapies are often based on recommendations or guidelines written by a group of specialists based on their expertise and available literature. This chapter focuses on the most relevant noninvasive strategies in the aftercare of patients with severe scarring after burn injury with special attention to compression therapy.

ferent conservative therapeutic strategies that are mostly used in the rehabilitation of patients with severe scars after burn injury. These strategies include pressure therapy, the use of silicones as a contact medium, massage, the use of moisturizers, splinting and positioning, exercise, and mobilizations. The relevance of the conservative therapeutic strategies will be situated within the field of the available scientific literature or guidelines.

According to the World Health Organization (WHO), annually nearly 11 million people worldwide are burned severely enough to require medical attention. Aesthetic and functional outcomes have become increasingly important, as overall mortality from burn injury has decreased. Hypertrophic scar formation is a common and bothersome complication after a severe burn injury or even after minor burns, due to its functional and aesthetic consequences. These scars, which usually develop after 6–8 weeks of wound closure, are typified by the following characteristics. The red to deep purple color of the scar reflects an enhanced microcirculation. The hypertrophic scar becomes more elevated, firm, warm to touch, hypersensitive, and itchy but the lesion remains within the confines of the original scar. The elevation, firmness, and retraction of the scar is probably due to an overabundant collagen deposition as a cellular response of the fibroblast during the proliferation phase of wound healing. The contraction of the scar has been linked to the presence of fibroblasts with contractile properties, called the "myofibroblasts." Generally, a period of at least 6–18 months is required for maturation of burn scars at which time the redness (erythema) of the scar subsides, the scar no longer appears inflamed, and the scar contraction diminishes.

Many factors can influence the presence or severity of hypertrophic scarring after a burn injury. Genetic predisposition, race, anatomical location of the burn, age, and depth of the burn are some of the factors that are known as "uncontrollable or extrinsic factors," whereas infection, type of wound healing (surgical intervention or not), and tension are factors that can be considered as "extrinsic or controllable" factors. The prevalence of hypertrophic scarring ranges from 32% to 72%. Female gender, young age, race or ethnicity, burn site (on face, neck, and upper limb), multiple surgical procedures, meshed skin grafts, time to heal longer than 2–3 weeks, more than 20% total body surface area (TBSA), and burn severity are some of the identified risk factors.

The scar management treatments in patients with burns have gained a lot of interest recently. This increase in interest is entirely correct, as the quality of life of these patients can be significantly influenced if one can improve the clinical parameters of scars. Burn scar-related symptoms show a proximal impact on health-related quality of life. Therefore, the scar management interventions have high interest in the improvement of quality of life of burn patients, especially those with visible scars and severe burns. Scar management in the treatment of burn patients includes a wide variety of aftercare methods and physio- and occupational therapeutic techniques such as pressure therapy, silicone therapy, massage, moisturizers, splinting and positioning, exercise, and mobilizations.

Of all the noninvasive therapeutic treatments, pressure therapy is one of the most successful, widely used, and evidence-based techniques in the prevention and treatment of hypertrophic (burn-related) scars [1]. In the late 1960s, Dr. Silverstein at Brooke Army Hospital in San Antonio observed that in a patient with burns, vascular support garments for the treatment of a postphlebitic syndrome decreased scarring after a burn injury and Larson noted the same effect with pressure-exerting splints on scar tissue. The use of compression in the prevention of burn scar hypertrophy was then further popularized at Shriners' Burns Institute in Galveston at the beginning of the 1970s.

Furthermore, silicone therapy is also a popular and evidence-supported conservative treatment to prevent or treat hypertrophic scars [2]. The first silicone applications were individually made as a pressure device or pad to solve concavity problems under pressure garments. The pressure pads are individually made using elastomer (medical grade with catalyst), putty, or foam, and

fitted directly on the patient. They are usually worn in combination with classical pressure garments, masks, and splints. Silicone applications can also be applied directly to the scar without any intention to augment or establish pressure on the scar. In the 1980s, silicone gel sheets were effectively used for the first time in the treatment of burn-related scars, however without clear standardized treatment protocols. Since the beginning of the 1990s, publications and protocols about the use of silicone sheets and gels as contact media in the prevention of hypertrophic scarring and contractures started to appear. They remain very popular as a conservative strategy ever since.

Concerning the other noninvasive treatment modalities, such as massage, the use of moisturizers, positioning and splinting, exercise, and mobilizations, the number of published controlled trials (randomized controlled trials [RCTs] of controlled clinical trial [CCTs]) for each category is rather low and within each category, different techniques or types of applications and products are used. In the field of rehabilitation, especially in burn rehabilitation, controlled randomized double-blind trials are practically and ethically extremely difficult to perform. Due to this shortcoming, except for the effect of pressure on the thickness of a scar, there is no real scientific consensus on the actual effect of the various treatment modalities. Therefore, most recommendations are mostly made based on guidelines and consensus meetings of experts [3–8].

Pressure therapy is indicated to prevent and treat skin grafts and wounds that take longer than 14–21 days to heal, because of the higher risk of hypertrophic scar formation. As soon as the healing skin tolerates compression and shear forces, pressure therapy is recommended for 23 hours per day until scar maturation. Continuous pressure on scars can be exerted by means of custom-fitted pressure garments, orthoses or transparent face masks, casts, or splints, measured by trained technicians or therapists. The optimal amount of pressure required remains controversial. Theoretically, pressures that exceed 24 mmHg pressure to overcome capillary pressure are required. However, good clinical results have been reported with levels as low as 5–15 mmHg pressure. Many authors however state or show that 15 mmHg or even higher, 20 mmHg to 30 mmHg, is necessary to accelerate the maturation process and that the effects of pressures below 10 mmHg pressure are minimal [1, 9]. Higher pressure increases the effect, but can also induce complications such as paresthesia, blistering, abnormal bone growth, limb necrosis, etc. The generated pressure plays a crucial role and needs to be monitored regularly (e.g., by using a simple pneumatic pressure sensor, such as for instance the Kikuhime pressure sensor). The Kikuhime pressure sensor has been tested in clinical circumstances and was found to be reliable and valid in the assessment of the efficiency of pressure garment therapy. The pressure of pressure garments needs to be checked every 2–3 months and, if necessary, they need to be replaced or modified to achieve optimal results [1]. Frequent washing and proper hygiene with a minimal use of ointments, lotions, or moisturizers that contain unsaturated lipid acids can help in reducing the aging and wearing of the garments.

There are mainly two different types of pressure garments that are used in the treatment and prevention of hypertrophic burn scars: elastic tricot and powernet structures. The first type of elastic tricot garments are mostly woven knit structures with a biaxial stretch and a multidimensional structure. These elastic tricot garments usually tend to be delivered with less tension (or pressure values on the scar) but maintain the pressure longer than powernet garments. The powernet structure garments have mostly one-axial stretch and a plenary open structure. The second type, the powernet garments are a bit more comfortable pertaining to water vapor permeability in summer or warm climates, but are more fragile due to their open structure. Also therefore elastic tricot garments offer a far better protection against UV rays, a property that cannot be underestimated since pigment changes are one of the most important sequelae after a severe burn injury with a higher risk for UV-induced malignant changes as result. Although the exact value for this protecting factor of the garments (UPF) is not defined, for textiles of common daily worn clothing this factor is set on a value of 50.

Pressure is strongly recommended to decrease scar height and scar erythema [1]. The working mechanism of pressure therapy is not completely understood. First, pressure can control collagen synthesis [9]. The realignment of collagen fibers and the reduction of development of whorled-typed collagen nodules might induce thinning of scars. Secondly, pressure might reduce the vascular flow to scar tissue, which leads to a decrease of nutrient and oxygen supply for cellular activities. It might diminish fibrotic activity (TGF-β reduction), accelerate cell apoptosis of fibroblasts, and reduce scar redness [9]. In addition, application of pressure commonly reduces pain and itching and alleviates edema associated with active hypertrophic scars [4, 9]. Based on the evidence framework of Sharp et al., pressure therapy is strongly recommended and found to be evidence based to decrease scar height and recommended to diminish scar erythema [1].

Silicone gel sheets or gels are also used in the prevention of scars after wound healing of more than 21 days and in the treatment of hypertrophic scars. Silicone gel sheets or gels can be used as soon as wounds are re-epithelialized and until complete maturation of scars [2]. The silicone gel sheets are typically worn 12–16 hours per day. The topical silicone gels are applied twice a day

[2]. Skin reactions such as allergy, dermatitis, itch, or skin breakdown may occur, but fewer when using silicone gels compared to gel sheets. Progressive building-up of wearing the silicone and hygienic precautions of both the product and the skin are important actions to reduce the risks of adverse effects, especially in warm weather or climates. Besides there are no clear benefits to using gels versus gel sheets or non-silicone versus silicone products with respect to the treatment effect [2]; the silicone-containing occlusive sheets have the most substantial amount of publications and references [3].

Silicones are recommended to improve scar erythema, thickness, and pliability [2, 3]. The universally accepted mechanism of action of silicone is hydration and occlusion of the stratum corneum [6, 10, 11]. Based on the guidelines of Meaume et al., silicone is the current gold standard and the first-line, noninvasive option for the prevention and treatment of hypertrophic scars [6].

In daily practice, silicone applications are worn in combination with pressure garments, masks, or splints to achieve the best outcomes. Silicone applications can be prefabricated sheets or individually made by specialized manufacturers as a pressure device or pad to solve concavity problems (chin, breast, clavicle, neck, and face) or in soft tissue parts of the face and neck.

Therapists routinely use *massage* in the treatment of (hypertrophic) scars, which can be applied manually or with the use of a vacuum device. Different manual massage techniques, such as the GAF techniques by Jaudoin D. and the "massage dermo-épidermique" by Godeau J., are described to limit fibrosis of scar tissue and to free adhesions. Depending on scar age and/or inflammatory status of scar tissue, the applied technique can vary between applying a mild pressure combined with a "translation" of the epidermis and a moderate pressure to create a skinfold combined with small rotations in different directions. Also a mechanical suction device can be used for mature scars. This therapy is called "vacuum therapy" or "depressomassage." Using this mechanical massage, a skinfold is created in a treatment head with negative pressure after which the skinfold can be manipulated.

Massage therapy is used in the treatment of hypertrophic scars and skin grafts to improve pliability and to reduce pain and itching [3]. The mechanical disruption of fibrotic scar tissue explains the improvements in pliability. The gate theory of Melzack and Wall support the reduction of pain and pruritus. Following the literature, the applied massage therapies differ in the type of manual techniques and mechanical settings, with or without moisturizer, duration, and frequency. However, to our knowledge, massage therapy is applied daily using progressive techniques to obtain the best outcomes. The manual or mechanical technique depends on the inflammation status of the scar (immature scar versus mature scar).

Moisturizers and lotions are used in the treatment of hypertrophic scars, which are typically dry skin and often itchy. Hypertrophic scars show increased transepidermal water loss compared to healthy skin [12, 13]. Hydration can restore the skin barrier function. Little is known about the ideal composition of moisturizers and frequency of application for burn scar treatment [13], but we believe in an application of a water-based, neutral lotion or cream at least thrice a day.

Positioning and splinting are indicated in each burn rehabilitation phase. In the acute phase, positioning and splints aim to control edema and to bring pressure relief. In the intermediate phase, positioning and splinting are indicated for soft tissue or skin graft protection and tissue elongation, whereof the last indication is also important in the long-term phase. Positioning after a burn injury corresponds with an anti-comfort position. There is no universal position, but burn depth and location must be considered when determining optimal anti-contracture positioning. Positioning may be active, which is ideal for cooperative patients, or passive, which requires the use of splints. Three different types of splints are commonly used, a static, a static progressive, and a dynamic splint. Indication for one or the other type can be to protect a skin graft after surgery, to prevent or to treat contractures, or to improve joint mobility. However there is no consensus on the ideal splint-wearing schedule. The longer a splint is worn, the greater the benefit for tissue lengthening. Some suggest a regime of 2-hours-on, 2-hours-off; others advocate active exercises during the day and splinting only at night. Schedules should be established and adjusted according to the changes in joint mobility and activity level of the patient [14].

Positioning and splinting protocols must be supervised regularly for effectiveness and require cooperation of both the patient and the burn team.

Exercising and mobilizations are important components of the daily treatment of patients after a burn injury. After a severe burn injury, patients have an increased catabolism that leads to loss of lean body mass and causes muscle weakness and decreased functional capacity. The prolonged bed rest and the lack of physical activity have an important impact on recovery after burn injuries in the rehabilitation process. Further, the hypertrophic scar formation leads to scar contractures and decreased range of motion. Therefore, the rehabilitation program starts with passive and active movements, strength training of upper and/or lower limb and progressively includes more challenging exercises such as bed cycling, sit-to-stand-transfers, and walking with or without assistance. Depending on the patient's cooperation, general condition, and cardiovascular and neurological status, mobilizations start already after 24–48 hours after admission to the burn unit or

surgical procedure, but always in dialogue with the attending physician.

In the literature, little is known about the best rehabilitation schemes to follow for adult burn patients. However, the aim of exercising is to maintain and restore the physical capacity, muscle strength, and autonomy of patients [15]. Mobilizations are required for realignment and lengthening of scar tissue, preventing joint and ligament stiffening.

Among experts, compression therapy is considered a first-line intervention in the aftercare of patients with severe scars related to burn injury while the use of all the other mentioned techniques are considered to be at least "best practice."

27.1 Conclusion

Although strong evidence is lacking for many of the different noninvasive therapeutic approaches that are used in the rehabilitation of patients with severe scars, all the interventions discussed in this chapter, that is, pressure and silicone therapy, massage, hydration, positioning and splinting, exercise, and mobilizations, are recommended and considered useful by the authors in the aftercare of these patients.

Take-Home Messages

- Pressure and silicone therapy have the best evidence in topical scar management.
- Massage is useful to treat pruritus and stiffness of scars.
- Combination strategies are mandatory and need to be individualized to optimize results.
- Hydration of scars is useful, but cost-effectiveness of the product that is used is also important.
- Positioning and splinting protocols must be individualized and supervised regularly for effectiveness.
- Physical activity and exercise are crucial to maintain and restore the physical capacity and muscle strength of burn patients.
- Mobilizations are required for realignment and lengthening of scar tissue as well as preventing joint and ligament stiffening.

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Minimal-Invasive Technologies for Treatment of HTS and Keloids

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Minimally Invasive Technologies for the Treatment of Hypertrophic Scars and Keloids: Intralesional Cryosurgery

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28.1 Background

A total of 100 million patients develop scars in the developed world alone each year as a result of 55 million elective operations and 25 million operations after trauma. Excessive scars form as a result of aberrations of physiologic wound healing and may develop following any insult to the deep dermis, including burn injury, lacerations, abrasions, surgery, piercings, and vaccinations. By causing pruritus, pain, and contractures, excessive scarring can dramatically affect a patient's quality of life, both physically and psychologically. Spray or contact cryosurgery is a nonsurgical therapy for the treatment of hypertrophic scars and keloids.

Cryosurgery is an effective and safe therapeutic regimen in the treatment of hypertrophic scars and keloids. Because of its major advantage of a low relapse rate, the technique, either as monotherapy or in combination, has been established as the treatment of choice for keloids and hypertrophic scars.

The cryosurgery freezing process includes four phases, which are termed "Thermal history." These phases include cooling rate, end temperature, hold time, and thawing rate. Each of these phases has an impact on the mechanism of injury on the frozen tissue. The tissue injury is induced by two synergistic arms – direct physical effects of cells freezing (intracellular ice formation) and by the vascular stasis that develops in the tissue after thawing. It is postulated that another factor in the effect on the tissue following cryosurgery is the immunologic response which is still under investigation.

Contact cryosurgery method uses metallic probes, which are circulated by a cryogen gas. This probe removes heat from the tissue and thus the tissue gradually cools. When the cryosurgical unit is activated and the probe is placed in firm contact with the tissue, an area of frozen tissue or ice ball appears, which extends radially from the cryoprobe. The lateral spread of freeze approximates the depth of freeze by a ratio of 1:1.3. Although the depth of freeze is time related, as the duration of freeze extends toward 100 seconds the lethal zone flats, that is, the deeper tissue is not affected. It has been shown that repeated contact cryosurgical sessions can exhibit a beneficial effect on keloids and hypertrophic scars and additionally prevent relapses. However, 1–20 treatment sessions using the contact cryosurgery were required to flatten those scars. In addition this method caused a high incidence of hypopigmentation. Therefore, the need for new, more potent, and quickly effective cryosurgical methods and instrumentation are warranted. Har-Shai et al. have developed the intralesional cryoneedle [1–15]. This technique exhibits an increased efficacy in the treatment of hypertrophic scars and keloids when compared with the contact method, due to the enhanced freezing area of deeply located scar tissue. In addition, fewer cryosurgical sessions are required, and less hypopigmentation is evident following the application of intralesional cryosurgery (Fig. 28.1).

28.2 The Technology: Treatment Technique – CryoShape [5, 10]

With the patient lying at a supine position, the skin surface of the scar is cleansed with disinfecting solution and draped. The area of penetration into the scar and the underlying subcutaneous tissue are anesthetized locally, by a translesional approach, with Bupivacaine hydrochloride 0.5% (marcaine) [7]. Thereafter, the sterile cryoprobe (CryoShape, Life by Ice Ltd. Haifa, Israel) (Fig. 28.2) is forced into the long axis, core, and mid-height of the scar in a forward rotary movement, which is parallel to the skin surface. The scar itself is grasped between the index and thumb of the other hand, until the sharp tip of the needle penetrates the opposite distal edge of the scar, thus maximizing the volume of scar tissue to be frozen. Attention is taken to prevent any penetration of the cryoneedle into the healthy surrounding skin. Sterile gauzes are placed under the proximal and distal exposed parts of the cryoprobe and care is taken to assure that the vent nostril is positioned away from the patient to prevent accidental freezing of adjacent skin or tissue (Fig. 28.3).

The proximal part of the probe is connected via an elongation tube to the cryogun (CryoPro Maxi 500 cc, Cortex Technology, Hadsund, Denmark), which is filled with liquid nitrogen to three-fourth of the cryogen volume and about 15 minutes beforehand in order to allow a sufficient pressure to build-up inside it (11 psi). A full pressurized cryogen can operate continuously for 1 hour, thus two to three medium-sized keloids can be treated successively without the need to refill.

The cryogun is grasped or placed on a steady surface, which is located higher than the scar to facilitate the liquid nitrogen flow downward with no direct contact with the patient body. By activating the cryogun trigger, the pressure valve is opened and the cryogen enters the cryoneedle, thereby freezing the scar. A forced steam of the liquid nitrogen gas flows out from the vent nostril during the entire freezing process. The strength of the steam flow, which is observed by the naked eye during the entire freezing procedure, indicates an appropriate working pressure. Two ice balls appear shortly at the two cryoprobe penetration sites of the treated scar and with time they gradually spread toward each other until a complete freezing of the scar is clinically evident. The

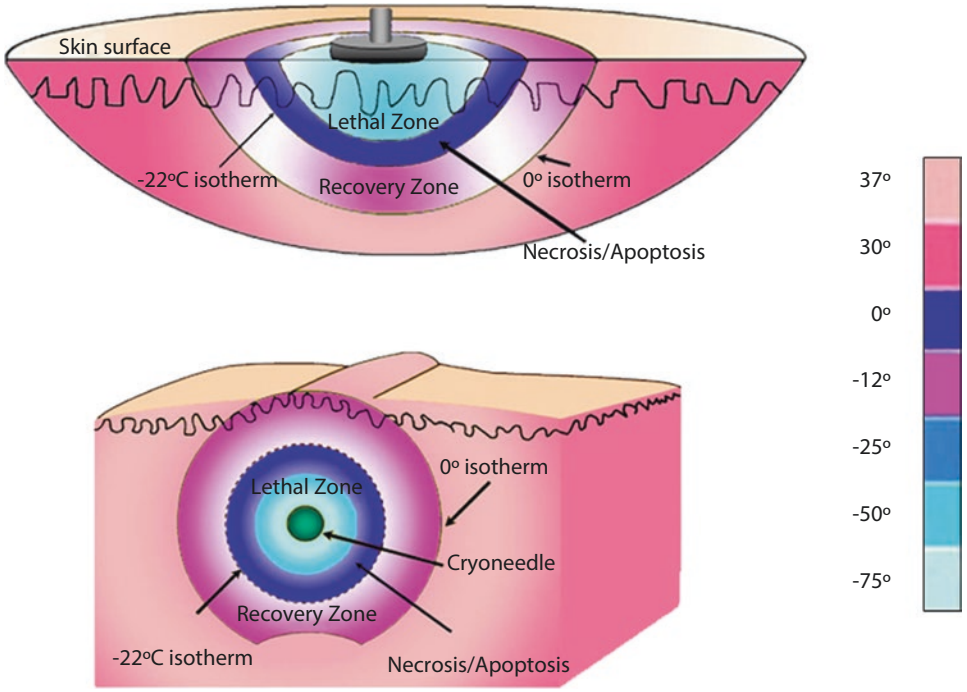

Fig. 28.1 A comparison between the contact and intralesional cryosurgery methods. Upper – Contact method: Ice ball induced by the contact cryoprobe. The interface between the ice ball and unfrozen tissue represents 0 °C isotherm. The volume of tissue located between −22 °C isotherm and contact probe is the lethal zone in which cells undergo cryonecrosis. Cells situated in the warmer region between −22 °C isotherm and 0 °C isotherm (recovery zone) generally survive the freeze. The melanocytes are located within the lethal zone. Bottom – Intralesional method: Ice ball induced by the intralesional cryoneedle. The interface between the ice ball and unfrozen tissue represents 0 °C isotherm. The volume of tissue located between −22 °C isotherm and cryoneedle probe is the lethal zone in which cells undergo cryonecrosis. Cells situated in the warmer region between −22 °C isotherm and 0 °C isotherm (recovery zone) generally survive the freeze. The melanocytes are located within the recovery zone

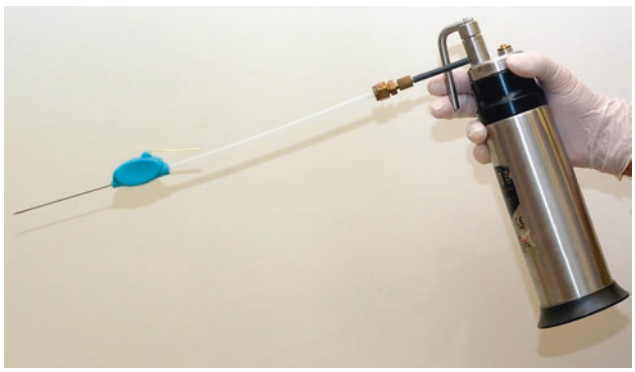

Fig. 28.2 The intralesional cryosurgery system composed of the CryoShape cryoprobe which is connected to the cryogen

length of the intralesional cryosurgery process depends upon the scar volume and ranges between minutes to 3 hours without the need of time taking. Following the complete freezing of the scar, the cryogun trigger is released to stop the freezing process and the cryoneedle is left to thaw for 1–2 minutes and is withdrawn in a reverse rotary movement. After a complete thawing of the scar is clinically noticed, slight bleeding from the penetration points of the needle requires the application of a sterile dressing. If active bleeding is evident, gauzes soaked with Tranexamic Acid will end the bleeding. The patient is instructed to wash daily the treated scar and to apply an antibiotic ointment until full healing is accomplished.

In cases where the scar is longer than the cryoneedle length (10 cm) or very wide, two or three parallel needles or successive insertions of the same needle are necessary to freeze the entire keloid in one session.

28.3 When to Use Contact or Intralesional Cryosurgery?

Contact cryosurgery can be used on very small HSK with a reduced volume in which the cryoneedle cannot be inserted into. All other HSK can be treated by the intralesional cryosurgery method. In very large or giant HSK, several cryoneedles can be inserted in parallel to facilitate the freezing process.

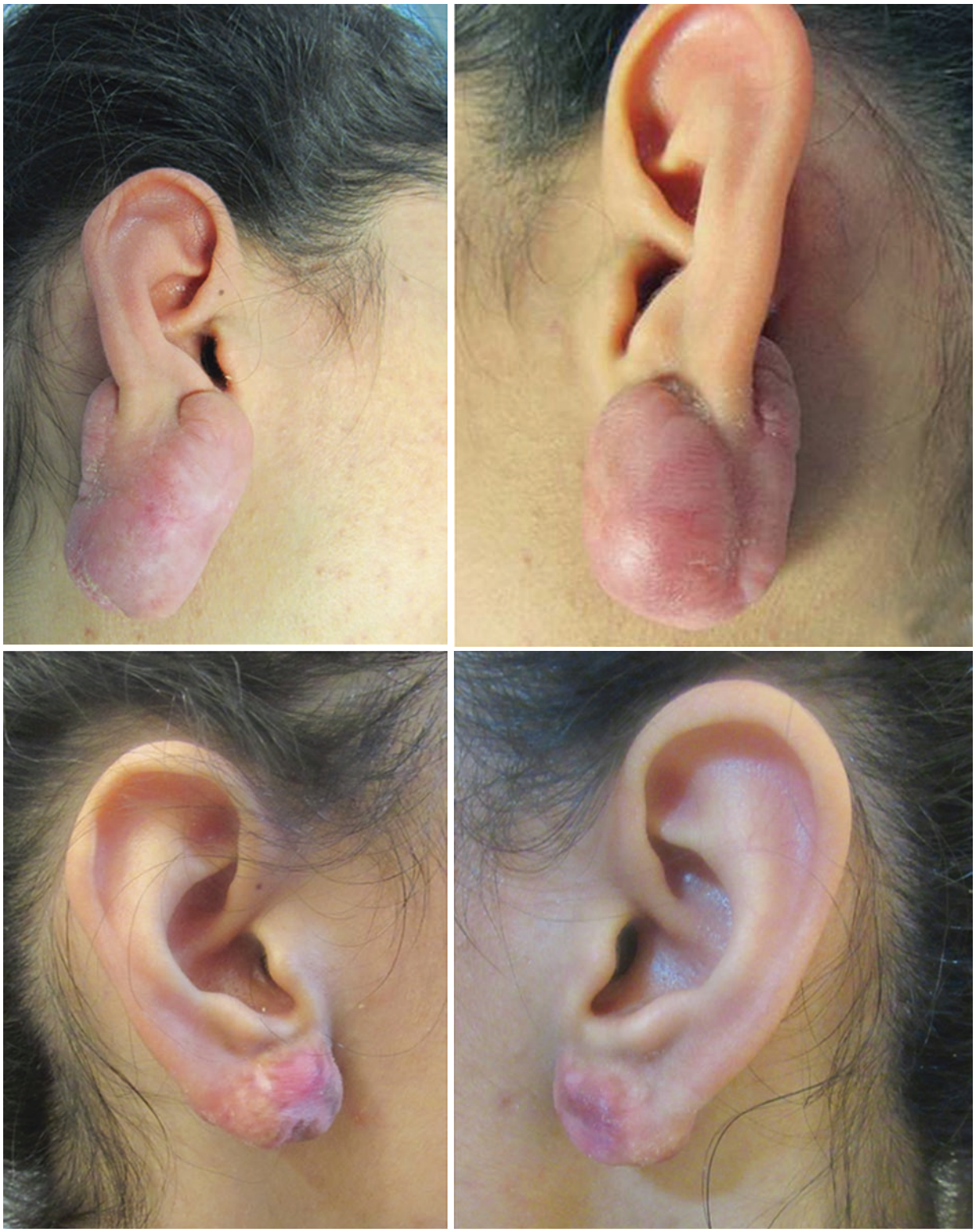

Fig. 28.3 *Upper* – Preoperative view of two large keloids on the anterior and post aspects of the right and left lobules following piercing. *Lower* – Postoperative view 6 years following a single cryosession of intralesional cryosurgery demonstrating complete involution of the scars with no distortion of the lobules and without hypopigmentation or recurrence

28.4 How Many Cryosessions Are Needed for Contact or Intralesional Cryosurgery?

A total of 1–20 treatment sessions using the contact cryosurgery are required to flatten HSK scars. The interval between sessions is between 2 and 3 months.

For the intralesional method, usually a single cryosession is needed to flatten the HSK. In few cases a second cryo-treatment is needed. The interval between sessions is 6 months.

28.5 Combined Treatment

Intralesional cryosurgery can be combined with intralesional excision of the HSK [14], topical silicone gel sheeting [8], intralesional injection of steroids, and pressure garments. Following the flattening of the scars by cryosurgery, fractional CO2 lasers can be applied to further smoothen the skin surface if necessary [16].

28.6 Conclusion

This simple to operate technology can be applied as an office procedure, is safe, cost-effective, and possesses a short learning curve. This evidence-based novel intralesional cryosurgery method for the treatment of hypertrophic scars and keloids was recently intro-

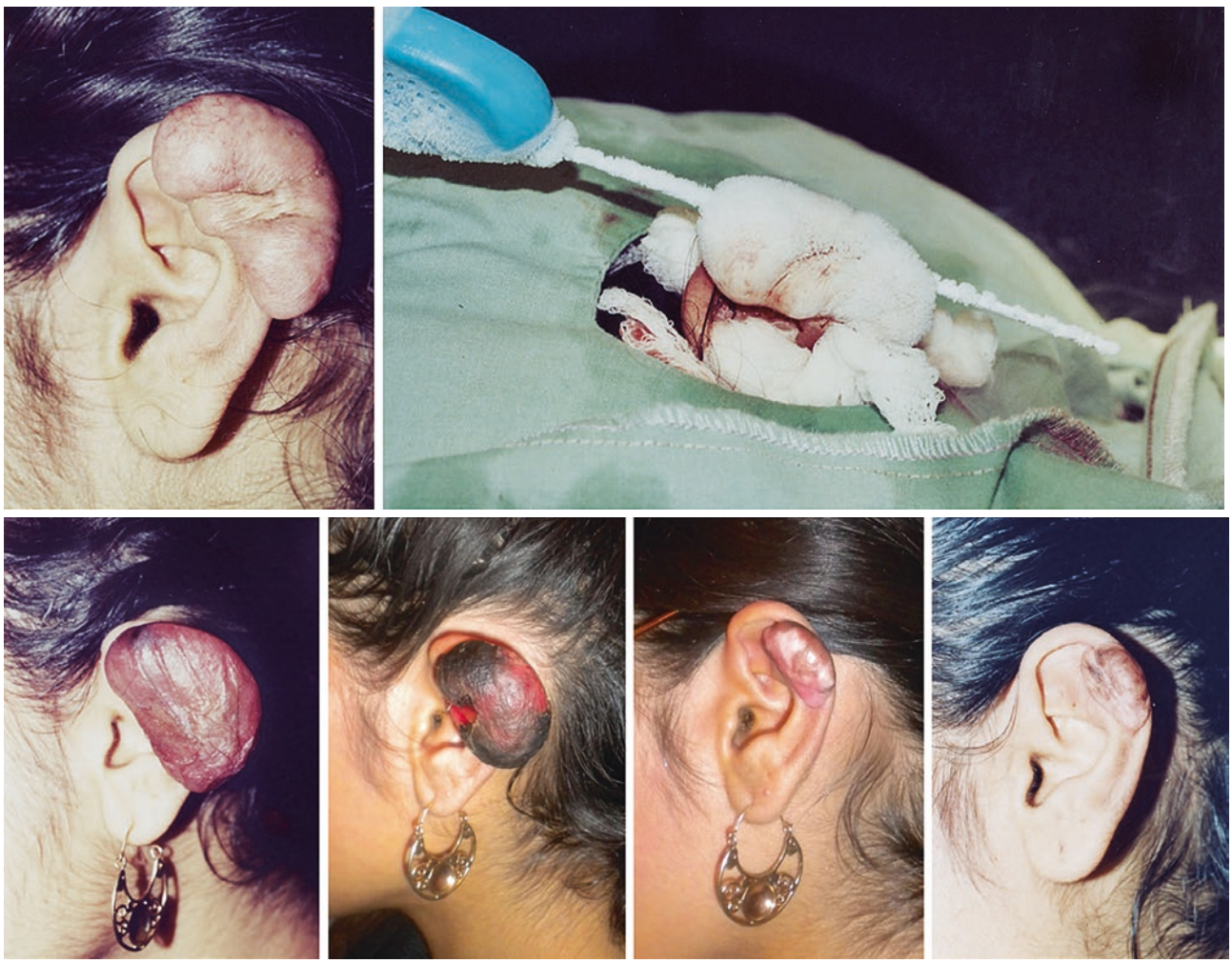

Fig. 28.4 Sequential steps of the intralesional cryosurgery procedure and final result. *Upper left* – Preoperative view of a large keloid of the left upper ear following piercing. *Upper right* – Following penetration of the cryoneedle into the keloid, two ice balls are formed at the two penetration points of the scar. Warm gauzes are placed opposite to the treated scar (posterior aspect of the auricle) in order to prevent cryoinjury to the auricular cartilage. *Lower left to lower right* – One week following the cryo-treatment a blister is evident; 3 weeks following treatment scar necrosis is evident; 6 months following the treatment the helical keloid has reduced significantly without distortion of the lobule and with almost no hypopigmentation; 4 years following a single cryosession, the scar is flat with some extra pliable skin above it which can be excised via an intralesional approach. No recurrence is evident

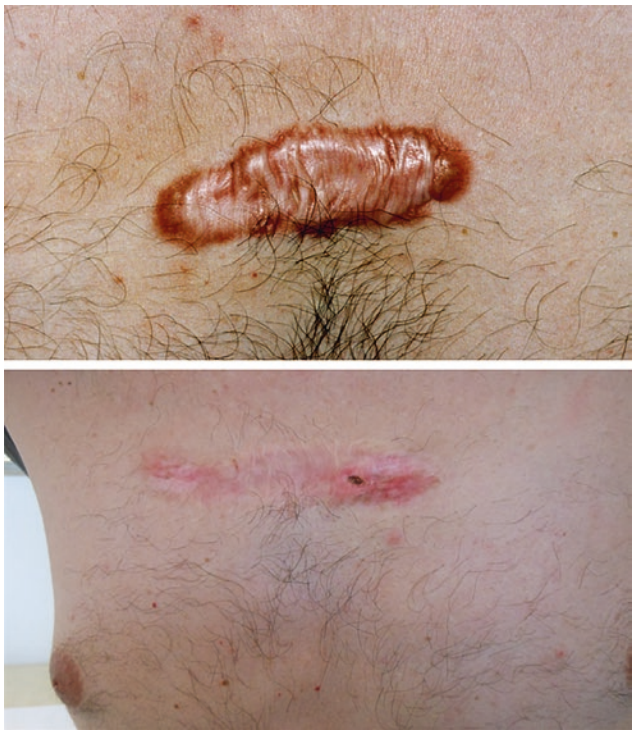

Fig. 28.5 *Upper* – Preoperative view of a large keloid scar on the anterior chest following acne. *Lower* – Postoperative view demonstrating a complete flattening of the scar 10 years following a single cryosession with no recurrence or hypopigmentation

duced. This method was shown to be effective in the treatment of hypertrophic scars and keloids, and has achieved significant superior clinical results when compared with the existing treatment modalities (Figs. 28.3, 28.4, and 28.5). In addition, it was demonstrated [4, 10] that this method has significantly reduced the patient concern and deformity scores in a scale from 1 (no concern and deformity) to 5 (severe concern and deformity) in 11 patients in whom keloids developed following aesthetic surgery. It was concluded that intralesional cryosurgery provides the plastic surgeon with an effective instrument to treat such scars following aesthetic surgery, thus reducing the dissatisfaction of patients.

The intralesional cryosurgery methods has two main advantages over the spray or contact cryosurgery techniques. Usually only a single cryosession in needed, and it exhibits significantly less hypopigmentation due to better survival environment for the melanocytes, thus can be effectively applied on black/darker-colored skin [1–3]. These beneficial advantages have an important clinical application for the treatment of hypertrophic scars and keloids especially on the face, which is the most crucial area of concern to the patient. Furthermore, the common treatment modalities which were mentioned to treat such a scar would necessitate several treatments and a long therapeutic period while the final results are unpredictable.

In summary, the intralesional cryosurgery technique might be added to the armamentarium of treatment modalities to effectively treat keloid scars. This method is easy to use, safe, can be applied on any size and shape of scars, requires a short learning curve, consumes less liquid nitrogen, and can be applied as an office procedure.

Take-Home Message

Intralesional cryosurgery, which is an evidence-based method, is probably the best treatment for a variety of HSK (small, intermediate, large, and oversized) that achieves remarkable clinical results in a high proportion of patients with minimal hypopigmentation and usually by a single cryo-treatment.

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Minimal-Invasive Technologies for Treatment of HTS and Keloids: Corticosteroids

Juhee Lee and Jihee Kim

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29.1 Background

Hypertrophic scars and keloids represent the consequences are the results of abnormal wound healing. Keloids are characterized by overproduction and deposition of collagen and extracellular matrix (ECM). Keloids often manifest as growing and infiltrative lesions toward the neighboring intact skin beyond the original boundaries. Abnormal fibroblast activity is a histopathological hallmark for keloid pathogenesis leading to prominent accumulation of dermal constituents. Due to sustained proliferation without regression, the patients often experience pruritus and pain which leads to functional impairment affecting quality of life. Recent findings have identified that elevated levels of growth factor and cytokines contribute to aberrant fibroblast activity. Among various singling molecules, transforming growth factor beta (TGF-β) family is a crucial mediator in scar formation.

Management of hypertrophic scars and keloids are yet ill categorized. Unlike keloids, hypertrophic scars may resolve partially without treatment, although treatment is required depending on patient desire for further improvement. The use of steroid for the treatment of excessive scarring was first proposed in the 1950s. The early case reports showed that corticosteroids administered during wound healing halted the growth of granulation tissue. In vitro fibroblasts subject to desoxycorticosterone failed to reach maturation, and there were notable morphologic changes [1]. In the following years, small numbers of patients with keloids were treated with systemic intake and regional injection of ACTH who showed inhibition of recurrence. In 1963, triamcinolone was first used for intralesional injection after surgical excision of keloids [1]. Since then, many groups have reported the successful application of intralesionally injected triamcinolone in scar treatment (Figs. 29.1, 29.2, 29.3, and 29.4).

In the past decades, intralesional injection has been proposed as a standard therapy for hypertrophic scars. The international guidelines on management on keloid scarring have recommended the use of corticosteroids as

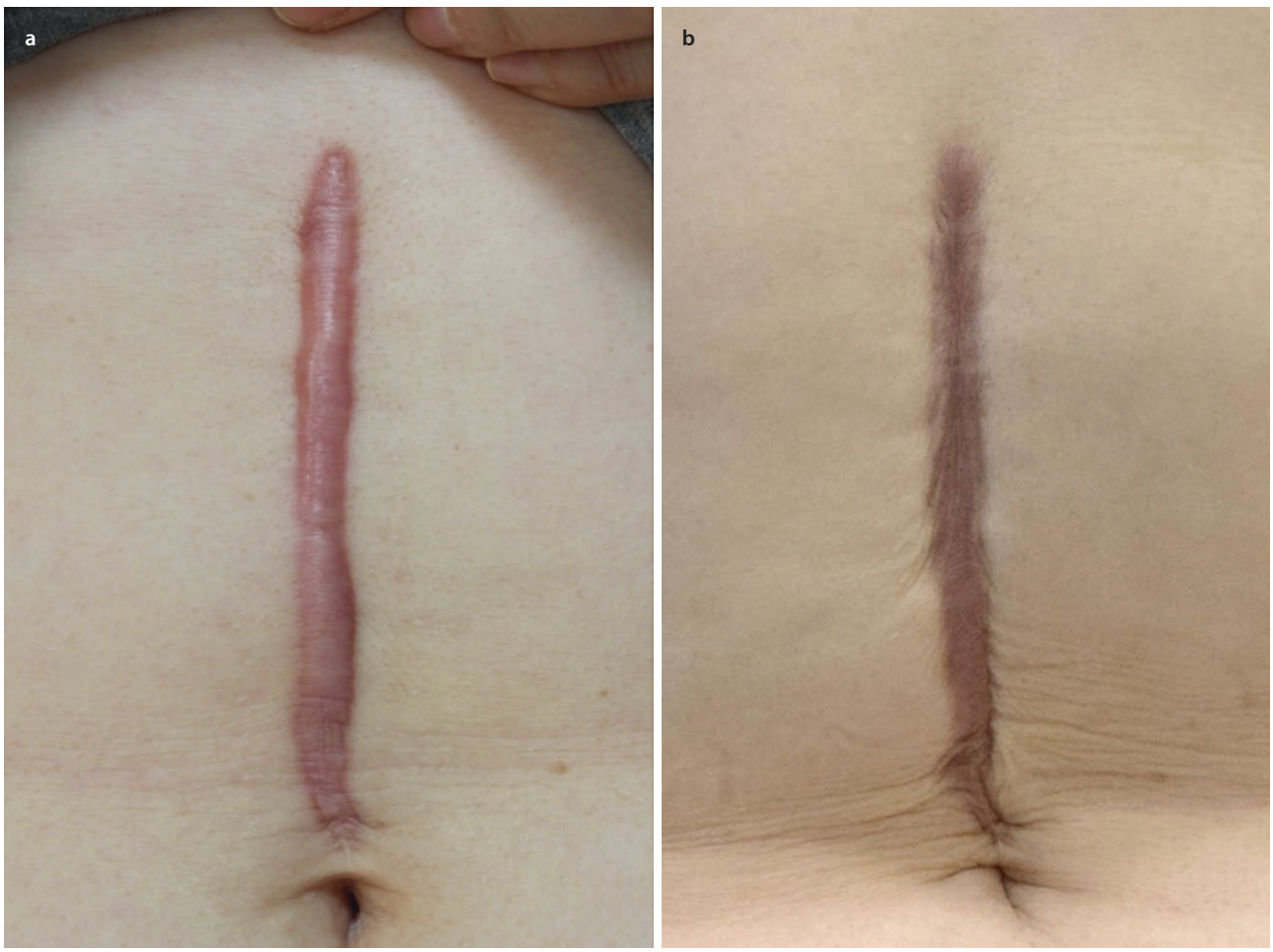

Fig. 29.1 **a** A 50-year-old man with keloid after total gastrectomy. **b** The patient underwent seven sessions of intralesional injection of triamcinolone (10 mg/ml) in 4 weeks interval

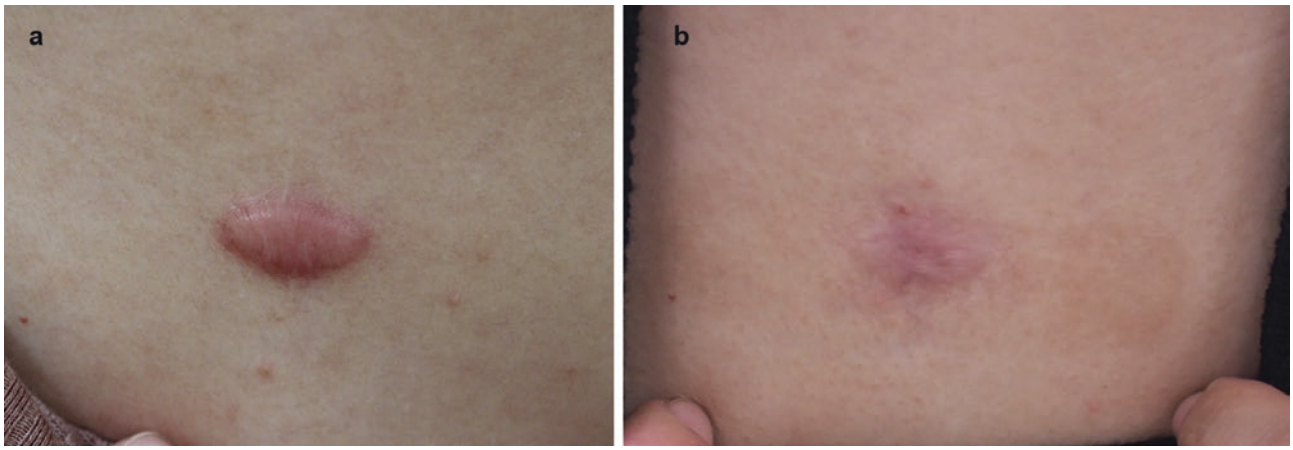

Fig. 29.2 **a** A 22-year-old woman with keloid on the chest. **b** The patient underwent four sessions of fractional CO_2 laser (eCO_2 Lutronic, Goyang, Korea. 60 mJ, 15% density) combined with intralesional injection of triamcinolone acetonide suspension of 10 mg/ml

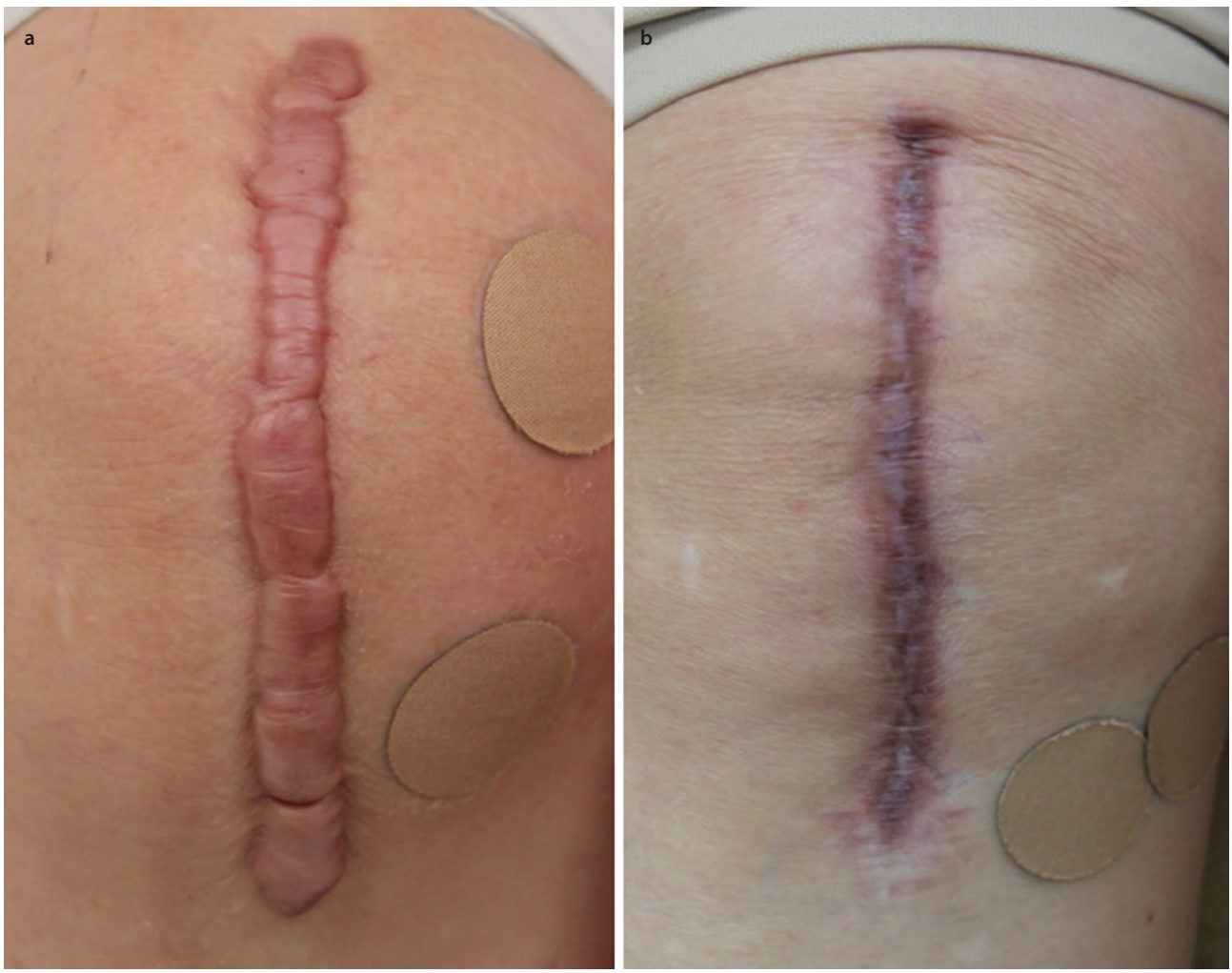

Fig. 29.3 **a** A 62-year-old women with keloid after knee replacement surgery. **b** The patient underwent seven sessions of combination cryotherapy and intralesional injection of triamcinolone (10~20 mg/ml) in 4 weeks interval

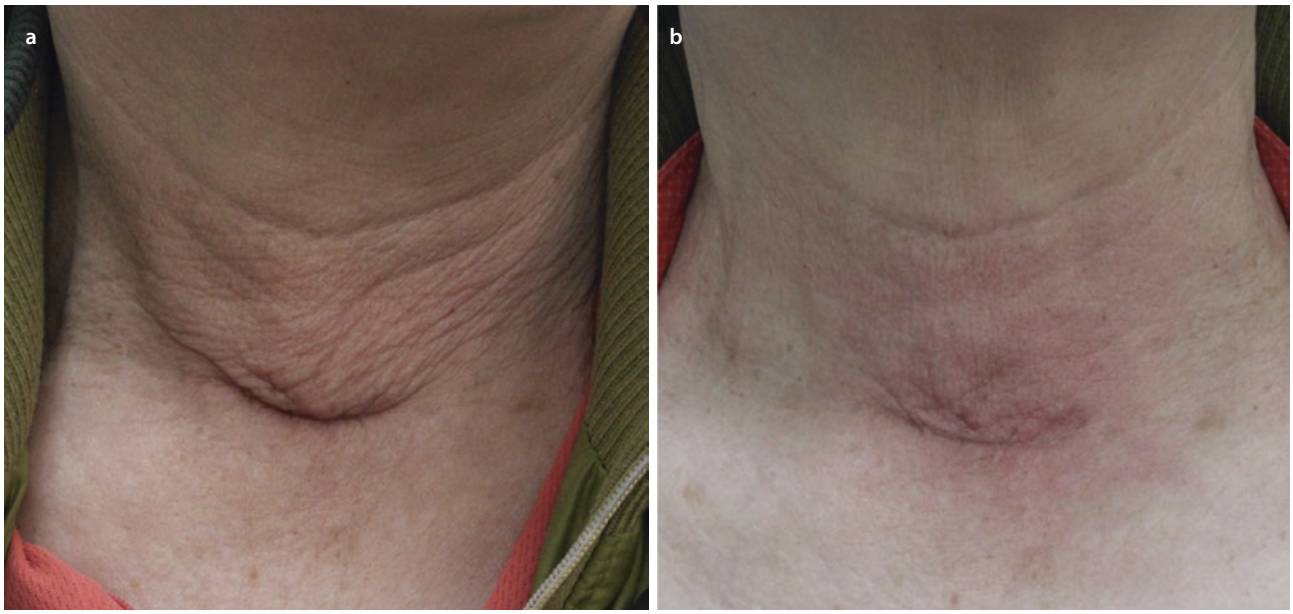

Fig. 29.4 **a** A 60-year-old woman visited 12 weeks after total thyroidectomy. **b** Postoperative lymphedema significantly resolved after single session of intralesional injection of triamcinolone acetonide (10 mg/ml)

a mainstay treatment [2]. Most commonly used corticosteroids for scar treatments are medium- to long-acting agents such as dexamethasone, methylprednisolone, and triamcinolone acetonide. Overall, corticosteroids inhibit all aspects of scar development including inflammation, fibroblast activation, and extracellular matrix accumulations. Thus, the use of corticosteroids efficiently reduces volume of scar tissue and relieves symptoms such as pain and pruritus.

29.2 The Corticosteroids

Corticosteroids are the most commonly prescribed anti-inflammatory agent in the medical field. Specific and nonspecific effects of steroids include immunosuppressive, antiproliferative, and vasoconstrictive effects. Besides systemic administration, proper use of topical and intralesional injection requires awareness of its potencies and various formulations.

29.3 Pharmacology and Mechanism of Action

All corticosteroids have basic skeletal structure comprising carbon atoms with three hexane rings and one pentane ring. Modifications in the basic cortisol structures result in systemic agents with different potencies, duration of action, metabolism, and mineralocorticoid effects. For example, triamcinolone was synthesized by fluoridation of the hydrocortisone molecule at the 9th position to enhance anti-inflammatory properties.

The free fraction of the corticosteroid enters the cell and exerts its effects by binding to a cytoplasmic glucocorticoid receptor. The glucocorticoid receptor is located within the multi-protein complex consists of heat shock protein and immunophilins. Binding of corticosteroid to its receptor leads to translocation into the nucleus and release from the multiprotein complex. Within the nucleus, the receptor forms a dimer and directly binds to glucocorticoid response elements in the promoter regions of the target genes. Eventually, the intranuclear binding affects the rate of transcription which induces or represses specific target mRNA and protein synthesis. Corticosteroid receptor also interacts with other crucial transcription factors regulating cell metabolism such as cAMP response element binding (CREB) protein. Cellular inflammatory response is modulated via nuclear factor-κB (NF-κB). NF-κB is an important transcription factor that induces the expression of genes regulating inflammatory mediators. Corticosteroids and its receptor inhibit the activity of NF-κB causing reduction of inflammatory process in cell. Additionally, the glucocorticoid receptor has an inhibitory effect on activator protein 1 (AP-1), which controls the expression of various growth factors and cytokine genes. Other key cytokines or proinflammatory molecule inhibited by glucocorticoids includes tumor necrosis factor-α (TNF-α); granulocyte-macrophage colony-stimulating factor (GMCSF); interleukins (IL). IL-1, IL-2, IL-6, IL-8; leukotrienes; and prostaglandins.

29.4 Corticosteroid in Scar Treatment

Unlike normal fibroblasts, keloid fibroblasts possess tumor-like properties, showing excessive proliferation and invasion of surrounding tissues. Enhanced migration and invasion of normal fibroblasts are critical factors for the development of keloids. TGF-β signaling has long been considered a pivotal fibrogenic factor in abnormal wound healing. Subsequently, anti-fibrotic strategies based on the blockade or elimination of TGF-β signaling emerged as an important pharmacological target for treating keloids [3]. The clinical response to corticosteroids in scar treatments is mainly achieved by reducing the prolonged inflammatory response during wound healing, inhibiting collagen and reducing excessive ECM synthesis by reducing fibroblast activity. Additionally, intralesional injection of corticosteroids enhances fibroblast and collagen degeneration.

In lesions treated with corticosteroids, thick collagen bundles are dissociated and ECM constituents are markedly reduced. In vivo studies have shown that corticosteroid, especially triamcinolone, can retard synthesis of pro-collagen and TGF-β1 and TGF-β2 expression [4]. Administration of dexamethasone induced reduction in vascular endothelial growth factor and angiogenesis in keloid-derived fibroblasts [5]. Further study on the effect of corticosteroids on keloid pathophysiology is required in the aspect of modulation of chemotaxis immunomodulation controlling fibroblast activity and collagen metabolism.

29.5 Topical Steroids

Topical steroids are the most frequently prescribed of all dermatologic drugs, yet its usage has been limited in scar treatment. There are different formulations available in a wide range of potencies and a variety of vehicles. Topical corticosteroids are categorized into four major potency groups and seven classes. The classes are developed based on vasoconstrictor assays and clinical studies which range from class 1 ultra-high potency to class 7 very low potency. Certain formulation is more potent such as ointment formulation, which can enhance percutaneous absorption through increased hydration of the stratum corneum. In selecting a topical glucocorticoid preparation for scar treatment, optimal potency should be selected based on scar extent, location, and thickness. Target site for topical steroids is the viable epidermis or dermis, and the clinical response to a formulation is directly proportional to the concentration of the drug achieved at the target site. When topical application is considered, it is important to monitor potential adverse skin reaction due to continuous application. When skin atrophy or purpura is noted, temporary discontinuation of a topical agent should be considered. For hypertrophic scar or keloid treatment, topical corticosteroids alone have failed to reduce pre-existing scar tissue or prevent scar development and not advocated as a preferred modality.

29.6 Intralesional Injection

Keloids and hypertrophic scars are often treated by intralesional injection of therapeutic drugs because the pathogenic target is accumulated collagen and ECM constituents within the dermis. Intralesional administration of corticosteroids allows bypassing the thick stratum corneum barrier and directly treating pathologic dermal lesions with higher concentration of corticosteroids at the site. Triamcinolone acetonide and triamcinolone diacetate are the most widely used corticosteroids for intralesional administration. After its administration, micronized crystals of corticosteroids persist in the skin and released over a period of weeks, thus being the most desirable delivery system for the treatment of chronic inflammatory skin diseases. Triamcinolone agents are available as micronized suspensions of corticosteroid crystals, favored than dexamethasone or betamethasone.

29.6.1 Administration

Typically 27- or 30-gauge needles are the most preferred because it causes less discomfort when penetrating the skin and allow greater precision in injecting the desired quantity. Needles with thicker caliber can be applied for the long-standing lesions with dense tissue. The common therapeutic dosage would be between 10 and 40 mg per mL. Available triamcinolone suspension should be diluted to achieve the final concentration just sufficient to treat the target lesion. Because the injections are administered monthly, the authors favor lower dosage 10 or 20 mg to prevent undesirable effects.

To reduce the discomfort on pain, 1% or 2% lidocaine can be used to dilute triamcinolone in desired concentrations. Lidocaine alone may not induce reduction in pain due to its acidity and sodium bicarbonate can be added. Injection with lidocaine and bupivacaine mixture subcutaneously beneath and around the target lesion few minutes prior to the treatment can be beneficial to minimize pain on administration and after the treatment. Other measures to reduce patient discomfort are to apply ice pack or spray cooling system prior to the injection. Topical lidocaine available in tape or cream formulation can be of benefit.

Before administration, it is important to gently shake to suspend the micronized suspensions evenly. Upon injection, the needle should be introduced to target the

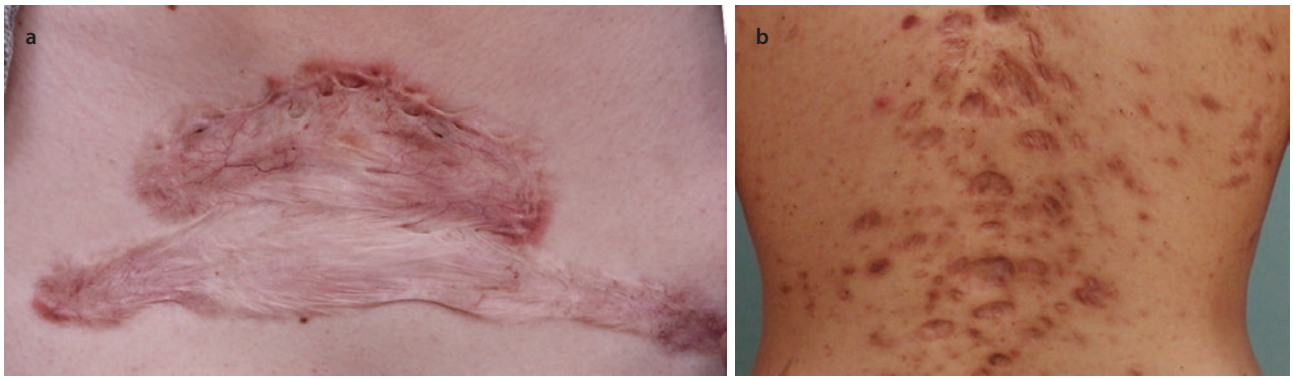

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Fig. 29.5 Localized side effect after corticosteroid intralesional injection. **a** Telangiectasia on the chest. **b** Permanent skin atrophy on the back

dermis where the target tissue is deposited. Resistance is felt when correctly injected to the dermis and when the drug is administered in the upper dermis, slight blanching can be noted. Direct injection to the subcutaneous tissue should be avoided which easily induces lipoatrophy. Long-standing keloid tissue with firm texture should be pretreated with liquid nitrogen to induce edema and subsequent softening of the tissue. Alternatively, injection can be performed to the periphery of the scar tissue directing the needle toward the scar tissue. Most treatment algorithms require multiple serial injections of intralesional steroid. In clinical practice, keloids are treated by a monthly injection until the resolution of clinical symptoms. The clinical response may differ between hypertrophic scars and keloids. While hypertrophic scars tend to be more responsive than keloids and generally flatten with time, keloids may require repeated interventions [6].

Currently, intralesional triamcinolone is the major first-line therapy for treatment of both hypertrophic scars and keloids. Its efficacy is well confirmed by numerous clinical trials and meta-analysis [7]. Intralesional triamcinolone injection effectively induced marked reduction in the size of the keloid. It was particularly efficient when administered after surgical removal of keloid lesions. Intralesional triamcinolone immediately after wound closure and at early postoperative visits, 20 mg/ml and 10 mg/ml respectively, resulted in 76.5% recurrence-free resolutions during a follow-up period of 18 months [8]. Combination treatment regimen with intralesional injection, 20~40 mg/ml, and potent topical steroid application yield favorable results with 85.7% recurrence-free on average of 32-month follow-up period [9]. Given the results of the clinical studies encompass different lesions occurring on different anatomical locations and durations, further clinical trials should be directed to overcome limitations of current repots including differences in timing of intervention, anatomical locations, inclusion and exclusion criteria, and inconsistent outcome measures.

29.6.2 Side Effects and Complications

Steroid-induced side effects include skin atrophy, telangiectasia, hypopigmentation, ulceration, and, rarely, systemic complications. Fortunately, the most commonly encountered side effects of intralesional corticosteroid injection are localized. The incidence of localized side effects is often reported in one-third of patients. Skin atrophy usually occurs over several weeks to months after the injection and may resolve spontaneously without treatment. However, atrophic lesion caused by repeated injection with high dosage persists longer and may induce permanent change. Telangiectasia may occur frequently on the site of injection. In most cases, the lesions do not regress spontaneously and further treatment is required. Laser or light devices such as pulsed dye laser or intensive pulsed light can be successfully applied for its treatment. Foreign body reaction to intralesional triamcinolone is rare but reported. Granulomatous reactions result from the failure of injected crystalized corticosteroid particle to disperse or incomplete absorption. Clinically, prolonged absorption of injected material presents as xanthoma-like lesions and resolves spontaneously over few months (Fig. 29.5).

Systemic complications are rare but occasionally observed. In children, cases of Cushing's syndrome following repeated injection of high dosage intralesional steroid is reported. In adults, the evidence for systemic complication is limited with few reported cases of Cushing's syndrome when patients are subjected to large doses due to extensive keloids. Monthly injection of large dosage of corticosteroids is often brought to account to cause menstrual irregularities. Although there is insufficient clinical evidence, it is unlikely that intralesional corticosteroid alone can cause adrenal complications.

Complications related to intralesional injections can be prevented by using the lowest concentration and the

smallest quantity of the drug needed. Increasing the concentration can be adjusted as needed after the repeated course of treatments. For patients with multiple or large lesions, alternating the treatment site or dilution to lower dosage is recommended. Additionally, scars across the joint area and periorbital area can be more susceptible to localized absorption of corticosteroids and higher concentration should be avoided. Although diabetes is not a contraindication to intralesional corticosteroid injection, patients should be approached with caution and appropriate monitoring should be considered.

29.7 Further Applications

29.7.1 Enhancing the Effect of Intralesional Corticosteroid

For long-standing hypertrophic scar lesions or large and firm keloids, the combination with cryotherapy can be highly effective. Cryotherapy with liquid nitrogen induces dissociation of accumulated ECM tissue along with possible vascular suppression and apoptosis of fibroblasts. Open spray technique is most commonly used in combination with intralesional injections. When used in combination, injections should be made after defrosting of the lesion. There are several reports showing marked improvement of hypertrophic scars and keloids after either superficial or intralesional cryotherapy. To prevent hypopigmentation from melanocyte destruction or other associated side effects of cryotherapy, shorter exposure (10~30 seconds) is recommended with fewer (two to three) freeze thaw cycles.

In addition to intralesional injection of triamcinolone, localized injection of antimetabolite agents are reported to be beneficial for scar treatments. 5-Fluorouracil (5-FU) is an antimetabolite inhibiting DNA synthesis which increases fibroblast apoptosis and inhibit proliferation. The use of combination triamcinolone and 5-FU has been demonstrated to be as efficacious as triamcinolone alone. Although there are possible side effects from 5-FU including injection site irritation or delayed wound healing, it lacks atrophy or erythema associated with corticosteroid injections. The pain upon administration was a major drawback in 5-FU treatment, while its combination with triamcinolone relieved excruciating pain. Combination of intralesional 5-FU injection with topical corticosteroids yields successful result in scar treatment [3]. Given the requirement for repeated treatment sessions and pain associated with intralesional injection of corticosteroids, other modalities such as lasers and efficient delivery systems are suggested.

29.8 Conclusion

The management of keloids and hypertrophic scars continues to challenge clinicians, and there is no universally accepted treatment algorithm. Although there are myriad of treatment options, selection of treatment modality largely depends on the patient desire. The use of corticosteroids has remained mainstay of the treatment for more than half century. While potent topical corticosteroids can be of limited use to address pruritus, intralesional injection of triamcinolone is the mainstay in treatment. Intralesional triamcinolone injection is thought to reduce scar formation by suppressing inflammation, inhibiting fibroblast proliferation, and inducing collagen remodeling. Corticosteroid is cost-effective because it does not require additional equipment, and thus readily applied in patients' regular clinical visits. Further studies are warranted to identify the optimal combination with other modalities for scar treatment.

Take-Home Messages

- Intralesional injection of corticosteroid is effective first-line treatment for the treatment for keloids and hypertrophic scars.
- Corticosteroid inhibits fibroblast growth proliferation and collagen synthesis by effecting on TGF-β signaling and promoting collagen degeneration.
- Intralesional injection of triamcinolone acetonide (10–40 mg/ml) is desired and lower concentration is more favorable for the initial treatments.
- The use of smaller gauge needle and syringe allows better control of the injection and minimize patient discomfort.
- For long-standing and firm scar lesions, combination with cryotherapy is required to achieve optimal penetration.

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Minimally Invasive Technologies for Treatment of HTS and Keloids: Low-Dose 5-Fluorouracil

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30.1 Introduction

30.1.1 Hypertrophic Scar and Keloid Information

Keloid is the most difficult pathological scar to treat and cure and it is characterized with uncontrolled growth, invasion into normal skin, and expansion beyond the original wound boundary with severe pain and itching [1]. In addition, high recurrence rate after various therapies is a common feature of keloids. These characters similar to those of tumors render keloids more like a "benign skin tumor" rather than a fibrotic tissue per se. Because of this, anticancer therapies such as chemotherapy and radiotherapy have been applied to keloid treatment.

HTS is another type of pathological scar, characterized with the deposition of excessive amounts of collagen matrix along with significant angiogenic process, which eventually leads to a raised and red scar with severe tissue contracture and painful and itching symptoms. HTS eventually resolves by itself after tissue maturation. Nevertheless, this process can take 1–2 years or even longer with disturbing symptoms and functional disability, which needs to be intervened for improving symptoms and preventing patients from disability. With this perspective, anticancer therapy approaches such as chemotherapy and radiotherapy might be also applied [2, 3].

30.1.2 Chemotherapy for Keloids and Hypertrophic Scar

Intralesional injection is a routine procedure for keloid treatment, and steroid injection alone could lead to recurrence rate higher than 50% [2], indicating the necessity of involving others drugs as a combined drug treatment. Chemotherapy for keloid was tried as early as 1989 [1]. The common drugs for keloid chemotherapy include 5-FU, Bleomycin, and Mitomycin C, etc. [2, 3]. The usual delivery way is intralesional injection of chemotherapy drug alone or combined injection of both chemo-agents and steroids.

In recent years, chemotherapy on HTS has been tried either as intralesional injection or combined with post-laser therapy with positive results [3]. Because of its self-resolving nature, chemotherapy for HTS remains an exploratory area for its balanced value between the efficacy and the side effect. Therefore, most studies of pathological scar chemotherapy focus on keloids and it will be the focus of this chapter as well.

30.1.3 5-FU and Its Combined Use of Steroids

Among the various chemotherapy agents, 5-FU, a pyrimidine analog with antimetabolite activity, might be the most commonly used drug for keloid chemotherapy. Dr. Fitzpatrick R.E. started intralesional injection of 5-FU for both keloid and HTS since 1989 using the concentration of 50 mg/ml with positive results [1]. Later, Gupta and Kalra [4] and Nanda and Reddy [5] also reported their 5-FU applications in keloid treatment with a dose of 50 mg/ml, and the intralesional injection was administered weekly, lasting for 12–16 weeks with positive results. With this dose, pain is the most common side effect and ulceration could occur as high as 21.4% [5].

5-FU intralesional injection was listed as an emerging therapy for keloid and HTS in "International clinical recommendation on scar management" [2], but was listed as a formal therapeutic option for HTS and keloid with monthly injection interval in "Updated international clinical recommendations on scar management: Part 2 – algorithms for scar prevention and treatment" [3]. In addition, a combined use of 5-FU with steroids not only enhanced the therapeutic efficacy, but also reduced pain suffering post-injection [1]. In the literature, high-dose (40–50 mg/ml) 5-FU injection is usually combined with steroid at a volume ratio varying from 9:1 [1] to 7.5:2.5 [6].

According to published literatures [1–6], 5-FU is a safe drug with no obvious side effect for the use in a relatively short time period (such as 2–6 months). However, whether it can be safely used for a long term at the reported dose (40–50 mg/ml) remains unclear because the accumulated effect of chemotherapy agents would be a concern if they are continuously used for a long time.

30.2 The Rational of Using Low-Dose 5-FU Injection for Keloid Treatment

To address the potential concern of 5-FU's side effects, our group proposed the application of low dose 5-FU for keloid treatment because of the following reasons:

1. Keloid necrosis caused by high dose 5-FU injection should be avoided simply because any new wound will accelerate keloid development and worsen the clinical situation. Inactivating keloid cells and remodeling keloid tissue rather than destroying keloid tissue are the correct strategy for keloid therapy with intralesional injection.

2. A sustainable and long-term therapy (2–3 years) is usually required for keloid treatment in order to completely cure keloids and prevent their recurrence. To do so, a low dose of chemotherapy agent is necessary not only for safety concern, but also for proper working mechanism of tissue remodeling.
3. Low-dose 5-FU will be sensitive enough for inducing endothelial cell apoptosis/death and destroying neovascular structure during keloid development, and will also be enough to inhibit fibroblast activities such as proliferation, invasion, and matrix production.
4. This therapeutic model provides good basis for other conjunctive therapies including surgery, laser, and steroid injection to remove or to flatten keloid tissue by partial keloid destruction or tissue remodeling. It also avoids host production of risk factors that will trigger keloid development and recurrence, in which growth factors and neovascularization play significant roles.

30.2.1 Background

After careful literature review and exploratory testing, concentrations ranging from 1.5 to 5 mg/ml were decided as the low dose of 5-FU for clinical use with at least monthly injection interval in order to avoid any significant systemic side effect and local side effect such as adverse effect on hemopoietic system and severe pain and tissue ulceration. According to our clinical experience in treating more than 10,000 cases during the past 18 years of clinical practice, this method has been proved safe for patients with a therapeutic time period ranging from 2 to 5 years or even longer, and no severe side effect has ever been observed thus far. In addition, this dose also has the effective rate of more than 97.14% in term of relieving pain and itching symptom, softening and flattening keloid scar, and the recurrence rate is significantly decreased after long term therapy [7]. However, drug resistance to 5-FU was observed in some patients, and for these patients a bit higher doses could also be applied but were always limited to less than 9 mg/ml concentration to avoid significant side effects.

Importantly, low-dose 5-FU injection aims to disrupt or destroy neovascularity of keloid tissue and inhibit fibroblast proliferation, rather than to destroy keloid tissue; thus low-dose 5-FU will not be able to majorly flatten or soften keloid tissues, in which abundant collagen and other matrices need to be degraded with steroid's effect. Therefore, combined injection with steroid is needed in order to flatten and soften keloid tissue. Nevertheless, injected low-dose 5-FU is able to timely demolish neovascularity induced by steroid injection, and thus render treated keloids to become relatively malnourished post-drug injection and thus less possible to reoccur.

Meanwhile, reduced vascularity also allows the longer stay of the injected drug inside keloids due to the reduced drug absorption via tissue capillaries, and thus enhance the drug efficacy and reduce the side effects. The case 1 demonstrates how this strategy could be applied to treat keloid tissue with intralesional injection of combined 5-FU and steroid at a low dose in order to gradually remodel the keloid into normal-looking skin [8].

30.3 Clinical Protocol of Low-Dose 5-FU Injection Therapy

The protocol for intralesional injection of low-dose drugs includes the injection of 5-FU alone or 5-FU combined with steroid. In general, the combined injection of 5-FU and triamcinolone acetonide will be a preferred method, unless the keloid scar is heavily vascularized, which will need 5-FU injection first to demolish tissue vascularity before steroid injection. The key points of this protocol include the following:

1. *Drug preparation*: Triamcinolone acetonide should be mixed with 2% lidocaine, and then 5-FU stock solution can be further mixed with them to maintain the concentrations of 5-FU between 1.5 and 5 mg/ml and steroid between 3 and 9 mg/ml. Low concentrations of both drugs will enable better control of the side effects such as severe pain, tissue ulceration, and atrophy as well as the drug-induced angiogenesis. Also, the volume ratio between the drug and lidocaine should be 3–5:1 in order to reduce the pain suffering during and after the drug injection. As a routine, the concentrations should always start from relatively high (5-FU: 3–4 mg/ml; triamcinolone acetonide at 8–9 mg/ml) and gradually reduced as below described.
2. *Injection procedure:* To avoid pain, 1 ml syringe with 26–27G needles is generally recommended for the injection and multi-entrance manner should be applied. Briefly, each injection should deliver about 0.2 ml volume and then change the injection sites to make sure for even distribution of the drugs. When performing, the keloid tissue should be held between two fingers with pressure in order to prevent drug from oozing into surrounding normal skin. In addition, before injection, blood withdrawal should be tested to avoid direct drug injection into a blood vessel. When injecting, the drug should be pushed hard into the tissue in order to create a pressure in the tissue between the fingers and whiten the injected tissue, this manner will make sure that the injected drugs will deeply infiltrate inside the keloids, but not to noninjected region, and thus to enhance the efficacy and reduce the side effect.

3. *Adjustment of drug concentrations and injectional interval*: Here, an important concept is that this procedure does not try to destroy keloid, but rather to remodel the keloid tissue gradually via inactivating keloid fibroblast and degrading keloid matrices. Therefore, the drug concentration should be adjusted according to the status of treated keloids. The followings are the general principles:
   A. Steroid concentration should be gradually reduced when keloids become softened and flattened as overdoses of steroid will cause tissue atrophy. In addition, sudden withdraw of steroid is well known for causing reoccurrence of other steroid-treated diseases, such as autoimmune disease, and thus the principle of gradual steroid withdrawal should also be applied to keloid treatment.
   B. 5-FU concentration should be reduced when tissue angiogenesis is significantly inhibited or keloid is significantly inactivated with improved symptoms. Vice versa, a higher concentration of 5-FU should be used when significantly enhanced angiogenesis is observed or keloid remains highly activated and less responsive to the drug treatment.
   C. Adjustment of drug injection interval: With the progress of drug treatment, injection interval should also be gradually prolonged as a way of gradual withdrawal of steroid and 5-FU, and thus to better prevent keloid recurrence. In general, initial drug injection will be administered every 4 weeks for a few months. Afterwards, the injection can be adjusted for every 6 weeks to 10 weeks for several months, and finally adjusted to every 12 weeks with further reduced drug concentrations for several repeats. According to our experiences, most keloid will be resolved eventually without a high recurrence rate.
   D. Long-term therapy for localized nodule: As shown in case 1, localized nodule is often observed as the last part of noncured keloid or as the first sign of reoccurred keloid, which needs to be continuously injected with an interval of every 6 to 12 weeks until a final resolution (also see case 3).

30.4 Low-Dose 5-FU-Based Injection Therapy for HTS and Keloids

The best candidate for low dose 5-FU injection is the keloid type that usually exhibits relatively soft and flatten but red color with significant signs of inflammation such as severe pain, itching, erythema, and rapid invasion into normal skin (Fig. 30.1a). Keloid types that are more like tumors, such as cauliflower-shaped solid tissue with relative dark color, fit better for surgical therapy (Fig. 30.1b), but 5-FU-based injection can be well employed as well for preventing keloid relapse after surgical removal.

In general, single or multiple keloids with small sizes (diameter less than 2 cm) and located at various parts of the body are the best candidates for drug injection treatment.

Large-sized keloids will not be ideal candidates for drug treatment by intralesional injection because of potential side effects of both 5-FU and steroids.

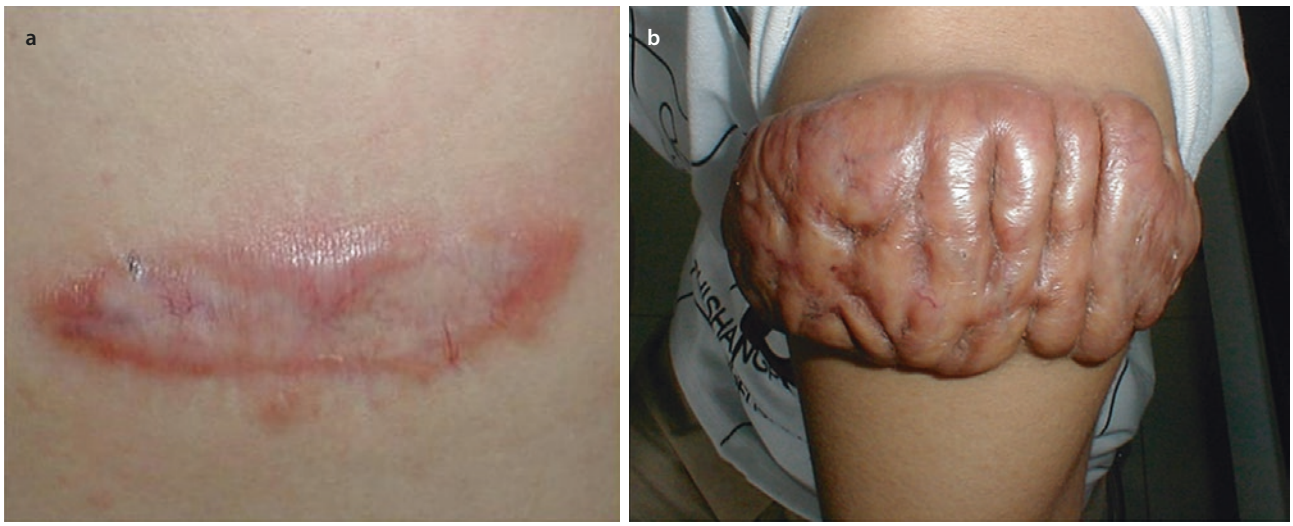

Fig. 30.1 Keloids are generally divided into two types: **a** inflammatory type; **b** tumor-like type

30.4.1 Important Concepts of Keloid Curing and Relapse Rate for Low-Dose 5-FU-Based Therapy

Insufficient treatment might be the most important reason for not being able to cure a keloid and preventing its reoccurrence

A softened and flattened keloid along with disappearance of the symptom does not necessarily indicate that a keloid is cured and the treatment is completed. Rather, the keloid is in a temporary inactivated stage under the drug pressure. Like cancer therapy, drug treatment can remove most of disease cells but there will always be a portion of cells (residue cells) that survive after chemotherapy and become quiescent and drug resistant [9, 10]. Once the drug pressure is relieved, these cells become reactivated and enter an active stage with rapid proliferation and production of matrices, growth factors, and angiogenic factors, and eventually lead to a reoccurred keloid.

To prevent this from happening, a continuous drug pressure should be applied to any of these residue cells to inactivate or remove them once they become activated. In the literature, most studies report the successful treatment of keloid with the criteria of flattening and softening of the treated keloid along with disappeared symptoms of pain, itching, and erythema as judged by Vancouver Score or Patient and Observer Scar Assessment Scale (POSAS). But the cessation of drug injection improperly will likely lead to keloid to reoccur simply because these treatments did not really remove or remodel the residual quiescent keloid cells into normal skin cell phenotype. This might be the key reason why high recurrence rate remains after keloid injection therapy, to which less attention has been paid in the literature.

In our group, it has been observed that 2–3 years are usually required for completely curing keloids by 5-FU and steroid injection in most cases. More importantly, preventive drug injection at a later stage aiming to prevent reoccurrence is essential and is performed by gradual drug withdrawal via reduced doses and prolonged injection intervals. As shown in case 3, there was a large-sized keloid in a woman's abdominal region, and a total of 6.5 years were spent to completely cure the keloid via combined injection of both 5-FU and steroids at a low concentration. During this process, the first 3 years were spent on treatment of the keloid, whereas the last 3 years were spent on preventive therapy to timely treat the reoccurred keloid nodules.

30.5 5-FU-Based Injection Therapy for Recurrence Prevention of Surgically Removed Keloids

Although low-dose 5-FU injection has been proven effective for primary keloid treatment and reoccurrence control, the efficiency would be too low to be an ideal method. As described earlier, the conversion of a keloid tissue into a normal-like skin will be a long-term process. On the contrast, preventing the conversion of normal wound cells into keloid cells would be much easier, in which 5-FU could play an important role.

Surgical excision has now become the first-line keloid treatment in our group because it is an efficient way of keloid treatment. In particular, keloids with a size larger than 2 cm in diameter and possible for primary closure after surgery are the best indication for surgical therapy. Most importantly, the use of low-dose 5-FU injection along with other procedures enables us to prevent the development of new keloids in a surgically created wound. Therefore, the "treatment model" of injection therapy will be shifted to the "prevention model" of surgical treatment, and 1-year time period will be usually long enough to achieve satisfactory results in most keloid patients as shown in cases 4 and 5.

There are three key issues that are essential for the success in this surgical procedure, including (1) anti-tension procedures by proper multilayer suturing and anti-tension device application; (2) wound irrigation with combined 5-FU and steroids during the surgical procedure; (3) post-surgery radiotherapy and combined 5-FU injection. The procedures are described in the following sections.

30.5.1 Surgical Procedure for Keloid Excision

Briefly, after local anesthesia with 2% lidocaine injection, the keloid will be surgically excised followed by multilayer suturing (including fascia and dermal and epidermal layers). 5-FU wound irrigation was reported valuable for preventing keloid recurrence from surgical procedure [11]. Thus, wound irrigation with combined 5-FU (about 3 mg/ml) and triamcinolone acetonide (about 8 mg/ml) should be performed, and excessive drug liquid should be extruded out of the wound before its closure. With the clinical experience over 3,000 cases, no failure of wound healing has even been observed when a wound was irrigated at this dose.

After wound closure, tension-reduction device such as "zipline" should be applied immediately to guarantee a tension-free zone in the wound area. Afterwards, the patients should receive irradiation on the wound within 24 hours post-surgery with a dose of 4–5 grays once a day for a total of 4 days using electron beam as the irradiation source.

30.5.2 Postsurgical Monitoring and Preventive Injection of 5-FU

After the procedure, the patients are advised to visit the clinic monthly to closely monitor the status of surgical site and silicone gel is generally needed for application on the wound site. In most cases, the above procedure is enough to keep the sutured wound quiescent and non-activated, and the wound tissue will maintain erythema-free and symptom-free for pain and itching (see case 4). If this maintains with no further signs of recurrence, the tension-reduction device can be removed after continuous wearing for at least 6 months.

For high-risk patients, including those who have previous history of postsurgical reoccurrence, multiple keloids, or previous recurrence after surgery plus radiotherapy, early injection of low-dose 5-FU into the wound subcutaneous tissue should be applied as early as 4 weeks post-surgery, which is maintained for another five injections every 4 weeks until the sixth month post-surgery. Afterwards, 5-FU injection should be given whenever there is sign of pain, itching, and erythema to make sure that early management of recurrence is applied (see case 5).

For non-risk patients, or patient without previous surgery, an indication for low-dose 5-FU injection will be the minor level of erythema and the feeling of pain and itching. The injection should be given one more time after disappearance of these early signs.

30.6 Anti-indications of Low-Dose 5-FU Injection Therapy Combined with Steroids

Children are generally not the candidates for 5-FU-based chemotherapy in both keloid and HTS. In addition, female patients are recommended not to prepare for pregnancy during the treatment time period until 6 months after the cessation of the treatment. In addition, a blood cell count test is recommended every 2 months to monitor potential adverse effects on hematopoietic system. Close monitoring of steroid side effects is needed, and the cessation of the therapy is needed at once in case any side effect is confirmed.

30.7 Representative Case Reports

30.7.1 Case 1. Remodeling of Keloid into Normal-Looking Skin [7] (Fig. 30.2)

A 53-year-old woman with 28 years of spontaneous formation and development of her chest keloid with previous history of cryotherapy and steroid injection. The keloid grew rapidly in the last several years with unbearable pain (++++)[1] and itching (++++). Physical examination revealed a big keloid in her chest skin with dimensions 10 cm wide, 7 cm high, and 0.3 cm thick along with severe erythema (++++), and hard tissue texture (++) (Fig. 30.2a). The patient was first given nine intralesional injections of 5-FU (mostly 3.45 mg/ml) in 2% lidocaine every 2 weeks in order to control growth and abolish vascularity. The drug injections led to decreased erythema (+), thickness (0.15 cm), hardness (+), reduced itching (+), and also pain disappearance.

Afterwards, the patient received three injections of triamcinolone acetonide in lidocaine (8.3 mg/ml) every other week, resulting in flattened and softened scar with no pain and itching despite the fact that some minor elevated scar areas remained (Fig. 30.2b). Due to re-increased erythema (++) caused by injected steroid, the patient received four injections of a mixture of steroid (7.58–7.35 mg/ml) and 5-FU (2.94–2.27 mg/ml) in lidocaine to achieve both drug effects simultaneously, and this further decreased erythema (+), while maintaining flattened and softened scar without symptom (Fig. 30.2c). Because of improved symptom and physical sign, the patient was given a much lower dose of combined drugs (steroid: from 2.83 to 2.40 mg/ml, 5-FU from 2.27 to 1.42 to 0.96 mg/ml) for six times with 3–8-week intervals in order to prevent relapse and to remodel the scar. During this time, relatively high dose of drugs remained necessary in some small re-growing areas. When followed up 4 months later, it was surprising to find that some keloid areas became grossly invisible and normal-looking skin had appeared (Fig. 30.2d).

Encouraged by this result, another five injections of low-dose combined drugs (steroids: 3.77 mg/ml, 5-FU: 1.42 mg/ml) were administered only to the remaining elevated scar areas with an interval of 4–8 weeks. After another 9-month treatment, scar portion further decreased, and normal-looking skin further expanded with skin color, surface, and texture close to those of normal skin (Fig. 30.2e). After 3 years of tissue remodeling therapy, the treatment was completed and

1 Represents the level of pain, itiching or thickness of the scar, sort of semi-quantitative analysis.

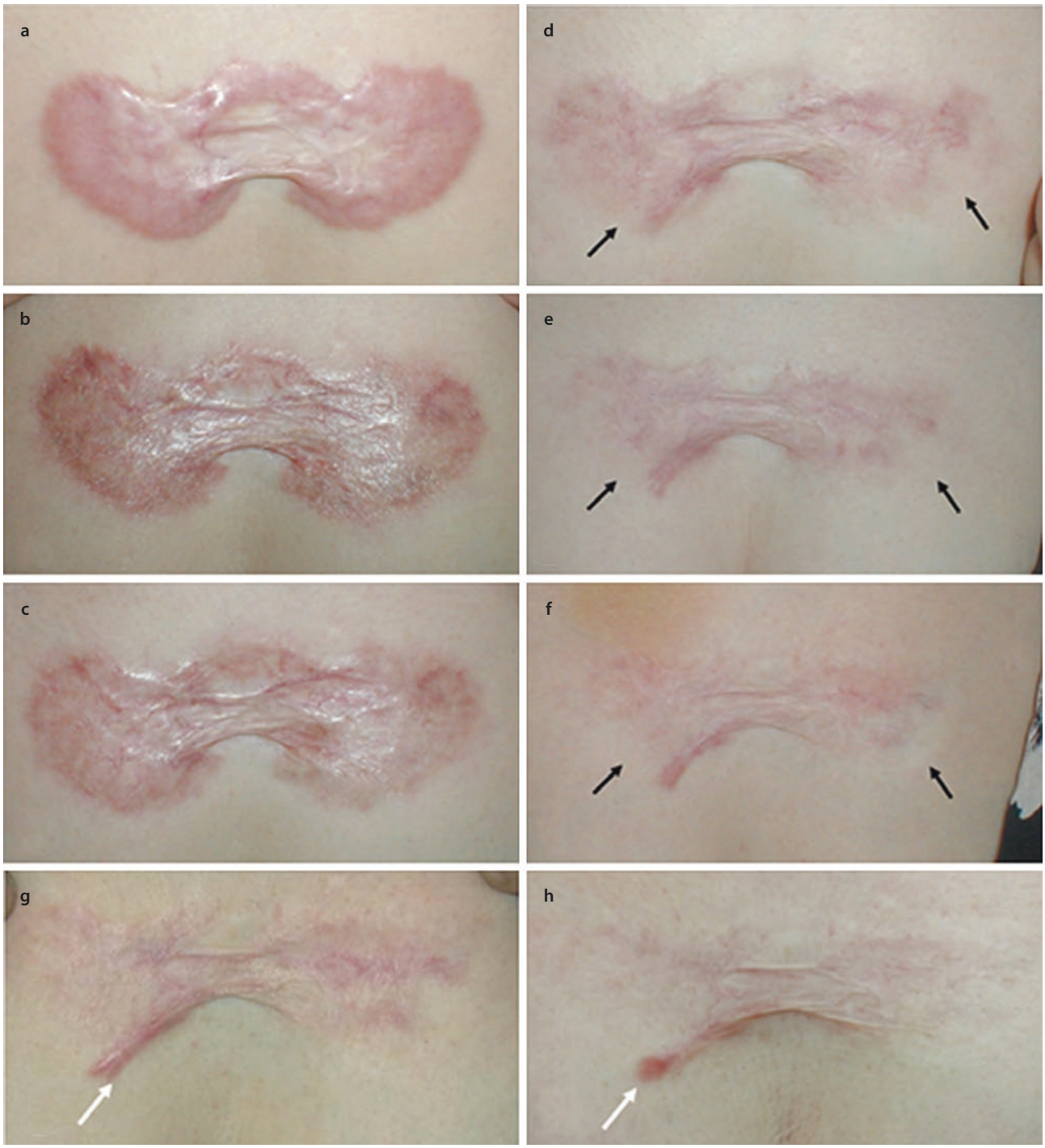

Fig. 30.2 Case 1: Remodeling of keloid into normal-looking skin at various stages. Black arrows indicate the areas that are under continued tissue remodeling. White arrow indicates reoccurred keloid nodule. (See details in the text)

no further relapse was observed at 14 months post-therapy (Fig. 30.2f). Blood cell counts maintained normal during and after therapy.

Two years after the cease of the treatment, a small nodule with redness and pain and itching recurred at the left lower corner (Fig. 30.2g, white arrowed), and further injections with 5-FU (about 3 mg/ml) mixed with triamcinolone acetonide (about 9 mg/ml) were given at intervals of every 3–6 months for 2 more years and once a year for another 3 years. The complete cure of the scar was observed at 9 years after the initiation of the treatment except for an even smaller active nodule (Fig. 30.2h, white arrowed), which may deserve another therapy modality such as radiotherapy.

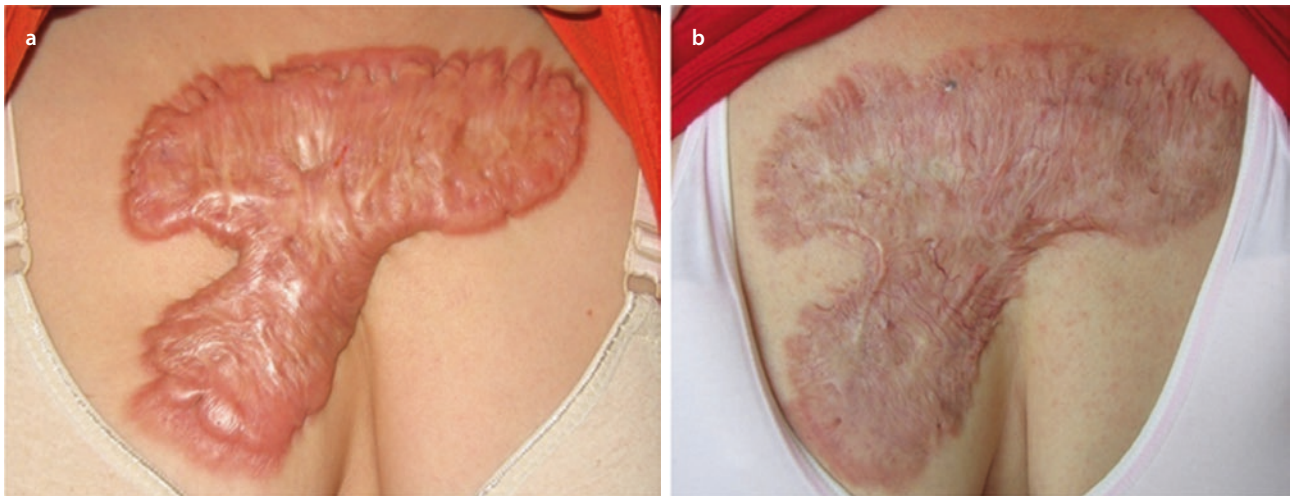

Fig. 30.3 Case 2: Intralesional injection of low-dose 5-FU and steroids for the treatment of large-sized keloids before **a** and after **b** treatment. (See details in the text)

30.7.2 Case 2. Intralesional Injection of Low-Dose 5-FU and Steroid for a Large-Sized Keloid

A 50-year-old female patient visited the clinic with a chest keloid spontaneously forming for 5 years, which developed quickly along with the symptoms of pain and itching. The keloid revealed a size of 15 cm in width, 12 cm in length, and 0.5–1 cm in thickness with server erythema (Fig. 30.3a). The patient was treated with intralesional injection of combined 5-FU and triamcinolone acetonide at low doses as described earlier. This big-sized keloid was divided into four regions, and the injectional therapy was given in a manner of region by region that lasted for 4 years and eventually resulted in a completely remodeled scar that was flattened and softened without erythema and symptoms (Fig. 30.3b). Afterwards, the keloid was generally stable and inactive except for some minor nodules that needed occasional injection.

30.7.3 Case 3. Sufficient Therapy Is Essential for Curing Keloids

A 22-year-old female patient with a large-sized keloid (18 cm in length, 6 cm in width, and 0.5–1.5 cm in thickness) in the abdominal area visited the clinic for her keloid treatment (Fig. 30.4a). The total keloid was roughly divided into three regions for one-by-one treatment. Due to high vascularity of the keloid, the patient was first given 5-FU injection alone at the dose about 3 mg/ml every 3–4 weeks for three times to reduce the vascularity via inducing endothelial cell apoptosis. Once the scar became darker with less erythema, combined 5-FU (2.6 mg/ml) and triamcinolone acetonide (7.5 mg/ml) was used for intralesional injection every 4 weeks. At the seventh-month posttreatment checkup, the top two-thirds of the keloid had already became softened and flattened with the disappearance of pain and itching and reduced erythema (Fig. 30.4b). The patient was further treated for the rest of the keloid in a similar way and the total keloid area became completely softened and flattened without symptoms and with further reduced vascularity at the 24th-month posttreatment (Fig. 30.4c). Then, reduced drug dose (2.6 mg/ml for 5-FU and 4.5 mg/ml for steroids) and prolonged injection interval (6–8 weeks) were applied to focus on remodeling keloid and improving tissue texture. At the 32th-month posttreatment, completely remolded keloid with tissue texture similar to normal skin and minimal level of redness was observed, except for a few isolated active keloid nodules which remained over-vascularized at the bottom region (Fig. 30.4d). Afterwards, the treatment focused only on activated keloid nodules with an injection every 6–8 weeks and whole keloid was completely remodeled when observed at the 68th-month posttreatment except for a few nodules located at the stich markers that remained activated at the 63th-month posttreatment (Fig. 30.4e). Following that time point, the nodule treatment remained and most nodules were completely remodeled after another 15 months of treatment with 3-month interval. The whole keloid has been completely remodeled, which became stably inactivated with whitened color and soften tissue texture when observed at the 78th-month posttreatment (Fig. 30.4f). Afterwards, the whole keloid never reoccurred, and the treated nodules also completely inactivated after several more injections. After more than 6 years of treatment with low-dose 5-FU, the patient delivered a completely healthy child at 2 years post-

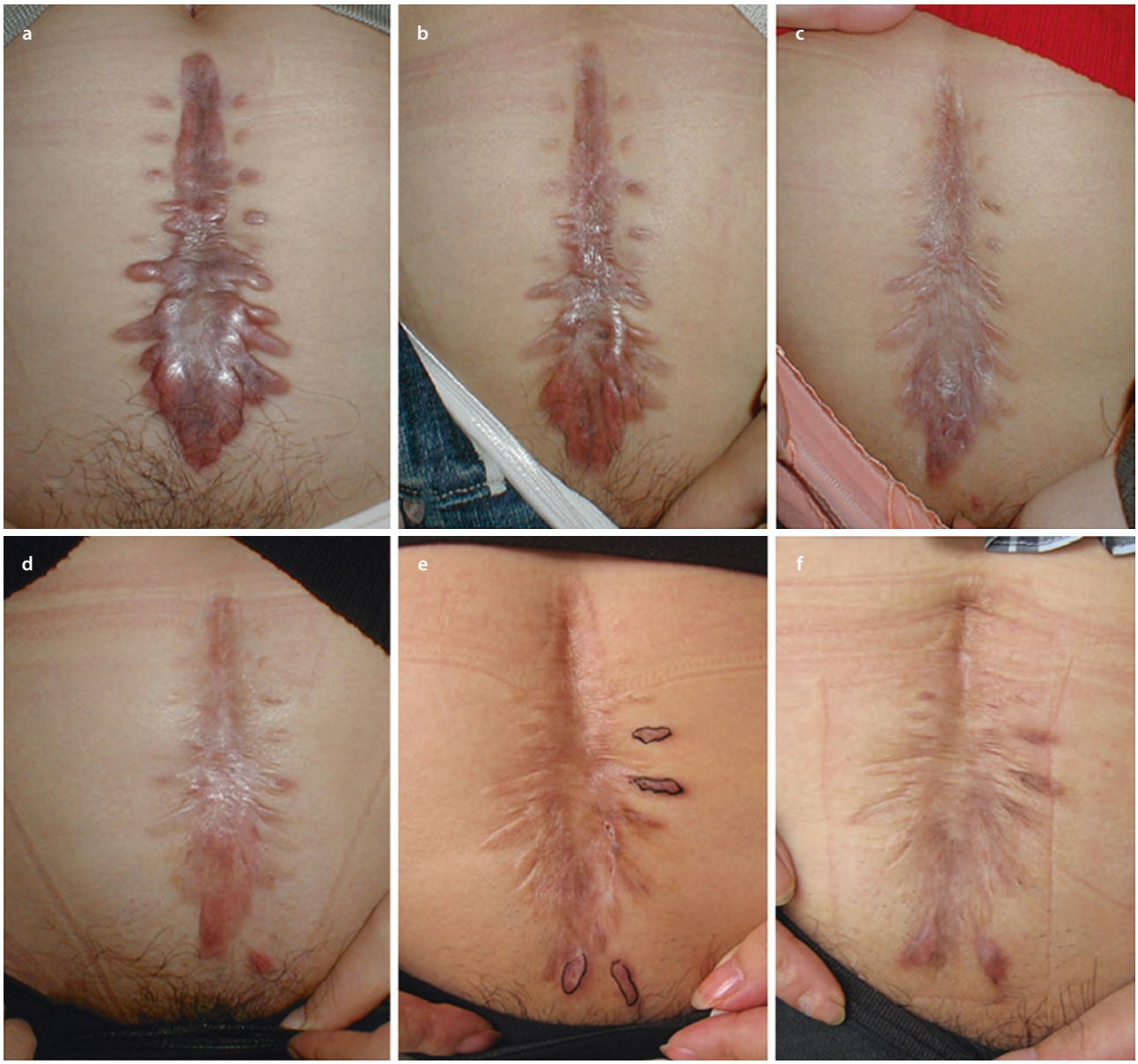

Fig. 30.4 Case 3: Sufficient therapy is essential for curing keloids with image presentation of an evolved keloid treated with low-dose 5-FU and steroid injection. (See details in the text)

cessation of the treatment. This exploratory treatment indicates the importance of sufficient treatment for preventing keloid reoccurrence.

30.7.4 Case 4. Low-Dose 5-FU for Preventing Keloid from Reoccurrence After Surgical Excision

A female patient who had a chest keloid (3 cm in width, 2 cm in height, and 0.5 cm in thickness) with severe pain and itching visited the clinic to request keloid treatment (Fig. 30.5a). The patient received surgical excision of her keloid, and then the wound was irrigated with combined 5-FU (2.6 mg/ml) and triamcinolone acetonide (7.5 mg/ml) followed by primary wound closure with multiple tissue-layer suturing. A tension-reduction device was immediately applied on the closed wound and the patient was asked to keep wearing the device for at least 6 months after the surgery. The patient received radiotherapy within 24 hours post-surgery with a dose of 4 grays per time and per day for total 4 days. The patient was followed up every 4 weeks post-surgery with no sign of reoccurrence, and a linear white scar was observed at 13 months post-surgery without any sign of reoccurrence (Fig. 30.5b).

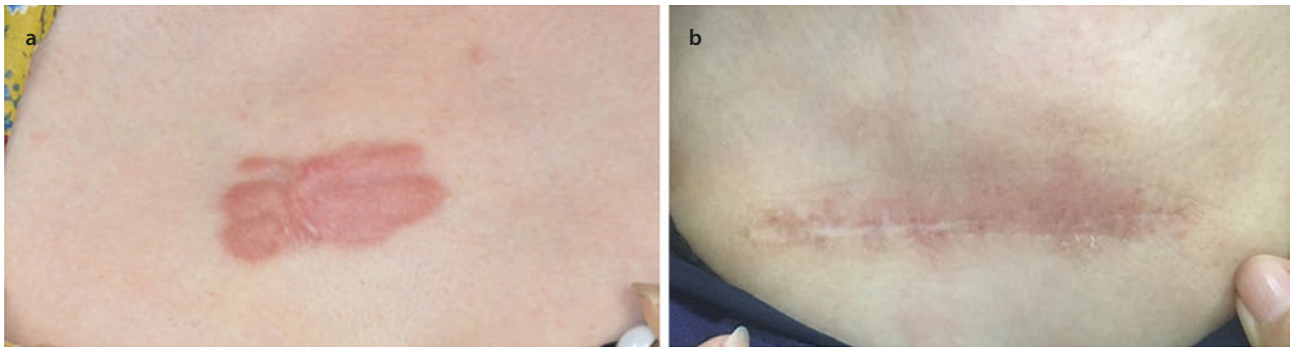

Fig. 30.5 Case 4: Low-dose 5-FU for preventing keloid from reoccurrence after surgical excision. **a** Before the surgery; **b** 13 months post-surgery. (See details in the text)

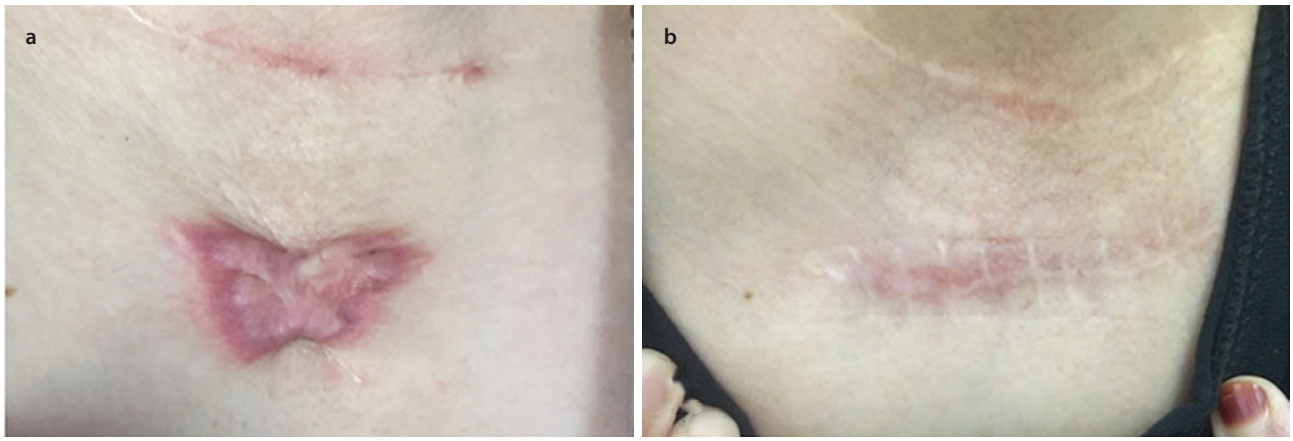

Fig. 30.6 Case 5: Low-dose 5-FU for combined chemoradiotherapy to prevent keloid from postsurgical reoccurrence. **a** Before the surgery; **b** 2 years post-surgery with multiple 5-FU injections. (See details in the text)

30.7.5 Case 5. Low-Dose 5-FU for Combined Chemoradiotherapy to Prevent Keloid from Postsurgical Reoccurrence

A female patient with multiple keloids on her neck, chest (Fig. 30.6a), and left arm visited the clinic and requested keloid treatment. Her chest keloid (4 cm in width, 2 cm in height, and 1 cm in thickness) was heavily vascularized with severe pain, itching, and rapid growth (Fig. 30.6a). The patient received surgical excision, wound irrigation, and closure and radiotherapy similarly as in case 4. However, relapse signs of itching and pain occurred early at 1 month post-surgery. Thus, the patient was given injection of low-dose 5-FU alone (about 3 mg/ml) at 1 month, 8 months, 10 months, 13 months, 16 months, and 19 months post-surgery and no further treatment after 19-month time point. At the 24th month post-surgery follow-up, a whitened linear mature scar was observed at the operational site with no sign of relapse (Fig. 30.6b).

30.8 Conclusion

Intralesional injection of low dose 5-FU combined with steroids for keloid and HTS treatment has been practiced by the authors since 2002 with more than 10,000 cases and proven safe and effective. The use of low dose drugs is to keep this procedure safe and sustainable for long term therapy that is essential for reducing the post-therapy recurrence. Gradual adjustment of drug dose and injection interval time and the management of reoccurred keloids at the earliest possible time are the keys for the success of this procedure.

Take-Home Messages

- Intralesional injection of low dose 5-FU (1.5–5 mg/ml) combined with steroids has been used for keloid treatment with proved safety and efficacy.
- The working mechanism is to inactivate keloid fibroblasts and to gradually remodel keloid tissue, rather to cause keloid necrosis which is a trigger for keloid recurrence.
- The procedure can be used for treating primary keloids or for preventing recurrence of surgically removed keloids.
- Sustainable long-term treatment with adjusted drug dose and injection interval and early management of reoccurred lesions are the keys for keloid successful treatment and recurrence prevention.

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Minimally Invasive Technologies for Treatment of HTS and Keloids: Pulsed-Dye Laser

Sebastian P. Nischwitz, David B. Lumenta, Stephan Spendel, and Lars-Peter Kamolz

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Background

Hypertrophic scars and keloids can be a major medical concern with varying impact.

Depending on the literature one chooses, prevalence between 30% and 70% for postsurgical hypertrophic scarring is reported; looking at burn injuries, the numbers even range from 60% to 90%. Keloids on the other hand, show a prevalence of about 4–14% in Afro-Americans. Given the fact, that the number of people developing significant scars after surgery or trauma ranges in the lower hundred millions every year, one can easily imagine, that scars can be more than an unavoidable side effect after trauma and pathologic scars are not rare.

Besides the cosmetic appearance and the psychological impact (especially after burns), those pathologic scars tend to be responsible for physical and functional impairing symptoms like pruritus, erythema, (neuropathic) pain, and in extreme cases even restriction of movement. The therapy has a wide variety from topical applications to complete surgery – all being covered in this book.

Since the management of cutaneous scars has and often still does rely on personal preference and experience, rather than large-scale and high-quality studies, to date no standard-of-care for the optimal therapy could be established, at least not based on solid scientific evidence.

Many treatment modalities are accompanied by high recurrence rates and with variable effect, which emphasizes the value of and need for minimally invasive technologies. This and the following chapters introduce and focus on several laser technologies as minimally invasive technologies in the treatment of hypertrophic scars and keloids.

On the following pages, the pulsed-dye laser (PDL) is delineated and its significance in the treatment of hypertrophic scars and keloids discussed.

31.1 Historical Development

Among the wide variety of available treatment options, laser applications are considered more recent technologies. Medical use of the physical properties of light dates back to ancient times, when Egyptians, Greeks, and Romans used some form of heliotherapy thousands of years BC. However, none other than Albert Einstein first described the stimulated emission of radiation, the base of laser technology, in 1917 [1]. In 1955, 38 years later, the manuscript of the first functioning precursor of a laser, the *MASER* was published by Gordon, Zeiger, and Townes [2]. Schawlow and Townes, who filed the first US patent for a laser in 1960, altered the ***M****icrowave* ***A****mplification by* ***S****timulated* ***E****mission of* ***R****adiation*-device (MASER) to visible *L*ight wavelengths (LASER).

In the same year, Maiman built the first functioning laser, which used a synthetic pink ruby crystal as active medium [3]. In the early 1960s, the laser was first used for medical purposes in humans [4], and Townes along with two others (Prokhorov and Basov) were awarded the Nobel Prize in Physics for their work based on the MASER (1964). In 1981, Schawlow (along with Bloembergen) shared this honor for his contribution in the development of the laser spectroscopy.

After the development of the first laser, different kinds of light amplification devices have been developed using all kinds of active media.

The first dye laser was introduced in 1966 by two teams more or less simultaneously: the Americans Sorokin and Lankard at the Thomas J. Watson Research Center, as well as the German Schaefer at the University of Marburg developed the apparatus. While Sorokin and Lankard published the invention [5], Schaefer's manuscript was rejected. After resubmission, the journal *Applied Physics Letter* asked Sorokin to review the manuscript, who finally made a publication possible [6], and also acknowledged Schaefer as the first to describe the dye laser's advantage of adjustable wavelengths.

In 1983, Anderson and Parrish described the principle of selective photothermolysis, which enabled further research to adapt and better understand the medical possibilities of the laser and its tissue interactions [7]. First results of the use of the pulsed-dye laser (PDL) in Naevi flammei were published in the same year [8]. Also in that year, hypotheses for the application of lasers for the treatment of hypertrophic scars were made public [9].

Alster and colleagues were the first to issue their positive results in the treatment of hypertrophic scars ($n = 14$; [10]) and keloidal post-sternotomy scars ($n = 16$; [11]) with the 585 nm PDL.

Of note is that these positive results of the PD laser have so far failed to be reproduced in subsequent studies, and only minimal improvements in scar texture have been reported.

31.2 Technique of a Laser

The following section outlines the principle of a laser with a focus on the basics and the most relevant properties for a clinical understanding.

The mode of action of a laser is based on the emission of light by active medium molecules in an excited state, as described by Einstein [1]. This requires an energy source that is able to excite these molecules. To enhance this effect of excitation and reach higher energy levels, an additional resonator is used. These three components are the key elements of a laser (◘ Fig. 31.1).

Atoms in the active medium, which can be of solid (e.g., ruby crystal), liquid (dye), or gaseous (CO_2) state, are excited by supplying them with energy from the energy source. Depending on the used active medium, the time of decay varies until the atoms return to their ground state. The longer the time of decay, the more time remains for an incoming photon to interact with the excited atom, which in turn makes it return to its ground state and emits an additional photon of the same wavelength and frequency (◘ Fig. 31.1, Detail). This doubling ignites a chain reaction leading to the required high intensity of a laser. The resonator, which can be embodied by (various numbers of) plane or curved mirrors, in between the photons are reflected, enhances this effect additionally. One of these mirrors is subtotal-reflective, creating an exit for a part of the photons. In lasers that use dye as active medium, the resonator holds another function. Being equipped with a dispersive element (grid, filter, prism), the wavelength of the emitted light becomes tunable, as described by Schaefer as adjustable wavelengths (see ► Sect. 31.2).

The main difference between laser and regular light lies in its coherence, which allows a monochromatic (just one specific wavelength), high energetic, low divergent emission of light. It can also be applied as continuous wave or in short pulses of up to a femtosecond (one quadrillionth of a second), which allows for a temporal selective application.

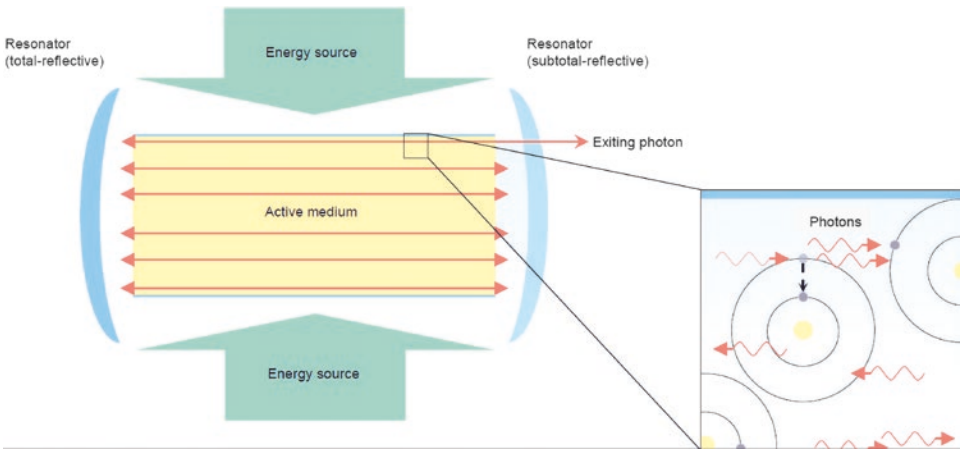
31.3 Tissue Interaction of Laser

The effect and clinical impact of a laser is determined by its interaction with the irradiated tissue. The interaction can basically be distinguished in reflected, scattered, and absorbed photons. While reflective light is predominantly relevant for diagnostic use of lasers, scattering limits the depth of focusing of the laser beam by attenuation. The therapeutic effort is caused by the absorption of light, which can be used for various therapeutic effects. Due to the relevance for the present topic, we only deal with the photothermal effect; other effects can be comprehensively looked up in laser textbooks (see Further Reading).

Since every tissue component shows a different absorption coefficient, which equals the reciprocal of the distance that a photon can travel in that component until it is absorbed, therefore, every tissue component reacts differently to a specific type of light. While, for example, bilirubin and melanin show good absorption of visible light, water (H_2O), the main component of human soft tissue, has its absorptive maximum in infrared wavelengths (◘ Fig. 31.2).

The penetration depth of a laser also depends on the wavelength; the higher the wavelength, the higher the penetration depth in the visible spectrum (blue to red).

The photothermal effect describes the transformation of electromagnetic energy (light) to heat by absorption and thereby photoexcitation of matter. Photothermal therapy is the most common application of laser therapy.



◘ Fig. 31.1 The working principle of a laser is displayed (simplified). An *energy source* causes excitation in atoms of the *active medium* that, amplified by the *resonator*, leads to a chain reaction with the photons ultimately exiting through the subtotal-reflective resonator. The detailed view shows photons interacting with excited electrons of the active medium and emission of additional photons of the same energy

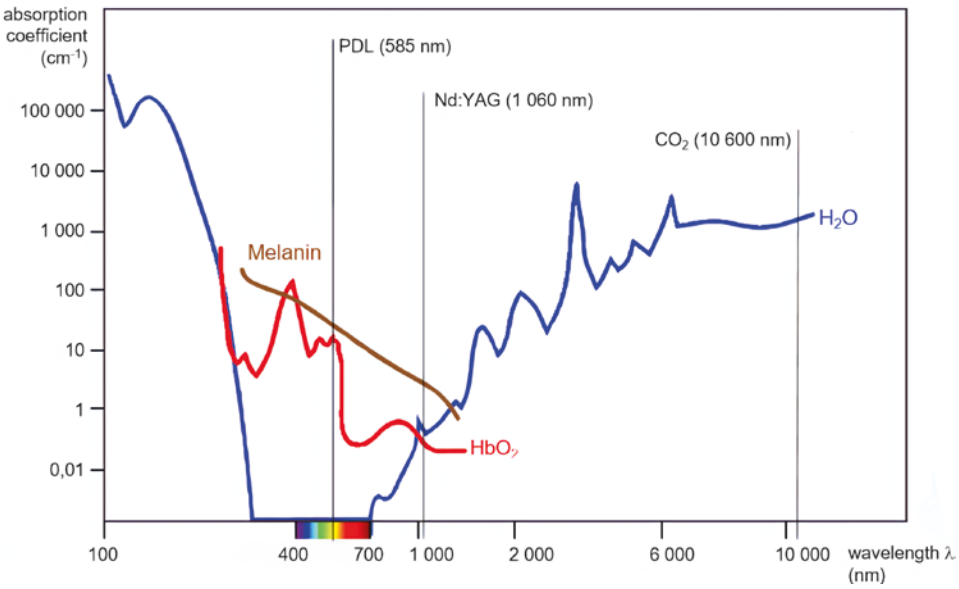


Fig. 31.2 The wavelength-dependent absorption coefficients of H_2O, oxygenated hemoglobin (HbO_2) and melanin are displayed; the wavelengths of pulsed dye (PDL), Nd:YAG, and CO2 laser are presented exemplary. The wavelength of visible light ranges from about 400 to 700 nm. (Design: Dr. med. univ. Hanna Luze, Graz, Austria. © All rights reserved)

The absorptive properties of the irradiated tissue together with the properties of the used laser determine the exact location and effect of the irradiation. The more energy the irradiated matter absorbs, the more heat is produced, therefore explaining the correlation between the absorption coefficient and the different laser wavelengths.

Depending on the temperature reached, edema and apoptosis induction (≥ 45 °C), coagulation, and denaturation of proteins (≥ 60 °C), and even ablation and cutting by vaporization (≥ 100 °C) can be induced.

Another important aspect determining the amount of damage is the fluence. It is given in J/cm^2 and describes the energy deposited on a certain area over a certain amount of time. This makes it an excellent parameter suitable for description of a treatment protocol.

31.4 Selective Photothermolysis

Selective photothermolysis describes a principle that enables selective damage to wavelength-specific pigments within the skin without harming the surrounding or above lying tissues.

The photothermolysis-induced damage is not only transmitted by direct local interaction, but also by heat diffusion additionally irradiating surrounding tissue layers; this principle is of particular importance for calculating selectivity and precise interaction of the laser with adjacent tissue layers.

A basic condition for selective photothermolysis is for the desired target to have a higher absorption coefficient than the surrounding tissues. By pulse-wise-specific irradiation of the target tissue a higher thermal energy is deposited in the target pigment with the higher absorptive coefficient than the surrounding tissue, and directs damaging temperatures only to the target pigment. Due to the pause in between the pulses, there is enough time for the target tissue to cool down by heat diffusion before applying another pulse. On the one hand, depending on the exposure time of the pulses, the amount of damage is relatively well-adjustable to the target area. On the other hand, the wavelength of the chosen and applied light determines the target area. For instance, light of around 580 nm (red light) is predominantly absorbed by hemoglobin, while water has its absorption maximum in the infrared wavelengths and melanin absorbs light throughout the visible region of the electromagnetic spectrum with a decrease toward higher wavelengths. The selectivity of the physical properties allows for a certain approximation of the beam to the target area including a pulse-dependent diameter of several millimeters around it. The downside of this specificity results in a relatively narrow therapeutic spectrum for each type of laser. Due to the monochromatic property of a given laser (emission of light of just one wavelength) and from a technical point-of-view, this leads to different therapeutic targets requiring individual lasers of a different spectrum. This latter fact has made the PDL with its active medium dye and the tuneability (see ► Sects. 31.2 and 31.3) predestined for exploiting this physical principle generating various targets with the same active medium.

31.5 The PDL and Its Application on Hypertrophic Scars and Keloids

The PDL is based on the principle of selective photothermolysis and was developed to damage and destroy small cutaneous vessels without harming epidermal

structures. Being initially developed with a wavelength of 577 nm, the current models mostly work on a spectrum of 585 or 595 nm. Small cutaneous vessels absorb energy at these specified wavelengths. Consequently, the vessels are destroyed, ultimately leading to hypoxemia by diminution of the vascular supply. Then, by allegedly reported secondary effects, disulfide bonds are dissociated, collagen production is reduced, and expression of enzymes such as matrix metalloproteinases is induced [11, 12], leading to a loosening and restructuring of the fibrous structure in hypertrophic scars and keloids. However, there is no ultimate and scientifically proven consensus about the exact mechanisms promoted by PDL.

Hypertrophic scars and keloids often show significant characteristics like erythema and pruritus, which can be caused by hyperemia. Destruction of small cutaneous vessels can therefore significantly reduce these symptoms.

The mentioned restructuring procedures may be responsible for the observed improvement of pliability and height [13].

The properties of PDL and its modes of action also suggest the application in the prevention of hypertrophic scars, since some authors suggest an early laser application after surgery [14, 15].

In support of this theoretical recommendation (early use after surgery) is that the PDL proved to be less effective in thicker scars (>1 cm) due to its restricted penetration depth.

Side effects are relatively rare and include edema, scab formation, and pigmentary disorders (temporary often, permanent rarely), but also range from hypotrophic to hypertrophic scarring [16], but may be related to the therapeutic context of PDL application.

While most PDL work with 585 nm, more recently the 595 nm long-pulsed dye laser has been introduced. Longer pulses have been promoted on the basis of a more effective destruction of larger vessels by higher deposition of energy, and less posttreatment hyperpigmentation. In contrast to that, 585 nm lasers have reportedly ameliorated the scar texture; it remains to be seen if this also applies to the next generation of 595 lasers.

All in all, no scientifically solid high quality studies exist, and the above-mentioned studies do not support the development of definite recommendations for a PDL protocol on hypertrophic scars or keloids. The only common denominator seems to be the minimum requirement of greater than two PDL applications every 4–12 weeks across the scanned literature.

31.6 Selected Studies and Evidence

The first publications of hypertrophic scars treated with the PDL date back to 1994. Alster presented 14 cases of patients suffering from hypertrophic and/or erythematous scars after trauma or surgery [10]. After treatment with one or two sessions of 585 nm PDL within a 6-week interval, they showed an improvement in erythema and scar flattening of 57–83% as evaluated by two different and independent observers. The fluence used in this study was 6.5–6.75 J/cm^2.

One year later, in 1995, Alster and Williams described another series of patients (n = 16) that had developed keloidal or hypertrophic scars after a median sternotomy [11]. Those patients had half of the scars treated with a similar protocol (mean fluence: 7.00 J/cm^2, two sessions, 6–8 weeks apart) and afterwards evaluated by two independent, blinded observers. Significant amelioration of pruritus, tenderness, burning, scar height, pliability, and erythema was observed 6 months after laser treatment, as compared to untreated scars.

Subsequently, no study was able to reproduce these initially promising results. While several studies described changes in scar erythema, pliability, height, and volume, very few demonstrated a statistical significance (also due to the low number of scars treated). Significant improvement in Vancouver Scar Scale scores and pigmentation could be shown by Bowes et al. [17] and Chan et al. [18] for patients treated with PDL compared to no treatment intra-individually, respectively. Alster further showed a significant reduction in pruritus by adding intralesional injection of triamcinolone [19] in contrast to Wittenberg et al. who could not observe a significant reduction of pruritus in hypertrophic scars treated with PDL over patients treated with silicone gel sheeting [20].

Another study by Asilian et al. could reach a significant participant-subjective, inter-individual overall improvement from baseline and a reduction of erythema in patients treated with PDL, intralesional injection of triamcinolone, and 5-fluoruracil compared to the controls treated with the intralesional injection alone [21].

Ouyang et al. (2018) reached significant improvement in height, vascularity, pliability, and Vancouver Scar Scale in 56 patients with fresh (immature), red hypertrophic scars [22], suggesting an early application and possible prevention strategy in conjunction with a recommendation of an international panel of experts [23].

To summarize, data on PDL treatment in hypertrophic scars and keloids is scarce. Studies were conducted with no or insufficient control groups, no standardized treatment protocols, small numbers of participants, or lack of differentiation between the scar types treated.

The exact mechanisms of PDL application in hypertrophic scars or keloids remain elusive and precise recommendations cannot be made on the given evidence.

Nonetheless, PDL may serve as effective additional (second-line) therapeutic strategy given the relatively low side-effect spectrum; application in fresh pathologic, erythematous, itching scars and use for preventive strategies can be considered. PDL use is limited by its low penetration depth (thick scars) and higher amount of melanin as concurrent absorber (darker skin types).

31.7 Clinical Relevance

Since most of the published research demonstrated inconclusive results of the use of PDL for hypertrophic scars and keloids, no solid recommendation can be derived from the given literature. Hypertrophic scars tend to involute over time, and without the evidence served by adequate control groups in published research, it remains difficult to support them. Since medical device regulations will require more published research in the future (notably for device registration in the European Union), future therapeutic registration or re-registration might add in encouraging industry to support more science-driven studies.

Active hypertrophic scars as seen with the clinical sign of erythema or symptom of pruritus can be treated by PDL with a low level of side effects but only if used in conjunction with other more proven methods.

Limiting factors are thick scars (>1 cm) and dark skin types. As a result the PDL can play a role in the prevention of pathologic scars. Future studies should aim toward more standardized research with an adequate selection of control groups (e.g., intra-individual comparison), and are still necessary to reach the actual potential of the PDL.

31.8 Conclusion

This chapter dealt with the minimally invasive treatment of hypertrophic scars and keloids with the pulsed-dye laser. Being the first chapter about laser technology, an introduction on lasers, their functioning, and an outline of the temporal development were given. We then explained the principle behind the PDL, called selective photothermolysis, and clarified its relevance in the treatment of pathologic scars. Lastly, selected studies in terms of clinically applied PDL were presented, the evidence was analyzed, and the clinical relevance delineated.

The reader should now be able to sort the relevance of PDL for treatment of hypertrophic scars and keloids in the whole arsenal of treatment methods for pathologic scars.

Summarizing, we want to emphasize one more time that laser technology itself is a rather new technology, which certainly holds many advantages – not least its minimal invasiveness and low side-effect profile. With only few studies available, we refrain from giving absolute recommendations. We rather want to encourage the reader, if interested in this topic, to help creating more evidence and perform further research on this specific topic. PDL holds potential, that still is to be grasped comprehensively.

Take-Home Messages

- Pulsed-dye laser is based on a principle called selective photothermolysis.
- Its wavelength ranges from 585 to 595 nm.
- PDL's main targets are cutaneous vessels that are coagulated by the irradiation.
- PDL should be applied a minimum of two times every 4–12 weeks.
- PDL application can reduce symptoms like pruritus or erythema.
- PDL should NOT be used for thick scars (>1 cm) and/or in dark skin types.
- PDL should only be used in combination with other treatment modalities to achieve the most effective treatment.
- The low risk and side-effect profile makes the PDL a valuable alternative for the prevention of pathologic scars.
- Long-term outcome and high-quality intervention studies are necessary to provide proper evidence for PDL application in hypertrophic scars and keloids.

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Long-Pulsed 1064 nm Nd:YAG Laser Treatment for Keloids and Hypertrophic Scars

Rei Ogawa

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_32

32.1 Background

Keloids and hypertrophic scars are fibroproliferative disorders of the skin that are caused by abnormal healing of injured or irritated skin [1]. Both disorders have similar histological features: the epidermis and the papillary layer of the dermis are almost normal apart from slight inflammation, and the only abnormality is in the reticular layer of the dermis [2]. While keloids typically exhibit marked hyalinized collagen deposition as a result of prolonged and strong inflammation, this feature is less pronounced in hypertrophic scars [3]. Thus, it is possible that hypertrophic scars and keloids are manifestations of the same fibroproliferative skin disorder and just differ in the intensity and duration of inflammation. These features may in turn be influenced by genetic, systemic, and local risk factors. It is possible that keloids arise largely as a result of genetic and systemic factors that promote massive and extended inflammation, while hypertrophic scars are more likely to be due to local factors. Genetic factors may include single nucleotide polymorphisms [4, 5], while systemic factors may include hypertension [6, 7], pregnancy [8, 9], hormones, and cytokines. The most important local factor is skin tension on the edges of the scar [10–12].

Our understanding of the pathogenesis of keloids and hypertrophic scars has improved markedly in the last 10 years, and these previously intractable scars are now regarded as being treatable. This has dramatically improved the quality of life of patients with these heavy scars [3]. There are many therapeutic options for keloids and hypertrophic scars, including surgery, radiation, corticosteroids, 5-fluorouracil, cryotherapy, laser therapy, anti-allergy agents, anti-inflammatory agents, bleaching creams, and make-up therapies. In terms of laser therapy, we have used long-pulsed 1064 nm Nd:YAG laser (Cutera Inc., Brisbane, CA) to treat keloids and hypertrophic scars and have reported its indications and limitations previously [13, 14].

32.2 Laser Therapies for Keloids and Hypertrophic Scars

Pulsed dye laser (PDL) has long been the therapy of choice for cutaneous vascular diseases, including telangiectasia, hemangioma, and vascular malformations [15–17]. It has also been used to treat keloids and hypertrophic scars because they have more blood vessels than normal skin. However, although PDL is effective for vascular diseases that affect the superficial skin layers (i.e., the epidermis and the papillary layer of the dermis), it does not penetrate deep enough to reach the deep dermal regions (i.e., the reticular layer of the dermis). Thus, PDL is not particularly effective for keloids and hypertrophic scars. By contrast, 1064 nm Nd:YAG laser reaches more deeply than PDL. As a result, it is increasingly being used to treat keloids and hypertrophic scars [13, 18–21]. It has been suggested that it acts by suppressing neovascularization and the dilatation of blood vessels.

Long-pulsed (not Q-switched) 1064 nm Nd:YAG laser plays an important role in our treatment algorithms for keloids and hypertrophic scars. This laser was developed for the treatment of vascular diseases, including inflammatory scars that exhibit neovascularization. It is also used to remove hair and to rejuvenate the skin [13]. The depth that is reached is determined by the spot size, the laser power, and the fluence: the larger the spot size, power, or fluence, the deeper the laser beam penetrates. Therefore, a large spot size and/or power are used for deep targets such as hair follicles and the blood vessels in the reticular layer of the dermis. However, since larger power increases the risk of cutaneous burn injury, the power should be determined on a case-by-case basis.

32.3 Indications and Limitations of Long-Pulsed 1064 nm Nd:YAG Laser for Keloids and Hypertrophic Scars

Keloid and hypertrophic scar development is due to chronic inflammation of the dermis during the course of wound healing. This associates with prolonged angiogenesis and collagen production. As mentioned above, long-pulsed 1064 nm Nd:YAG laser treatment may effectively treat keloid and hypertrophic scars because it reduces their vascularity. This reduction in vascularity may in turn decrease cytokine or growth factor levels in the tissue, which then promote collagen deposition. This notion is supported by the ability of several vascularity-suppressing treatments to improve inflammation and thereby ameliorate abnormal scars. One such treatment may be compression therapy, which is widely used with heavy scars, especially for hypertrophic scars that arise from burn wounds. This therapy may force the collapse of blood vessels in the scar, thereby decreasing cytokine or growth factor levels in the tissue. Moreover, it has been suggested that radiation therapy is effective for keloids because it suppresses angiogenesis. However, studies elucidating the mechanisms underlying long-pulsed 1064 nm Nd:YAG laser treatment efficacy in abnormal scars are warranted.

Our previous study [13] suggests that repeated tension on the edges of scars that is imposed by body movements prolongs scar inflammation: we observed that the patterns of mechanical force distribution around keloids

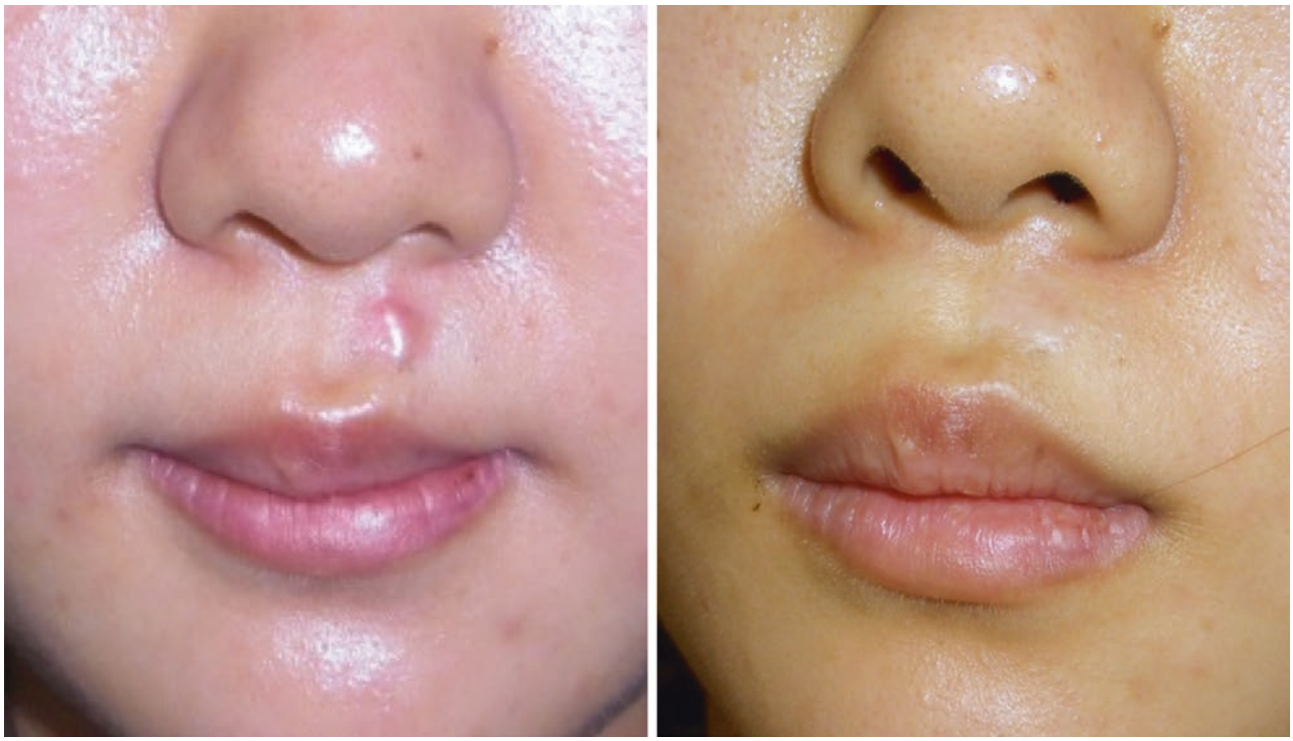

Fig. 32.1 Upper lip hypertrophic scar. Left: before treatment. Right: 1 year after treatment. Two years before her referral to our clinic, a 20-year-old female received an abrasion injury to her upper lip that turned into a hypertrophic scar. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 65–70 J/cm^2, 25 ms, and 2 Hz. After 1 year of this treatment, the scar continued to exhibit a textural difference, but its redness and elevation had improved. (This figure is cited from Ref. [13] with approval from the publisher. © All rights reserved)

and hypertrophic scars are largely consistent with the shape of the scar. In particular, our study suggests that keloids grow into the direction of the dominant prevailing skin tension. This mechanism explains why keloids on different regions of the body adopt specific shapes, such as the butterfly on the shoulder, the dumbbell on the upper arm, and the crab's claw on the anterior chest. These observations suggest that, if scars will continue to be subjected to strong tension due to the daily movements of the body, long-pulsed 1064 nm Nd:YAG laser will not be successful. Indeed, our experience suggests that scars on less stretched areas (i.e., the face and anterior lower leg) respond better to this therapy than scars on highly stretched areas (i.e., the anterior chest wall and scapula). We also found that (1) less inflamed scars (i.e., the typical hypertrophic scar) (Figs. 32.1, 32.2, and 32.3) respond better than highly inflamed scars (i.e., the typical keloid) (Figs. 32.4, 32.5, and 32.6); (2) thinner scars respond better than thick scars; (3) small scars respond better than large scars; (4) single scars respond better than multiple scars (Fig. 32.7); and (5) if even a little scar redness and induration remains after long-pulsed 1064 nm Nd:YAG laser treatment, these scars are highly likely to recur.

32.4 Treatment Settings of Long-Pulsed 1064 nm Nd:YAG Laser for Keloids and Hypertrophic Scars

The laser should generally be applied to the skin surface with the following standard treatment settings: a spot diameter of 5 mm, an energy density of 75 J/cm^2, an exposure time per pulse of 25 ms, and a repetition rate of 2 Hz. However, in the case of the face (Figs. 32.1 and 32.2) or pediatric patients, the treatment should start with a lower energy density (60–70 J/cm^2) to reduce the possibility of a burn injury. The best way to prevent such burn injuries is to cool the tip or air-cool the targeted skin before and immediately after irradiation. Each session should consist of three passes unless the patient feels strong pain at the second pass; in this case, the session should be stopped. Even if the patient feels no pain after the third pass, the session should be stopped. Local anesthesia is not necessary. However, if the patient expresses concern, anesthesia cream or tape can be used. The intervals between the sessions should generally be 2–4 weeks depending on the patient's schedule.

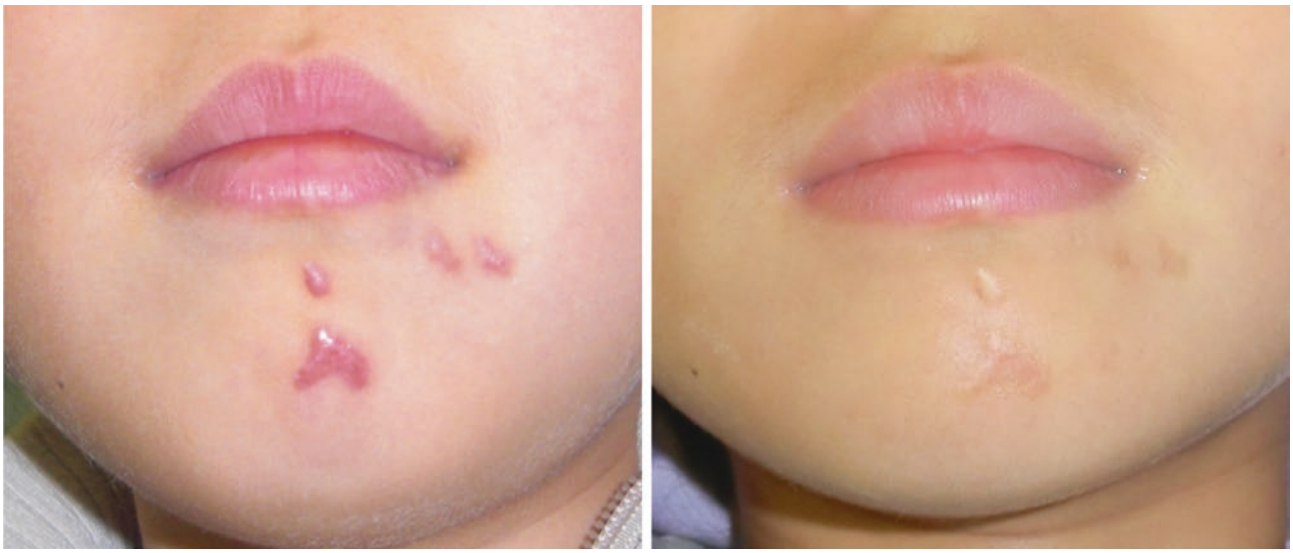

Fig. 32.2 Lower lip hypertrophic scar. Left: before treatment. Right: 1 year after treatment. One year before her referral to our clinic, an 11-year-old female received an abrasion injury to her lower lip that developed into hypertrophic scars. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 60–70 J/cm^2, 25 ms, and 2 Hz. After 1 year of treatment, the scars continued to display textural differences and elevation, but there was clear improvement in their redness. (This figure is cited from Ref. [13] with approval from the publisher. © All rights reserved)

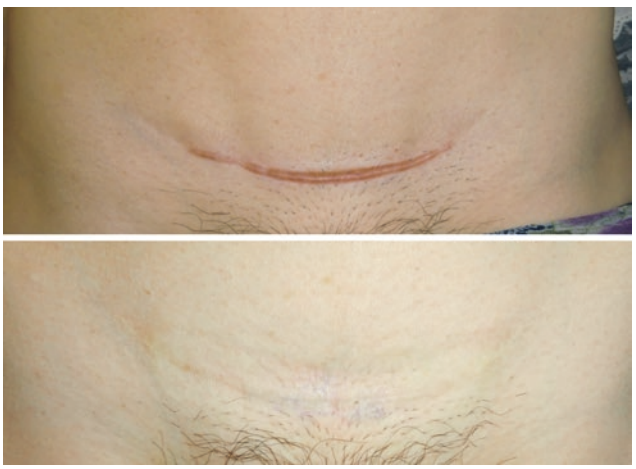

Fig. 32.3 Abdomen hypertrophic scar. Upper: before treatment. Lower: 1 year after treatment. Four years before her referral to our clinic, a 50-year-old female developed hypertrophic scars on her abdomen after uterine myoma surgery. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 75 J/cm^2, 25 ms, and 2 Hz. After 1 year of treatment, the scar had almost disappeared. (This figure is cited from Ref. [13] with approval from the publisher. © All rights reserved)

Steroid tape is often used to decrease the inflammation in keloids and hypertrophic scars; this practice is particularly common in Japan and several other countries [22]. We use fludroxycortide tape (Drenison®, Dainippon Sumitomo Pharma Co., Ltd., Tokyo, Japan) with or without 1064-nm Nd:YAG laser (Cutera Inc., Brisbane, CA, USA) to treat pathological scars, including keloids and hypertrophic scars in recent years [23]. A retrospective cohort study [23] was performed to determine whether adding contact mode 1064-nm Nd:YAG laser therapy to conservative therapy (steroid tape) reduces the treatment time for hypertrophic Caesarean-section scars. In the results, combination of Nd:YAG laser and steroid tape treatment effectively decreased the total treatment time of hypertrophic Caesarean- section scars [23].

32.5 Follow-Up of Keloids and Hypertrophic Scars

It is important that patients with keloids and hypertrophic scars who undergo sequential treatments are followed up over the long term and that they are appropriately educated about scar management [3]. This is true regardless of the treatment that is being used. This is because, if patients develop pathological scars in the first place, they may be particularly prone to recurrence or the development of new pathological scars in

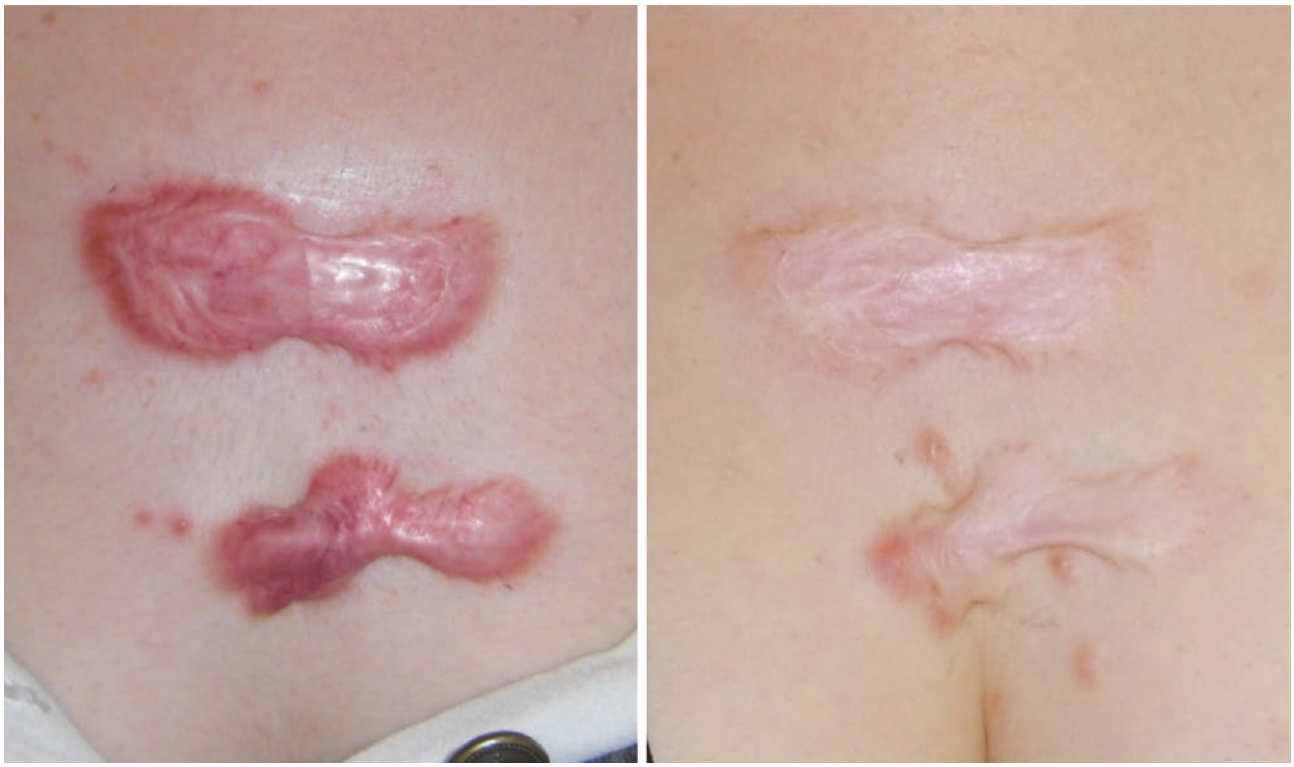

Fig. 32.4 Anterior chest wall keloid. Left: before treatment. Right: 1 year after treatment. Eleven years before her referral to our clinic, a 29-year-old female developed butterfly-shaped keloids on her anterior chest. Treatment with steroid ointment and tape at other clinics did not improve these scars. Long-pulsed Nd:YAG laser was used at the following settings: 5 mm spot diameter, 65–75 J/cm^2, 25 ms, and 2 Hz. After 1 year of treatment, the textural differences and elevation had improved but there was remaining redness on some parts. (This figure is cited from Ref. [13] with approval from the publisher. © All rights reserved)

response to minor stimulation. Thus, these patients should be educated in the self-management of both their abnormal scars and new wounds. In particular, they should be encouraged to apply steroid tape/plasters during the early stages of scar development. This will rapidly reduce the inflammation in the scar and improve its appearance. Moreover, laser therapy, anti-allergy agents (including tranilast), anti-inflammatory agents, bleaching creams, and make-up therapies can be used on a case-by-case basis [3].

32.6 Conclusion

Long-pulsed 1064 nm Nd:YAG laser has been used to treat keloids and hypertrophic scars. This laser was developed for the treatment of vascular diseases, including inflammatory scars that exhibit neovascularization. The depth that is reached is determined by the spot size, the laser power, and the fluence: the larger the spot size, power, or fluence, the deeper the laser beam penetrates. The standard treatment setting is a spot diameter of 5 mm, an energy density of 75 J/cm^2, an exposure time per pulse of 25 ms, and a repetition rate of 2 Hz. Moreover, it is important that patients with keloids and hypertrophic scars who undergo sequential treatments are followed up over the long term and that they are appropriately educated about scar management.

Take-Home Messages

- It has been used long-pulsed 1064 nm Nd:YAG laser to treat keloids and hypertrophic scars.
- Long-pulsed 1064 nm Nd:YAG laser was developed for the treatment of vascular diseases, including inflammatory scars that exhibit neovascularization.
- The depth that is reached is determined by the spot size, the laser power, and the fluence: the larger the spot size, power, or fluence, the deeper the laser beam penetrates.
- The standard treatment setting is a spot diameter of 5 mm, an energy density of 75 J/cm^2, an exposure time per pulse of 25 ms, and a repetition rate of 2 Hz.

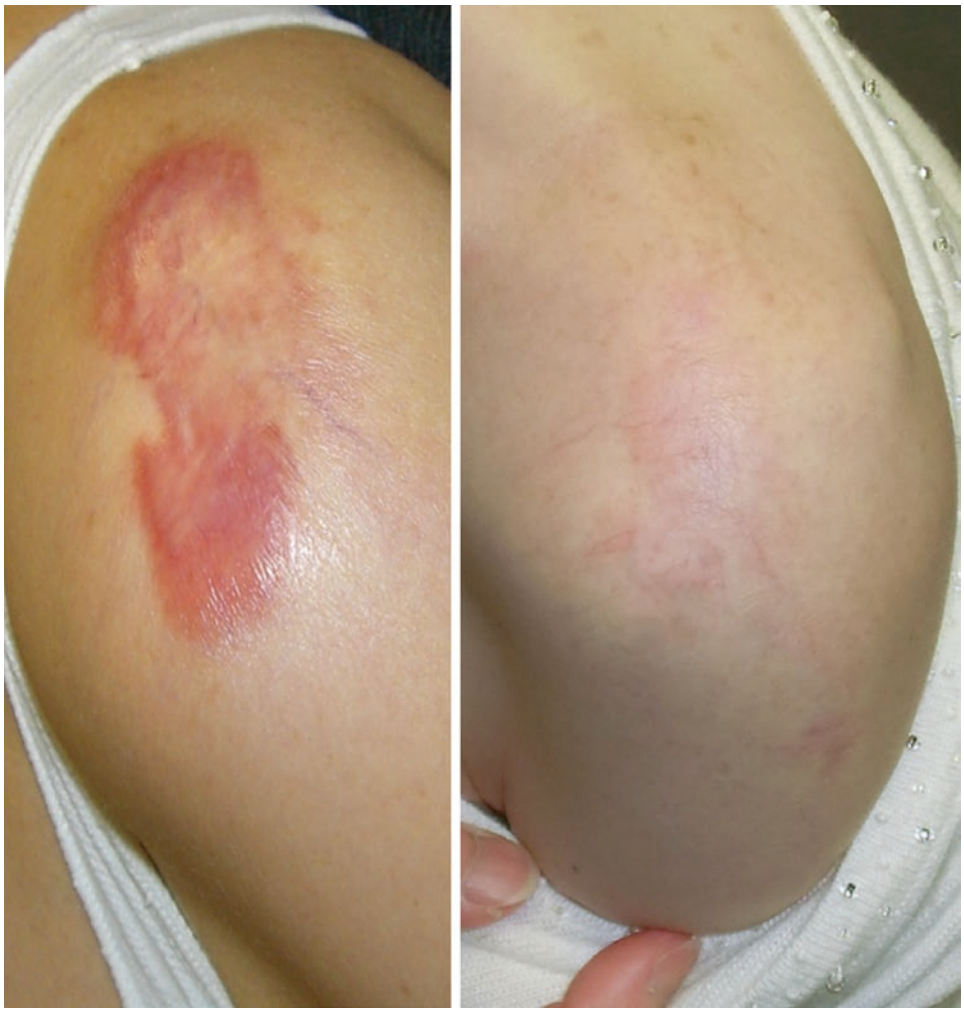

Fig. 32.5 Shoulder keloid. Left: before treatment. Right: 30 months after treatment. About 20 years before her referral to our clinic, a 52-year-old female developed butterfly-shaped keloids on her upper arm and shoulder. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 70–75 J/cm^2, 25 ms, and 2 Hz. After 1 year of treatment, there were clear improvements in the textural differences and elevation but there was remaining redness on some parts. There was also some capillary dilation that was the result of steroid injections in the past. (This figure is cited from Ref. [13] with approval from the publisher)

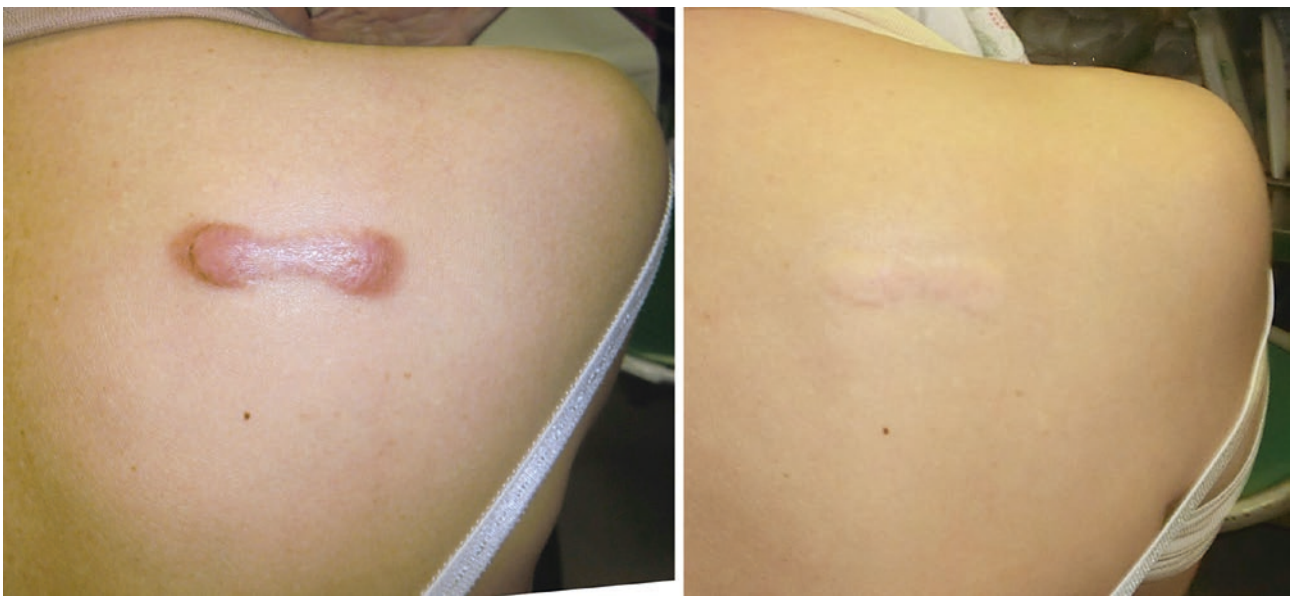

Fig. 32.6 Scapular keloid. Left: before treatment. Right: 3 years after treatment. About 30 years before her referral to our clinic, a 52-year-old female developed a butterfly-shaped keloid on her scapula. Steroid injections and tape at other clinics yielded little improvement. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 70–75 J/cm^2, 25 ms, and 2 Hz. After 2 years of treatment, the texture, redness, induration, and elevation of the scar had clearly improved. (This figure is cited from Ref. [13] with approval from the publisher)

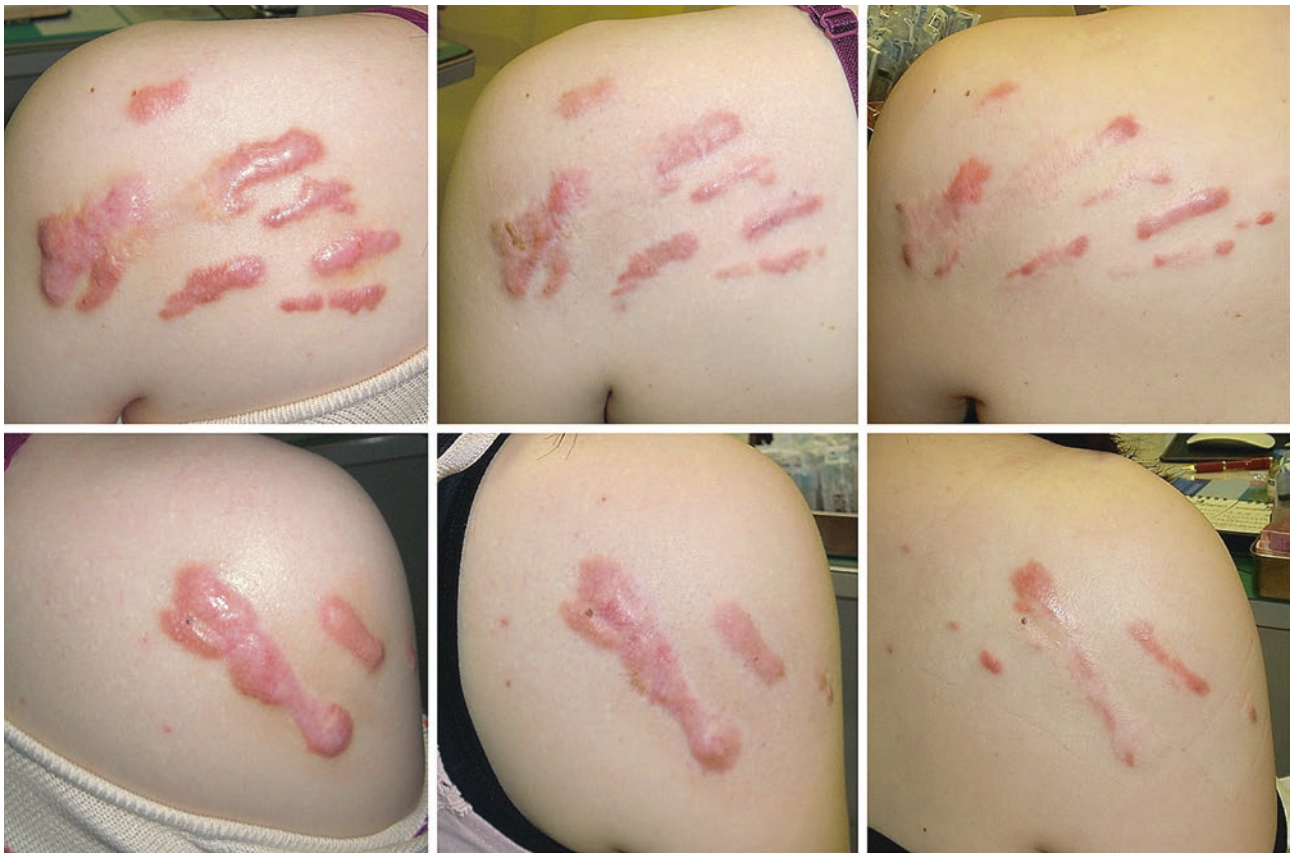

Fig. 32.7 Scapular keloid. Left images: before treatment. Middle images: after 1 year of treatment. Right images: after 4 years of treatment. About 30 years before her referral to our clinic, a 42-year-old female developed multiple keloids on both the left (top images) and right (bottom images) scapular areas. The keloids had been slowly increasing in size. Steroid injections and tape treatment at other clinics yielded little improvement. Long-pulsed 1064 nm Nd:YAG laser was used at the following settings: 5 mm spot diameter, 75 J/cm^2, 25 ms, and 2 Hz. Moreover, a Chinese herb (Saireito) was administered every day. After 4 years of treatment, the texture, redness, induration, and elevation of the scars have improved. However, the scars are not yet completely cured

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Minimally Invasive Technologies for Treatment of HTS and Keloids: Fractional Laser

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_33

33.1 Introduction

Hypertrophic fractional laser and keloid scars present a spectrum of disorders that are difficult to treat. Multiple treatments have been tried, to ameliorate the clinical sequelae of scarring, such as erythema, pruritus, functional limitation, reduced range of movement, dyschromias, hyper and/or hypopigmentation. Early international clinical recommendations on scar management first recognized the importance of laser therapy in this armamentarium [1]. Within the years that followed, laser technology and the understanding of how it modulates the underlying processes that leads to hypertrophic and keloid scarring have experienced a quantum leap [2] and are still evolving. Lasers also present a considerable financial commitent, and it is possible, in the authors' experience, that limited early results partially stemmed from limited availability of multiple lasers with consequent attempts to overstretch the indications for what was available.

This chapter presents a state-of-the-art insight into the use of fractional laser for the management of this complex problem. In particular, we focus on the management of complex scars such as those occurring post-burn injury and split-thickness skin grafting.

33.2 Method of Action

Light energy can be used to modulate or ablate specific targets in the skin through selective absorption of energy and specific heat energy dissipation properties [3]. The theory of selective photothermolysis, first described in 1983, laid the foundations for subsequent developments and standard practices [3]. When used to induce a controlled thermal injury, lasers initiate information processes to increase vascular permeability and modulate matrix metalloproteinase production of collagen fiber deposition and tissue hypoxia caused by targeted vascular ablation [4]. Through these processes, wound healing specifically in the remodeling phase may be manipulated, resulting in scar maturation and obviation of symptoms [5]. Different types of lasers are useful in targeting the different components of this disease scar tissue and it is important that the laser practitioner has the essential range of appropriately powered tools required to produce an optimal effect.

The choice of fractional laser in the management of a hypertrophic spectrum scar depends upon whether an ablative or non-ablative effect is desired, the target chromophore, the background skin type, the thickness of scarring, requirement for laser-assisted drug delivery (LADD), and the patient's compliance with postoperative downtime and regimes. The Azzopardi classification of chromophores also helps the practitioner rationalize the likely target and downstream metabolic effects [6]. Fractionated lasers with established effectiveness include CO_2 and Er YAG (nanosecond modality). More recently, fractioned, picosecond Nd: YAG has emerged as a potent platform in this context.

33.3 Fractioned Laser Platforms

Fraction laser resurfacing creates microscopic columns of ablation in epidermis and dermis, termed microscopic treatment zones. The relationship of these zones to intervening blocks of normal tissue permit rapid heat dissipation yet deliver enough energy to allow immediate changes in scar pliability, and instigate scar remodeling and neocollagenesis. The use of non-fractioned platforms such as pulsed dye and KTP (532 nm) are well documented and discussed elsewhere.

Fractioned CO_2 (10,600 nm) and Er:YAG (2940 nm) are the two main ablative modalities in use, targeting water and collagen to produce mass transfer zones (MTZs) of defined diameter (70–100 μm) and depth, tissue vaporization, and coagulation.

At the molecular level, fractional ablative laser treatment induces upregulation of heat shock protein, upregulation of matrix metalloproteinase, fibroblast apoptosis, downregulation of transforming growth factors and basic fibroblast growth factors, and modulation of collagen-type ratios. These changes are evident beyond the microscopic treatment zones, yet the spared tissues contribute to rapid, normalized wound healing. A major difference however between CO_2 and Er:YAG laser is the potential to achieve immediate coagulation and hemostasis: CO_2 laser is 10 times more effective in this regard. This is critically important when considering resurfacing of extensive areas and when considering LADD, as in our experience, bleeding results in plugging and reduced LADD efficacy. Moreover, the waveform characteristics of a CO_2 laser have a significant bearing on the potential for side effects.

33.4 Fractioned CO_2 Laser

Indications and timing: The latest version of consensus international guidelines for prevention and treatment of pathological scarring (2014) reserve the use of fractional laser therapy for scars refractory to pulsed dye laser; widespread hypertrophic burn scars that failed to improve with treatment with silicone gel or sheeting, pressure garments, and/or onion extract preparations for 8–12 weeks; minor keloids that failed to improve within 8–12 weeks with silicone gel sheeting and intralesional corticosteroids; and major keloids resistant to improvement with intralesional

corticosteroids and 5-FU may be treated with ablative fractional laser or PDL therapy. This philosophy has been challenged by recent literature.

First, the use of fractioned CO_2 has since been successfully used (to date, off-license) with extensive and well-documented success, as an adjunct facilitating transdermal delivery (see below) [7]. Pulsed dye is less effective in scars more than 1.2 mm depth, and do not allow for effective scar pliability that may substantially facilitate post-procedure physical therapy. From a basic sciences perspective, once it has been established that fractioned ablative laser may re-instigate appropriate scar remodeling, it would be more useful to target the scar during the remodeling phase once epidermal integrity is well established. Recent literature supports earlier intervention than the previous 6 months to a year postinjury dogma, in concordance with our experience. In our experience, a treatment interval of 4–6 weeks is acceptable. Further, given the tendency of corticosteroid to exacerbate telangiectasias, use of fractioned CO_2 first (±LADD) followed by vascular-type laser to correct any resulting telangiectasia may also be an acceptable and more time-efficient approach.

33.5 Settings for Ablative Fractional CO_2 Laser

Utmost caution is advised when deciding clinical settings as these will vary between platforms. Many superpulsed lasers can only produce a shark tooth–type waveform. This results in the need to impart substantially more energy for the therapeutic threshold to be achieved. This additional energy may be responsible for the increased risk of complications seen in the literature (both medical and legal) with these laser platforms. In contrast, lasers imparting a "top hat pattern" waveform impart only enough energy for the therapeutic threshold to be achieved. Further safety considerations include maintaining an inverse ratio of power to density, and ideally to avoid imparting a fluence that is above TRT, density sets the number of MTZs per unit area, which should not be above 10%. Ideally, for purposes of safety, pre- and post-cooling regime should also be considered. A cold-air blower provides excellent pre-and post-cooling as well as being an effective analgesic.

Further settings include the size, shape, pulse stacking, and depth. Shape and size of the fractioned beam can be changed according to prevailing need. Whether the beam should penetrate beyond the scar thickness is still being investigated; however, injuries beyond the dermis may well lead to scarring and should be avoided [8].

33.6 Fractioned Erbium:YAG

The clinical efficacy of Er:YAG in keloid scars is limited. Cavale et al. combined Er:YAG with twice daily topical betamethasone under occlusion until therapeutic maximum was achieved, resulting in 50% improvement (median, $n = 70$), but recurrences also occurred in 22% of lesions [9]. One factor which may explain this disappointing result is the limited ability of current Er:YAG technology to penetrated deeply, and lower hemostasis.

33.7 Fractional Non-ablative Laser

Fractional 1550 nm Erbium-doped fiber laser reported overall improvement in scar texture after four treatments spaced 2 weeks apart, compared to the non-treated part of this split-scar study [10]. Literature reports that the response is mediated by heat shock protein, fibroblast proliferation, and consequent neocollagenesis [10].

A recent comparative RCT reports 1550 nm Er-doped fiber (70 mJ/23% coverage) to be superior to pulsed dye laser (7.5 mJ/10 mm/0.45 ms), with a 75% compared to 53% improvement reported [11, 12].

33.8 Picosecond, Fractioned, 1064 nm Nd:YAG

Management of hypertrophic and keloid scarring in darker skin types is a formidable challenge. Longer wavelengths, cooling devices, and lower treatment fluences have been shown to minimize complications [13, 14]. Recently, fractional picosecond 1064 lasers have reported good outcomes with very few side effects [15]. Compared to the conventional nanosecond domain QS Nd:YAG laser, the ps-Nd:YAG can produce significantly higher peak powers at the same energy level [16]. It is therefore expected that such technology works principally through photomechanical rather than photothermal effects [17]. The inhibitory effect of the 1064-nm Nd:YAG laser against dermal collagen formation is documented in the literature [18–20]. More recently, the use of fractioned 755 nm picosecond laser has been reported to be effective and safe in patients with Fitzpatrick skin types 4–6 [20].

33.9 Cautions and Contraindications

Caution is advised with any underlying process that impedes wound healing. History of herpes simplex virus, especially if lasering is to be attempted in the peroral

area, should prompt prophylactic management. Oral antivirals or more recently bromelain should be considered [12, 21, 22]. Current depth of penetration for ablative fractional devices is approximately 4 mm, and therefore management of deeper scars is less likely to be as effective [22].

33.10 Preoperative and Postoperative Regimes

No consensus exists with regard to preoperative preparation. Some prepare skin with chlorhexidine solution and moistening hair-bearing areas prior to treatment [23]. Others, including the authors, are content with cleansed, dry skin [24]. It is important to note that whatever preparation method is favored, that moist and humid surfaces result in reduced ablation, and increased heat latency since the primary target, water, is now in increased abundance.

Several factors influence the choice of anesthesia, depending on the age of the patients, available equipment, and extent of surface area treated. However, overarching principles governing the practice of both authors include the use of the safest, least-invasive modality first, pre-optimization, and dual effect of skin cooling in increasing safety as well as providing an analgesic effect. Within this context, pretreatment with topical anesthetics of increasing strength coupled with cold-air blowers may provide the mainstay of analgesia requirements [25].

Where general anesthesia is required, it is possible to apply topical anesthesia immediately after fractioned CO_2 lasering. However, the facilitation of transdermal delivery will facilitate increased absorption (see below), and therefore it important to consider the maximum safe dose to avoid anesthesia-related toxicity. Use of ice-water packs immediately following treatment provides additional modalities for heat dissipation and analgesia [26].

Again, postoperative regimes vary widely, depending on resource, patient compliance, and experience. Use of antiseptic moisturizers, followed by a regime of moisturization is strongly advised, along with hydrocortisone for pruritus. Sun protection is mandatory. Patients may resume normal activity almost immediately, including physical or occupational therapy. Showering is permitted, with the exception of full immersion in standing (bath) water where ablative laser has been used. Some degree of edema is expected. Depending on the patient's tolerance, compressive garments may be worn immediately after, but they may cause shear of treated tissue, and therefore it is sensible to recommend waiting for 24–48 h before use.

33.11 Expected Outcomes

Benefits associated with CO_2 laser treatment include increased scar pliability and reduced tightness, but it is important to impress on the patient that laser treatment creates the *potential* for increased scar pliability which is *accomplished only* by compliance with aggressive physical therapy postoperatively. Appropriate patient selection is therefore paramount, as is the availability of experienced and motivating physical therapists. Further benefits include reduced scar height and thickness. Pruritus has been observed to decrease in several studies presumably because nerve endings are no longer encased in tight scar tissues.

Similarly, fractioned CO_2 laser may directly address the source of keloid formation, when this occurs in hair-bearing skin. Here, the hair follicle is encapsulated in the scar, which subsequently inflames, infects, and results in perpetuation of the insult-driving keloid growth. Scar remodeling results in amelioration of pliability, and in the authors' experience it is not uncommon to result in resolution of the insult-driving keloidal growth as well as regrowth of hair in the site.

By inversely relating density to energy settings, it is also possible to attenuate relative scar height, resulting in flattening.

33.12 Potential Complications

The principal complications reported in the literature include burns, infection (viral, bacterial, mycotic) postoperative pain, and abnormal pigmentation: Post-inflammatory hyperpigmentation as well as hypopigmentation have been reported. In those being treated for burn injury memory flashbacks to the original incident have been reported in the literature, therefore it is essential that patients are forewarned. It is of course important to discuss the potential of multiple treatments. A large prospective study performed by Hultmann and colleagues puts the overall complication rate at 3.9% of all treatments: in decreasing order of incidence, hypopigmentation, blistering, hyperpigmentation, infection, cellulitis of the adjacent skin, superficial mycoses, and oral herpes simplex [27].

Practical recommendations for improving patient safety are judicious use of fluence (especially in darker skin types), use of pre- and post-cooling regimes, single pass, and avoiding stacking pulses, intentionally or otherwise [8]. Multimodality treatment to one area within the same sitting is indeed possible, given the mastery of the underlying principles, correct understanding of the disease extent, the background skin type, and the patient's potential for healing. However, it significantly

increases the risk for adverse events and therefore best avoided, except where mandated by individual risk–benefit considerations and availability of experts with appropriate experience. The use of test-patching and initiation of treatment in non-cosmetically conspicuous areas are advocated. In addition, a readily available database of previous patient-specific settings allows setting optimization to be delivered based on previous successes or complications.

33.13 Fractioned CO_2 Laser as a Method for Potentiating Transdermal Laser-Assisted Drug Delivery (LADD)

Ablative fractional laser breaches epidermal integrity, producing newly formed, uniform, and deep channels into hard dermal scars. It is well established (but at time of publishing as yet off license) to harness this phenomenon as an effective method for trans-dermal drug delivery (Fig. 33.1). The two-fold advantages may be summarized as follows: less pain and more even distribution. First, traditional injection of volume into tight dermal scarring produces uneven distribution, creating blebs of volume while no treatment to adjacent areas. Volume injection into a tight scar also increases pain and discomfort [28]. Recent literature also points to various aspect of improvement this technique addresses, including pain tolerance, texture, dyschromia, and hypertrophy [26, 28, 29].

Pain relief: Intra-scar injection is often poorly tolerated pain-wise, especially when larger surface areas are being considered. Several studies have established that fractional Er:YAG pretreatment reduces up to twelve-fold the time required for topical anesthesia to take effect. However, within these studies, it is impossible to assess whether mild adverse events reported (including residual pain, redness, or mild-moderate swelling) was due to the needle or laser, as the effect was measured only after the needle was inserted. Typical settings for this indication are fluence of 250 mJ/pulse, a pulse width of 300 microseconds, and an estimated pore depth of less than 20 mm [30–32].

More importantly, this data demonstrates that application of local anesthesia post-procedure is likely to be more efficiently absorbed. While care needs to be taken with maximum dose due to altered absorption, post-procedure topical anesthesia may provide valuable pain relief, and is the standard practice of one of the authors (EA) when treating larger areas of sheet hypertrophic scarring post burns, with no side effects noted to date.

LADD has been used to potentiate transdermal delivery of both corticosteroid [33–37] as well as 5-fluorouracil [38] as well as combination treatment [38]. More recent evidence suggests that both are equally effective, but 5-FU does not lead to dermal atrophy or telangiectasia seen with corticosteroid delivery [39].

33.14 Consensus Practice

Established clinical consensus is that ablative lasers are significantly more effective per treatment for scar improvement than their non-ablative counterparts, especially for keloid and hypertrophic contracted scars, with significant gain in pruritus, pain, and physical mobility within days and up to 2 weeks posttreatment. Usually, rapid improvement in dyspigmentation is followed by slower improvement in texture and range of movement [22].

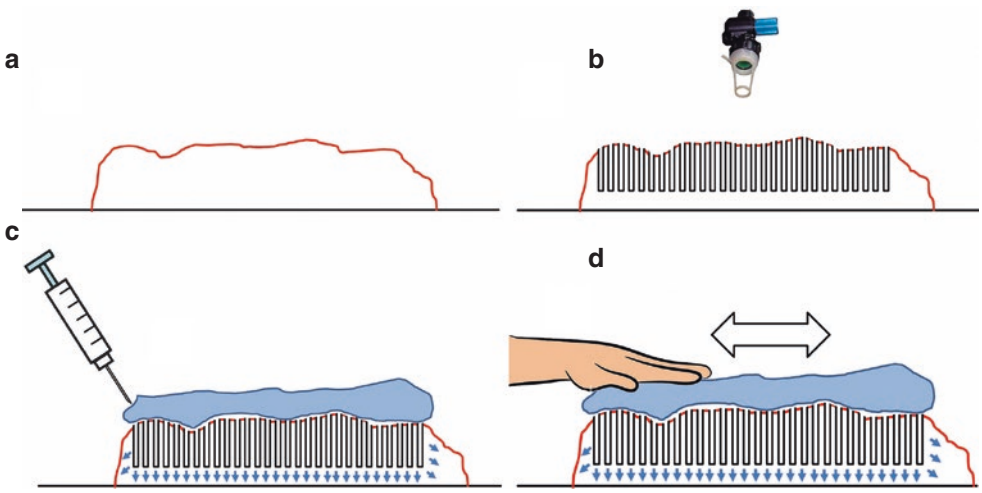

Fig. 33.1 In Laser Assisted Drug Delivery, is a recent advancement where laser energy is used to enhance trans-dermal drug delivery. For scarring **a**, typically, a fractioned ablative laser beam is used to create channels within the scar **b**. This is followed expeditiously with topical application **c**. The topical application is massaged in to the lasered area to enhance absorbtion **d**

Take-Home Messages

- Hypertrophic and keloid scars present a spectrum of difficult to treat disorders, and different types of lasers are useful in targeting the different components of this disease scar tissue.
- The choice of fractional laser in the management of a hypertrophic spectrum scar depends upon whether an ablative or non-ablative effect is desired, the target chromophore, the background skin type, the thickness of scarring, requirement for laser-assisted drug delivery (LADD), and the patient's compliance with postoperative downtime and regimes.
- Fraction laser resurfacing creates microscopic columns of ablation in epidermis and dermis, termed microscopic treatment zones.
- The relationship of these zones to intervening blocks of normal tissue permit rapid heat dissipation yet deliver enough energy to allow immediate changes in scar pliability and instigate scar remodelling and neo-collagenesis.
- Fractional ablative laser treatment induces remodelling changes that are evident beyond the microscopic treatment zones, yet the spared tissues contribute to rapid, normalized wound healing.
- The main modalities in use are CO_2 and Er:YAG laser. CO_2 has the potential to achieve 10-fold more immediate coagulation and hemostasis. This is critically important when considering resurfacing of extensive areas and for LADD.
- Picosecond systems act principally through photomechanical rather than photothermal effects and may be useful in darker skin types.
- Ablative fractional laser breaches epidermal integrity, producing newly formed, uniform, and deep channels into hard dermal scars. It is well established (but at time of publishing as yet off license) to harness this phenomenon as an effective method for trans-dermal drug delivery.
- There is no universally accepted skin prep regime, however moist surfaces result in reduced ablation, and increased heat latency.

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Minimal Invasive Technologies for Treatment of HTS and Keloids: Medical Needling

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34.1 Background

HTS (hypertrophic scars) and keloids remain a serious and challenging issue regarding medical and therapeutic intervention. Clinical symptoms such as pain or pruritus are followed by psychological deficits of stigmatization or even discrimination for the affected people. Considering the multifactorial pathogenesis of these pathological scars, the injury to the skin reaches the reticular dermis and causes subsequent aberrant wound healing. A secondary intention of wound healing is characterized by inflammation by promoting various tissue and immune cells. Hence, the vulnerable skin layer of HTS and keloids contains inflammatory cells, increased numbers of fibroblasts producing collagen and endothelial cells for a nutritive angiogenesis. This may promote chronic inflammation, which in turn may cause the invasive growth of keloids and explains clinical symptoms. The situation becomes even more complex with bacterial superinfection or other inflammatory responses, as proinflammatory cells and cytokines are highly upregulated. Pathophysiological parameters create a complex profile of HTS and keloids, which demand therapeutic attention and medical intervention.

34.2 Introduction

In this chapter, we are going to present medical needling as an ideal therapy for the treatment of hypertrophic scars and keloids. The past has shown difficulties in treating these types of scars that are characterized by a complex anatomy and a progressive degradation of the scar texture. Serious challenges for various therapy approaches are a rapid and uncontrolled growth, a lack of moisture and a rigid structure. Affected people are confronted with dysfunctional and aesthetic deficits in their daily life or suffer from further harm through stigmatization. For this indication, medical treatment is required that replaces surgical interventions and other ablative treatments. HTS and keloids are prominent scars that frequently occur in combination with persistent erythema. Widespread and deep damage of the skin layers is often followed by secondary wound healing, which enhances the formation of either HTS or keloids. Keloid scars occur when the skin overreacts to the injury, after which they continue to grow and get dark in color. The histopathology of keloid demonstrates an extensive tissue proliferation beyond the margin of primary wound. Dark skin types are predisposed for the development of keloids that appear when a forced wound closure proceeds under tension. That is why keloids can cause great discomfort, tightness, or a limited range of mobility if they develop near a joint such as the knee or ankle. An excessive stretching of skin creates uncomfortable pressure over the fibrotic tissue, which can cause itching. Because of their typical larger size, they tend to rub on clothing, causing unbearable irritation.

Whereas the development of HTS is fairly manageable, keloids reveal specific features concerning the parameters of size and growth. Keloid scars develop uncontrolled or excessive fibrogenesis and are a tremendous source of collagen that still causes clinical problems until now. Thus, keloid is an active tissue that demonstrates signs of inflammation such as redness, itch, and mild pain. The permanent tendency to uncontrolled growth exceeds the original wound area and reaches massive proportions due to uncontrolled fibrosis. The last-mentioned issue is associated with a dysregulation of growth factors, which leads to an overproduction of scar tissue and an uncontrolled synthesis of the extracellular matrix. Hence, therapeutic treatment of keloids differs from those of normal hypertrophic scars. Keloid is often recurrent, although it has been treated with either pharmacological agents or surgery. Dermatological approaches of scar removal are not based on ablative treatment methods. They include compression therapy, intralesional corticosteroid injections, and excisions. When injected into the keloid, appropriate medication helps shrink the scar for a short time. The patient is due to receive a series of injections once every month, which means a constant therapy in order to prevent renewed scarring. Moreover, the use of radiation therapy instead of laser therapy is a common practice. However, this method also means a radiation exposure, which is always a health hazard. Ionizing radiation should only be implemented when medical indication is given or other alternatives are not reachable.

With regard to HTS, ablative treatments such as surgical interventions show temporary success by reducing the scar tissue to the level of the surrounding skin. These circumstances support the risk of recurrence and a continuous degradation of scar texture and healthy skin. The majority of conventional treatments are based on ablative and radical principles that provoke short-term responses and only suited for the removal of HTS. For this reason, conventional therapy approaches show little success and permit poor access to an efficient treatment of keloids or HTS.

Against this background, the demand for less invasive and effective functional and aesthetic treatments is steadily growing and remains a permanent issue in modern medicine. The focus is clearly defined by the patient's satisfaction with the aim of maximal outcome and minimal risk at the same time. Medical needling seems to be an ideal method for what is postulated in many fields of modern medicine. PCI displays a simple regenerative technique that affects skin-related indications and in particular scars. Its success is manifested in skin regeneration particularly for severe and wide-

spread scars with hypertrophic and keloid features. The method of PCI requires neither expensive apparatus nor the need of complex instruments and sets a new trend in plastic and aesthetic medicine. By stimulating complex signal transduction pathways in the postneedling wound-healing cascade, the natural regeneration process is modified and, hence, is more efficient. According to that, medical needling improves the appearance and quality of scars with comparatively low risk and stress for the patient. The postneedling cascade induces gene expression and the proliferation of skin and stem cells that are important for dermal remodeling. The expression of specific proteins and reorganization of the extracellular matrix affect epidermal thickness and creates a stable and functioning skin barrier [1]. Furthermore, the PCI-induced synthesis of collagen and release of endogenous growth factors allow an association with scarless wound healing. Epidermal as well as dermal structures remain intact and histological findings show a complete re-epithelialization of the epidermis after treatment.

Current medical standards offer a diversity of noninvasive treatments (e.g., silicone patches) and minimal invasive procedures (e.g., cortisone injections) or surgical options such as scar excisions, tissue transfer, and W- and Z-plasties. Keloids show a limited therapy spectrum, which is mainly based on nonablative treatments (radiation, injections). Ablative methods such as laser resurfacing, dermabrasion, and deep chemical peels are all together defined by the same principle and find use in the treatment of HTS: they lighten the scar by destroying the skin structure and provoke an inflammatory response. As a result, the treated area is replaced by a thinner epidermis that shows flattened rete ridges and parallelly orientated scar collagen that is typical for fibrosis [2]. Furthermore, the skin is more vulnerable for bacterial or viral infections and external stress. These complications make a successful treatment of hypertrophic and keloid scars almost impossible, as they already have dysfunctional qualities. Complex structural and physical features of keloids have shown that common methods display temporary solutions that conceal the actual problem instead of improving the scar quality. In most instances, the scar quality of keloids or HTS would be much worse then. Compared to that, PCI has been proved to be a relatively simple, fast, and controlled method, which can be safely repeated and used in body regions where ablative or semi-ablative treatments have limited usage. Current studies on medical needling show a positive effect on hypertrophic scars regarding the parameters elasticity, moisture, transepidermal water loss, and erythema. In terms of dermal reorganization, high levels of structural proteins – glycosaminoglycans and proteoglycans – as well as an increased presence of physiological collagen are measurable after needling. PCI preserves dermal structures and promotes the formation of physiological collagen instead of scar collagen. For this reason, PCI overcomes shortcomings of other conventional methods that are available for treating problematic scars such as HTS or keloids. Study outcome has already shown the positive effect of medical needling on HTS in the past years and latest clinical data reveal similar results concerning keloids.

34.3 Method

Medical needling is based on a simple idea of puncturing the affected area repeatedly with a roller covered with needles of a specific length. Approximately 20 years ago, Camirand and Doucet had the experience that treating hypertrophic scars with a tattoo gun affects the scar texture and achieves significant improvements regarding clinical parameters [3]. Based on these ideas, Fernandes developed the technique of percutaneous collagen induction. In 1997, he realized this scientific discovery by establishing a roller equipped with needles in order to produce thousands of neighboring micro-wounds in the dermis, which cause intradermal bleeding. Thanks to targeted research within the last 15 years, scientific data have been provided by Aust et al. at first, and underline the efficacy as well as safety of medical needling.

In Germany, medical needling is now a licensed therapy for the treatment of scars and other related indications. The needling device is covered with needles of the desired length (0.5–3 mm) and needs to be rolled over the scar in three directions under constant pressure: vertically, horizontally, and diagonally. In the case of hypertrophic scars and keloids, surgical needling with a needle length of 3 mm is instructed in order to reach the scar collagen as deeply as possible. A straight guidance of the device is necessary in order to prevent shear forces and deeper damage. Relative to the extent of the scar size, this procedure requires 30–60 minutes of mechanical exposure. The penetration of the papillary dermis leads to thousands of micro-wounds and intradermal bleeding through the parenchymal canals. Minimal lesions of the epidermis do not impair basal layers containing stem cells with regenerative capacity. The increased expression of specific growth factors and release of structure proteins induce a modified wound-healing cascade with a great regenerative potential. The scar is sufficiently needled when multiple and confluent ecchymosis as well as skin swelling are clearly indicated. After 24 hours, epithelial cells close the channels and are reorganized into a natural protection barrier, which reduces the risk of potential postoperative complications such as infections. Therapy benefits are optimized by the application of nourishing products in first 24 hours. Swelling and local redness or edema of the treated area disappears after approximately 4–7 days. PCI is performed under general

Fig. 34.1 Roller device for medical needling

anesthesia in an operation theatre. When smaller areas are treated, the performance can be done under local anesthesia. Preoperative formalities include an informed consent form signed by informed patients or parents of patients younger than 18 years of age. Pre- and postoperative management is kept simple and includes the application of Vitamins A, C, and E as antioxidants [4]. According to latest research, maximal therapeutic outcome regarding epidermal thickness and a better prognosis for rapid healing can be expected. Postoperative monitoring is not substantially necessary. However, after surgical needling, a short down time of a few days needs to be considered, as the procedure requires general or local anesthesia. Therefore, a stay in hospital is only recommended, not obligated. Nevertheless, patients are able to get back to their daily life after a short time of recovery (Fig. 34.1).

34.4 Effects of Medical Needling

The intradermal bleeding caused by the mechanical procedure induces second-messenger substances of significant signal transduction pathways, which lead to a modified physiological regeneration of the skin. Specific features of both skin layers are not only preserved in their functional structure but also promoted in a positive qualitative way. Epidermis and dermis remain functionally intact and protect subcutaneous structures. Moreover, single layers of the epidermis become thicker, which guarantees great stability and a reduced vulnerability. Treated skin reacts less sensitively to damaging physical factors such as UV radiation that is associated with postinflammatory hyperpigmentation [5]. Furthermore, medical needling is also suited for all skin types. Treating dark skin is not followed by any dyspigmentation or even hypopigmentation, although dark skin is indeed predisposed for color shifts due to the naturally increased amount of melanin. Molecular and cellular processes induced by PCI affect neither the amount of melanocytes nor the mechanisms of synthesizing melanin. However, PCI specifically modifies the expression levels of the melanocyte-stimulating hormone (MSH) and Interleukin-10 (Il-10). MSH influences the activity of melanocytes and is downregulated within the postneedling cascade. On the other hand, high levels of Il-10 are evident, which is an antiinflammatory cytokine, and support immunological tolerance. As a targeted therapy, PCI concentrates especially on those areas that are aimed to be treated and also affects the surrounding healthy skin in a positive way. Due to the fact that needling does not create an open wound surface, there is a low risk for the development of viral or fungal infections, which could complicate a scar-free wound healing.

34.5 Needling Techniques

The needling treatment needs to be planned and prepared in advance. This includes the examination and categorization of the scars according to specific features. The selection of the appropriate length of needles depends on the type of scar, pain management, and expectation from the patient's side. From this perspective, downtime repetition capacities and aesthetic achievements are considered. Massive scars with intense deficits would be HTS and keloids that are predominantly treated by surgical needling. This means a longer downtime but also maximum results. Considering input and outcome, maximizing the patient's expected results is aimed to achieve.

In principle, medical needling can be classified into cosmetic, medical, and surgical needling. The difference depends on the length of the needles used and the intensity of the physiological effects as well as the postoperative regime they require. First mentioned types of needling play a minor role for the treatment of HTS or keloids, as the desired effects cannot be achieved.

Cosmetic needling is performed as a purely cosmetic treatment with needles 0.1–0.5 mm in length for structural and superficial skin modifications. The needling procedure does not cause any intradermal bleeding and hence any postinterventional reactions remain unnoticed. Using the minimal length of needles does not require any anesthesia and allows repeating the treatment daily. The patient does not experience any downtime and gets back to his daily routine without any complications. All together, the cosmetic needling is used as a penetration enhancer for topical skin care products.

Medical needling can be defined as PCI when the needles have a length between 1 and 2 mm. Needles of this length reach just beyond the basal membrane and lead to minimal petechial hemorrhages in the papillary dermis, which activate the TGF-ß signal cascade and give a skin-

regenerating effect. The needle length is proportional to the provoked bleeding, as it gets more intense when longer needles are used. However, intradermal lesions are so small that there is a minimal downtime without obvious edemas or bruises. Moreover, effective topical anesthetics can be used to make the process nearly painless. Afterward, the treated area might be reddened and needs a few days to recover and normalize.

From the perspective of clinical efficacy, surgical needling proves to be more intense and impressive when the performance is done with a needle length of 3 mm. That is why HTS and keloids are indications for surgical needling. This procedure is carried out under general or local anesthesia and can also require a stay in hospital. The puncture depth does not only affect the epidermis and dermis but also the upper layers of the subcutis including the vascular system that is responsible for the desired and controlled bleeding after needling. This mechanical prodecure affects the skin structure and function by provoking stress and regenerative resources at the same time which is aimed to improve the natural skin barrier with intact skin layers. For this reason this step needs to be performed wisely and carefully observed. The relatively painful procedure under local anesthesia provokes primary inflammatory wound-healing reactions with temporary erythema, swelling, and bruising. The needling device needs to be rolled over the affected area until these signs of sufficient needling are apparent. The potential for aesthetic correction and reduction of the scar is on the highest level and provides maximal outcome. When selecting a needle length of 3 mm, the patient is expected to accept a protracted downtime in order to achieve maximal results in the phases of recovery. According to that, longer recovery periods of weeks should be taken into account (Figs. 34.2 and 34.3).

The selection of the needle length varies relative to the indication and its intensity of cicatrization. Moreover, there are important differences notable: The shorter the needles, the more often treatments need to be carried out in order to reach desired effects. Longer needles are indicated when treating prominent kind of scars such as HTS and keloids. Summing up, the combination of the patient's expectations and the desired result decides the amount of therapies and the selection of the three possible needle lengths.

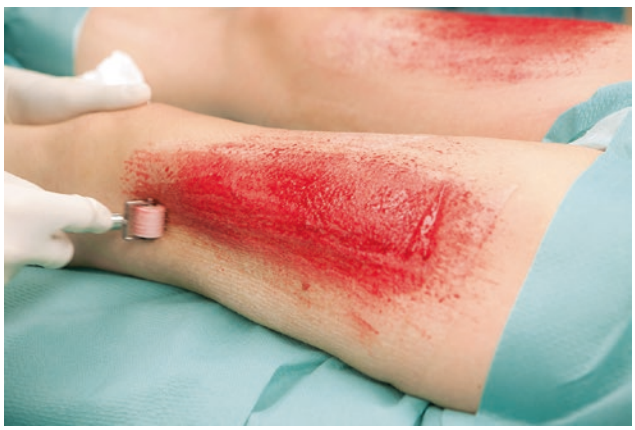


Fig. 34.2 Technique of surgical needling performed with a needle length of 3 mm. Desired bleeding and marked edema induce therapeutically effective collagen production during the postneedling wound-healing cascade

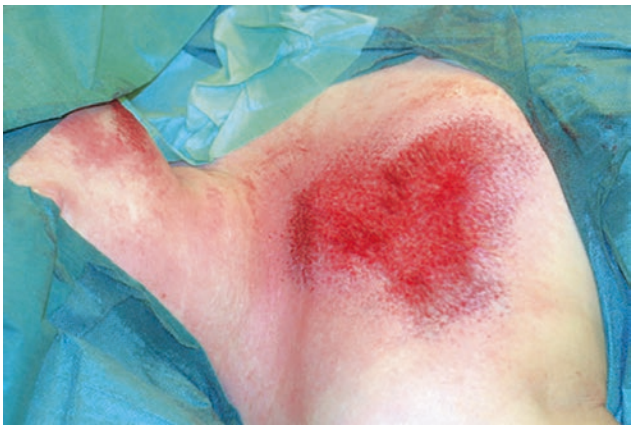


Fig. 34.3 A heavier bleeding caused by the 3 mm needling method

34.6 Postinterventional Treatment Measures

Postoperative Wound Management – For optimizing and maximizing therapy outcome, it is instructed to treat the skin sufficiently and effectively under pre- and postoperative circumstances. The application of vitamin A and antioxidants such as vitamin E and C is necessary to achieve best results. A specific skincare that combines the above-mentioned vitamins with a strongly recommended gentle cleansing washing lotion containing tea tree oil should be performed every 2 hours as long as the needling canals are still open. While the skin remains bruised and swollen, direct exposure to sunlight should also be avoided. A moist wound-healing regime of vitamin-based creams prevents crust formation after the initial bleeding, which could eventually impair the final results. The loss of serous fluid through the puncture holes in the immediate postinterventional period can lead to crusting, which needs to be carefully averted by washing off any surface serum. In consequence, preventing crusting reduces the risk of bacterial superinfections. Moreover, inflammation and secondary wound healing associated with the development of HTS or keloids can be avoided.

Managing Complications – As needling does not produce open wounds, the postoperative complication rate is very low and postinterventional monitoring is not necessarily needed. However, local edema

can develop with longer needles, especially done on large areas. It is recommended to keep the patient in the clinic for a few hours after treatment. It needs to be considered that after extensive surgical needling under general anesthesia, the patient may experience burning pain in the treated area. Therefore, pain should be managed with effective drugs particularly in the first hours postoperatively. The use of nonsteroidal antiphlogistic medication should be avoided, as the primary inflammatory response is desired. However, keloids and HTS require regular follow-up examinations in order observe wound-healing processes and to ensure that renewed scarring or proliferating tissue can be excluded. In the case of keloids, a further extension of the scarring is not that rare after treatment. Clinical data also reveal the formation of necrotic tissue when there is an inadequate blood supply. Special attention needs to be paid to patients with diabetes that shows difficulties in wound healing anyway.

The intradermal bleeding caused by PCI is the essential driving force in medical needling. In this context, the endogenous potential of natural wound healing induced by PCI differs from the conventional inflammatory response to traumatic incidences starting minutes after injury. Therefore, the difference between the postneedling regenerative cascade and the conventional wound-healing cascade becomes very clear. The PCI-induced regenerative process is based on completely different mechanisms that are associated with the desired bleeding, as plenty of blood vessels are pierced at the same time. However, an open wound surface is not created within this procedure that would need to be refilled by regenerative fibers in the course of conventional wound healing. Refilling can rapidly escalate into an overproduction of tissue fibers, which again supports the development of HTS and keloids. The extent of the initial bleeding and the excretion of serous fluids can appear in different intensities and mainly depend on the area treated as well as the needle length that has been specifically selected. In consequence, facial skin regions show a higher bleeding capacity, as they tend to react more sensitively to mechanical stress. Further, these regions are more affected by swelling and bruising because skin seems to be thinner and therefore reacts more intensely to operative interventions than the skin of other regions. Eventually, PCI-related results are achieved by replacing scar typical collagen with normal collagen of healthy skin [6].

34.7 Induction of the Post-Needling Wound-Healing Cascade

The intended trauma through the repetitive puncturing initiates a physiological wound-healing cascade. Platelets and neutrophils secrete growth factors such as the platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), tissue growth factor, and transforming growth factor-α and -ß (TGF-α, TGF-ß). The interactive cooperation of these factors provides blood coagulation, as well as the synthesis of dermal structures such as collagen, elastin, and fibronectin. Furthermore, the differentiation and migration of fibroblasts and keratinocytes contribute to regenerative processes. Fibroblasts have essential roles in synthesis of collagens I and III. Other cells that are represented in all tissues including the dermal layer are fibrocytes, dendrocytes, mast cells, and further immune cells secreting collagen I and collagen III protein. Seen from a dermatological view, TGF-ß has specific functions that have a key role in the postneedling wound-healing cascade. In general, wound healing can be divided into three phases interacting through numerous growth factors and other essential elements, into approximately month-long sequences: inflammation, proliferation, and regeneration (Fig. 34.4).

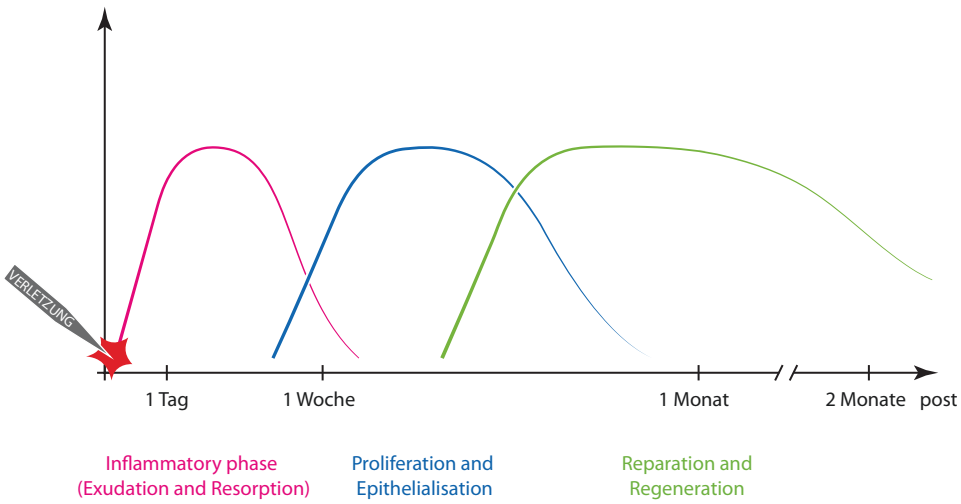


Fig. 34.4 Wound-healing course schematic representation

Right after the injury, the natural and typical reaction of inflammation starts by activating immune cells, blood coagulation, as well as vasoconstriction [7]. The following stage of proliferation is marked by growth factors, especially focused on TGF-ß, which is important for the regulation of growth processes. Dysregulated signal transduction pathways can lead to a malignant degeneration of cells, which can result in the development of cancer or malignant tumor in the worst case. Keloids have indeed characteristics that are similar to tumor cells. The persistent presence of TGF-ß1 and-ß2, as well as the absence of TGF-ß3 in the conventional wound-healing process, indicates the formation of typical rigid scar tissue. The activity of fibroblasts is necessary for the regeneration of the extracellular matrix and the synthesis of collagen. After the phase of regeneration, an intact skin barrier of renewed epithelial cells and a mechanically stable skin structure are evident. These are single steps described in a typical wound-healing procedure. On the contrary, the PCI-induced wound-healing mechanism is based on a modified principle of what is already known and described regarding wound healing. Special focus is manifested in the modified TGF-ß signal transduction pathway. Whereas TGF-ß1 and 2 are significantly downregulated in the postneedling cascade, TGF-ß3 shows a dominant activity 24 hours postinterventionally. Against this background, the traditional wound-healing paradigm is converted into a regenerative phase marked by the synthesis of structural collagen of healthy and vital skin instead of scar tissue. This is why there is a low risk for the development of hypertrophic or keloid scars where it usually comes to an uncontrolled hyperplasia of collagen fibers and an uncontrolled growth of the connective tissue. Very common consequences are rigid and difficult scars.

34.8 Effects of Medical Needling Regarding Different Parameters

Scarless Wound Healing – In order to avoid secondary wound healing, a controlled activity of growth factors is necessary. The close relation between TGF and the formation of collagen type I fibers represents a key role in repair and regeneration mechanisms. In this context, it needs to be considered that wounds healed by secondary intent tend toward an uncontrolled proliferation, which enhances the development of HTS or keloids. Type I collagen is the physiological desired collagen of lattice pattern structure in healthy and vital skin, whereas collagens type III shows parallelly orientated fibers that is typical for scars. TGF-ß1 and 2 are at their highest levels of activity when a dense collagen structure of type III in scars is built. Study results have proved that in keloids with excessive cell proliferation, the expression of procollagen I and III -mRNA as well as -protein is increased. In excessive cell proliferation of keloid tissue, there is a dominant presence of collagen III, although both collagen I and collagen III seem to be increased. Significant differences to normal skin are manifested in the shift of the collagen I and III ratio toward collagen III. However, a significant downregulation of TGF-ß1 and 2 is evident in scar-free, embryonal wound healing determined by TGF-ß3. Second kind of wound healing is still active in juvenile tissue to a lesser extent, but not present in adult tissue that is rather predisposed for the development of scars. High levels of TGF-ß3 in the postneedling cascade do not only induce the synthesis of collagen type I, but also manage the conversion from collagen type III to the desired type I collagen (Fig. 34.5).

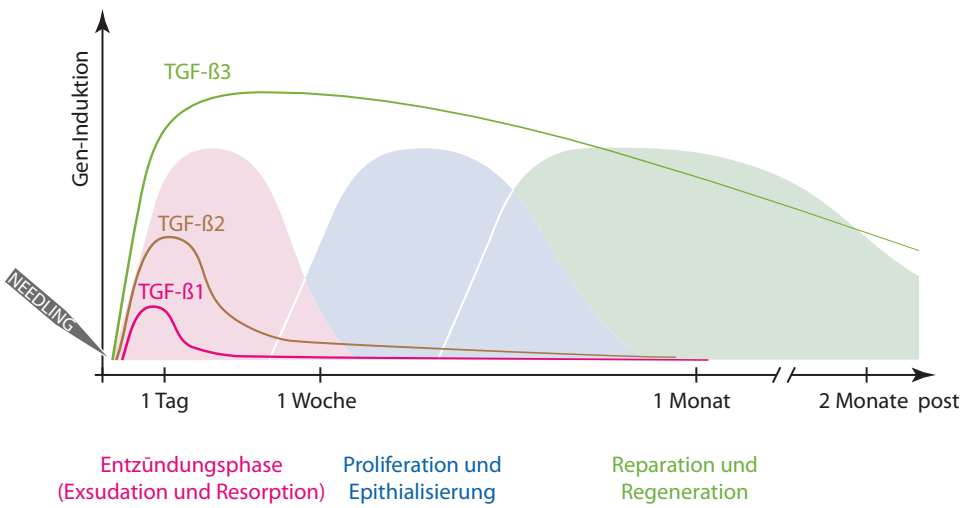
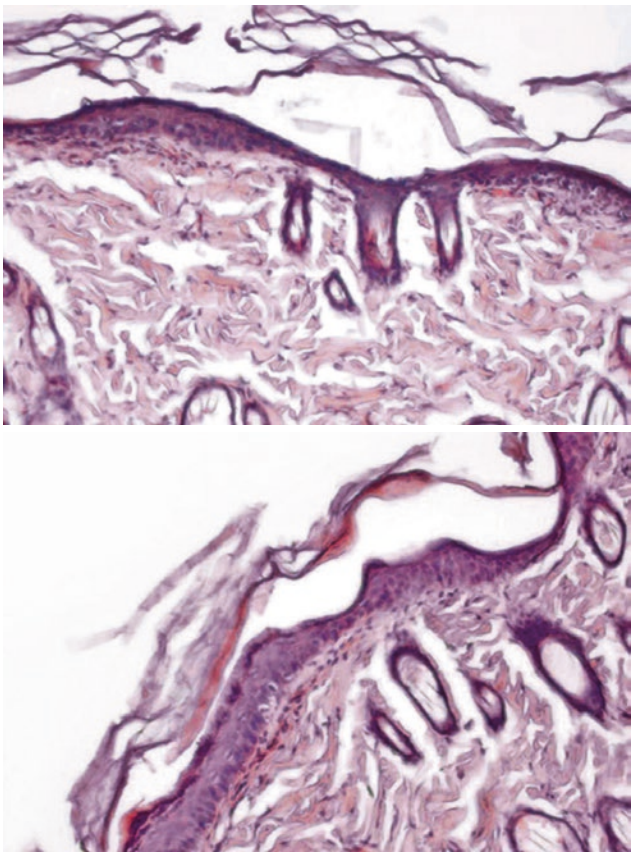


Fig. 34.5 Regulation of transforming and growth factor, TGF-ß3, and scarless healing. Microarray analyses of TGF-ß1, -ß2, and -ß3 expression levels in treated and untreated animals show that the needling treatment stimulates TGF-ß3 to a greater extent than TGF-ß1 or -ß2. Moreover, the induction of TGF-ß3 gene expression continues even beyond the initial wound-healing phase, whereas the two other genes are downregulated during the second week postneedling

34.9 Dermal Remodeling

Furthermore, PCI modulates the expression of relevant genes and molecules that are responsible for remodeling the extracellular matrix. The skin appears thicker, more vital, and rejuvenated. Therefore, PCI displays a method that is focused on both quantitative and qualitative improvement of dermal function and appearance. The release of structural proteins, including fibronectin and glycosaminoglycan molecules, as well as the activity of specific enzymes, achieves dermal remodeling. These components of the postneedling cascade stimulate the proliferation of keratinocytes and other skin cells in the basal layer of the epidermis, which changes the physical and biological characteristics of skin. The entire connective tissue framework seems to be thicker and denser. Other endogenous factors contribute toward improved skin elasticity in terms of dermal remodeling, as the amount of elastin is significantly greater after medical needling. A lack of elasticity is typical for HTS and keloids and one reason for their rigid structure, which puts the scar as well as the surrounding healthy skin under a great pressure. Hence, flexibility and mobility of the affected area are compromised, which might be a problem when regions close to joints are affected. Not only for this reason, TGF-ß3 reaches high levels of expression in the initial phases but shows a declining trend in the following phases of proliferation and regeneration. Based on Furguson's work, the initial dominant influence of TGF-ß3 is important for the PCI-related wound-healing mechanisms. However, clinical expertise shows that giving TGF-ß3 additionally in phases of normally low levels can eventually impair regenerative processes. In conclusion, the method of medical needling influences the release and immediate effect of TGF, as well as the synthesis of collagen type I interacting within the process of dermal reorganization and remodeling. Once again, the signal transduction pathway of TGF seems to be one of the most important PCI-related factors. Therefore, the method of PCI has a regulatory function of promoting a controlled activity of growth factors and other regenerative factors as well as cytokines. With regard on HTS and keloids, the main focus is on managing growth and hypertrophy by a controlled activity of growth, epithelial and vascular factors (Figs. 34.6 and 34.7).



Figs. 34.6 and 34.7 Regenerative effects on the epidermis through needling. One day after the treatment, Masson's trichrome staining shows no injuries in either the epidermis or the dermis. Both skin layers are functionally intact; there are no signs of ablation or cell damage. Figure 34.6 Untreated animal (control). Figure 34.7 24 hours postneedling

34.10 Improved Perfusion

Another factor showing high concentration during the postneedling regenerative cascade is VEGF. In terms of angiogenesis, its main function of creating new blood vessels and enhancing perfusion accelerates wound-healing processes. The method of PCI provides a controlled and limited release of VEGF in order to prevent dysregulated activity, which can lead to degenerative processes. High levels of VEGF are initially observed in the postneedling cascade, which are again not kept constantly high at all times. Hence, medical needling has a positive effect on subcutaneous structures conveyed by VEGF as an important indicator for active angiogenesis. The expression of this growth factor induces the vascular system by supporting the proliferation and activity of vascular endothelial cells [8]. This process happens after the initial inflammatory response of a vasoconstriction with the primary intention of stopping the bleeding as a typical reaction to an injury. The restricted perfusion is then followed by a massive vasodilatation in the wound-healing phase. The regulative effect on the vascular system explains the intense bleeding after the needling procedure, which is in fact an enhancer of the wound-healing progress. The better the blood perfusion of the skin tissue, the greater the bleeding after mechani-

cal stress induced by PCI, which accelerates healing processes. The limited activity of VEGF for a desired period of time (postinflammation) has the advantage of a rapid wound healing due to a better perfusion and a primary wound closure in a timely and effective way. For this reason, the risk of secondary wound healing can be excluded, as delayed wound-healing processes are very improbable and also not expected after needling. In this context, the development of HTS and keloids is once again kept at minimal risk.

34.11 Dermal Thickness and Erythema

An effective wound-healing process implies active vascularization and causes a temporary reddening of the skin, which is not associated with persistent erythema. After needling, the affected area is swollen and reddened due to a better perfusion in the course of effective healing processes. However, the problem of striking discolorations of especially hypertrophic and keloid scars remains a serious one for the affected people, as the scar color differs extensively from the surrounding healthy skin. Discolorations can reach from slightly reddened skin or persistent erythema to dyspigmentation or even hypopigmentation, which is quite typical for HTS. Untreated hypertrophic scars tend to a thin and vulnerable epidermis that is unstable and more transparent for local perfusion. This might support the appearance of erythema through a thin skin texture with a long-term impact. After needling, the intense blood circulation is less prominent and temporarily limited through a thickened epidermis. The entire tissue structure is more compact and makes the great optical difference between scar and surrounding skin less prominent. Either way, medical needling represents a skin-normalizing therapy method and creates a homogenous image of initially reddened scars toward healthy skin. Based on outcomes of objective measurement methods with the Mexameter, medical needling achieves a normalization of the skin color and an almost complete adjustment of the scar tissue toward healthy skin after repetitive treatments. As the method is based on percutaneous collagen induction, the synthesis of collagen improves vital thickness, which is directly associated with less transparency and a low risk for the development of erythematous hypertrophic scars (Fig. 34.8).

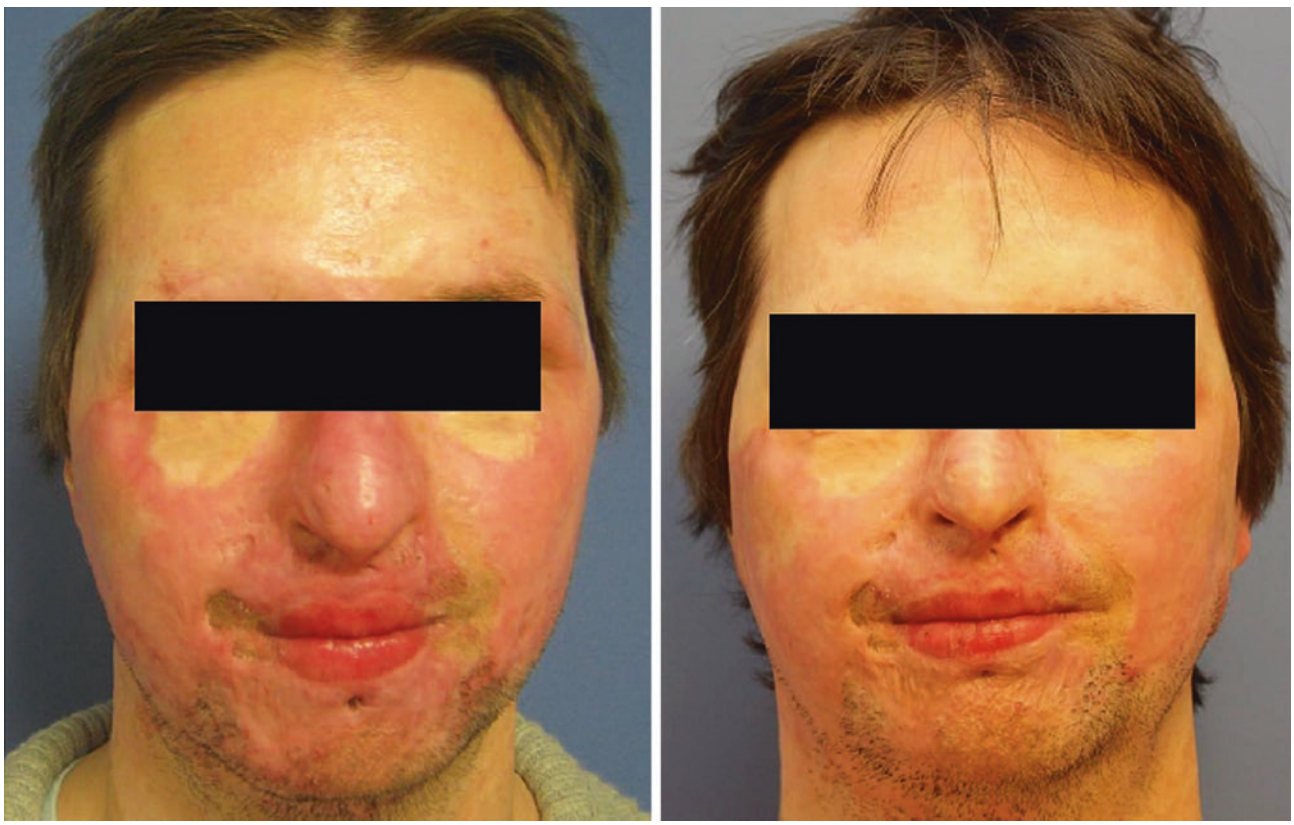
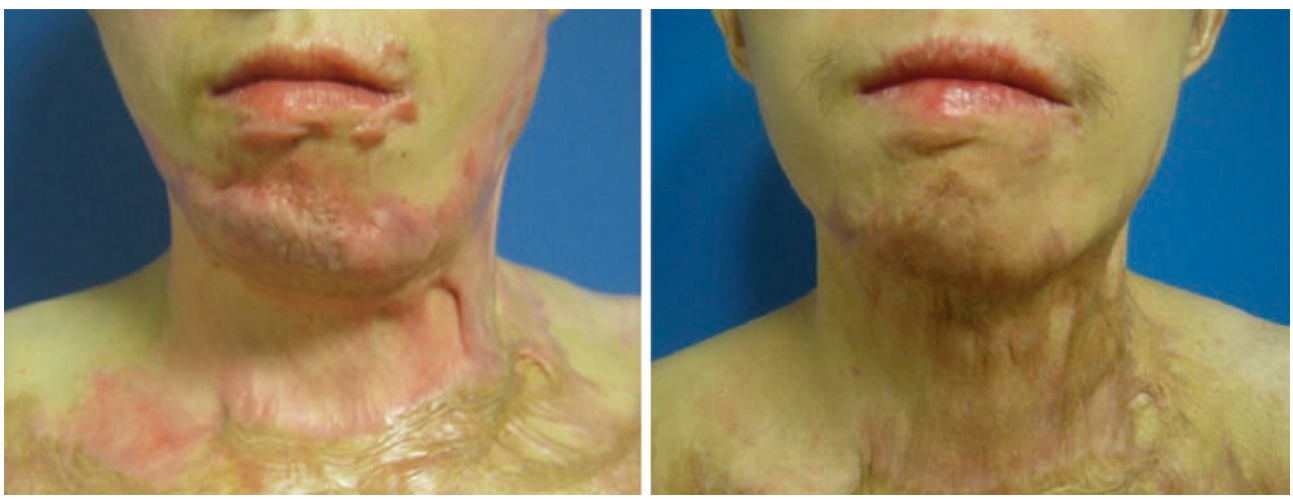


Fig. 34.8 Patient 1, frontal shot, preoperatively (left) and one year postoperatively after needling (right). Areas treated include the entire face. Reduced erythema and hypertrophy of the fibrosis

34.12 Richness of Moisture

HTS and keloids are especially characterized by a lack moisture, which combines typical visible anomalies with symptoms of pain and itching. The current difficulty of HTS resides in skin dryness and an insufficient water content of the epidermis [9]. Dehydrated scar conditions are the main cause of pruritus, which is not only considered a sensation disorder but a relevant clinical parameter. In fact, itchy and dry scars are closely related to structural deficits of the typical scar tissue. Fibrous tissue tends to have less skin appendages such as sebaceous and sweat glands and thus produces less moisturizing secretions, which leads to skin dryness, less flexibility, and a rigid scar texture. Moreover, a thin epidermis with parallelly orientated collagen fibers can impair the epidermal barrier function, which is marked by transepidermal water loss (TEWL). Severe and widespread burn scars, for example, hold the risk of an incomplete re-epithelialization of the epidermis due to a lack of stem cell reservoirs. It happens frequently that particularly those skin layers such as the basal layer of the epidermis are impaired by deeper and widespread damage of the skin. However, these components of the skin are able to provide stem cells that differentiate into functional skin or epithelial cells. Thus, a less functional epidermis enhances transepidermal water loss and a reduction of moisture. Therefore, patients suffer from dry, itchy, and painful scars followed by reddened and vulnerable skin. When protective features of epidermal layers are deficient, the skin reacts more sensitively to external factors and is more accessible for various pathogens, which can lead to progressive infections. In this context, medical needling ensures epidermal integrity in terms of regulating TEWL and reducing the risk of dehydration. Measurements with the Corneometer and Tewameter have shown that PCI improves the moisture content of the skin, which is closely related to the regulation of TEWL. Various studies on the effect of medical needling on moisture revealed remarkable improvements regarding skin roughness and rigidity, which both depend on the water content of the skin (◘ Fig. 34.9).

Conservative treatments for scars with deficits in moisture and TEWL include silicone patches or diverse moisturizing creams that are established cosmetic therapy methods. Provided that they are used permanently and several times a day over a longer period of time, they can improve the scar condition to a temporary extent. Concerning the water content of the skin, the fluid silicone gel preserves the moisture content, but does not affect the skin's own potential to produce sufficient moisture [10]. A permanent application of oily creams keeps the skin moist and smooth, but does not improve the scar in quality by itself. TEWL is least affected, as the epidermal barrier function is not influenced by the silicone. Once again, short-term results are frequent and considering TEWL, there are less satisfying results. These kinds of methods have a preventative character and are rather suited for short-term solutions. In the case of HTS or keloids nonablative, conventional treatments can be used in addition to needling or other invasive therapy methods as complementary therapies. Ablative treatments achieve exactly the inverted effect in terms of destroying epidermal structures and holding the risk of degradation. On the contrary, the established method of medical needling preserves the epidermis and improves the epidermal barrier function. The significant impact on the skin's water balance is manifested by regulating moisturizing processes and the passive movement of water (TEWL) through the epidermis.



◘ **Fig. 34.9** Patient 3, frontal shot, preoperatively (left) and one year postoperatively after needling (right). Areas treated include the face, perilabial, chin, and neck. Reduced erythema and greatness of the scar. Less tension in the fibrotic area

34.13 Conclusion

Based on the diverse profile of medical needling regarding different parameters of HTS and keloids, this therapy method is not only an innovative approach, but also rather an effective treatment method of problematic scars. The aim of improving the scar in quality and function is realized by a modified wound-healing cascade, which activates relevant signal transduction pathways for an effective regeneration. After needling, dysfunctional scar tissue gains vital features of healthy skin and shows functional progression months and years after needling. The focus is clearly set on sustainability, which is the major challenge for an effective treatment of HTS and keloids. As underlying causes for the development of these types of scars are various and the clinical research potential on HTS and keloids is still not yet exhausted, medical solutions are required from modern medicine. Common therapy approaches are characterized by different moderate success that does not provide long-lasting outcome. Improvements are temporarily restricted and rather accumulate in the beginning of the therapy. HTS and keloids often tend to reach a nonresponder status in the course of repetitive conventional treatments. Surgical interventions are less attractive for the affected people and are often followed by a structural degradation up to uncontrolled cell death. In terms of not confronting the patients with serious consequences and other complications, medical treatment should be scientifically defined as effective and sustainable. PCI comes very close to what is expected from a medical point of view not only for the supplier side but especially for the demand side. Innovative and patient-friendly therapy approaches aim to be more convenient for patients relative to the required effort. In this context, medical needling seems to be a very promising therapy method that guarantees persistent effect on HTS and keloids. PCI displays a relatively simple and controlled treatment of difficult scars that opens new pathways for modern medicine.

Take-Home Messages

- HTS and keloids are pathological scars with a characteristic histological and clinical profile.
- Persistent lesions to deeper skin layers promote the development of HTS and keloids followed by an inflammatory response.
- Medical approach and success have been quite restricted to minimal outcomes and improvement in the past.
- The greater knowledge of pathomechanisms allows the establishment of targeted intervention.
- Medical needling overcomes deficits of conventional treatment therapies combining minimal invasivity and long-lasting effects at the same time.
- Important clinical endpoints (erythema, pruritus, pain, and moisture) and not only clinical parameters are positively affected by PCI.
- Dysfunctional scar tissue gains vital and healthy features after treatment with PCI.
- Outcomes are up-to-date and underlined by evidence-based clinical research.

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Usefulness of Local Flaps for Scar Contracture Release

Rei Ogawa

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35.1 Background

Local flaps are useful for reconstructing scar contractures on mobile areas such as the joints, the neck, the axilla, the digital web, and the mouth commissure. They are superior to skin grafts because the latter can contract, thereby leading to secondary contractures. Moreover, the color and texture match of local flaps is better than that of grafted skin. Consequently, local flaps generally provide superior aesthetic outcomes. Thus, if there is healthy skin adjacent to the scar contracture, local flaps should be the first choice. Based on the type of movement needed to place the flap, local flaps can be classified as advancement flaps, rotation flaps, and transposition flaps. A more recent advance is to design these flaps as perforator flaps. The inclusion of perforators in the flap provides great freedom in terms of flap shape and the movement and rotation arc of the flap: the propeller flap method is a particularly good example of such flaps. Moreover, flap combinations such as the bilobed flap and the square flap method can expand the possibilities offered by local flaps.

35.2 Selection of Local Flaps

Several approaches that elongate the scar and thereby release linear contractures have been reported. Z-plasty is one of the best-known options when it comes to releasing linear contractures [1]. The theoretical final scar length for the 60° angle z-plasty is approximately 1.73 times the original length of the scar. W-plasty also allows contracture release to some degree due to its so-called accordion effect: this reflects the fact that zigzag-shaped scars elongate in an accordion-like fashion over time [2]. However, these methods are mainly used for "linear" contractures. If the scar is wide, the scar cannot be removed and then sutured primarily. In this case, the scar should be divided by a local flap to obtain contracture release.

In terms of local flap selection, it is necessary to choose between a skin-pedicled flap and an island flap. We showed recently [3] that 6 months after surgery, skin-pedicled flaps associate with greater scar extension rates than island flaps (Fig. 35.1). Notably, skin-pedicled and island flaps, respectively, extended the scar by 1.53- and 1.28-fold 6 months after surgery. Thus, local flaps, especially skin-pedicled flaps, elongate the scar as effectively as z-plasty. It should be noted that if the scar is large, it is effective only by dividing the scar with the local flap. However, the flap size can be slightly smaller than the deformity size (although how much smaller depends somewhat on how extensible the flap type is): it is not necessary that the flap is as big as the open wound after scar division or scar removal.

In the case of the local flap design, it can be affected not only by the ease of the technique but also by the geometry of the scar and open wound tissues. Thus, selecting between the skin-pedicled flap and the island flap should be performed on a case-by-case basis. However, the greater extensibility of the skin-pedicled flap means that it should be the primary choice in the

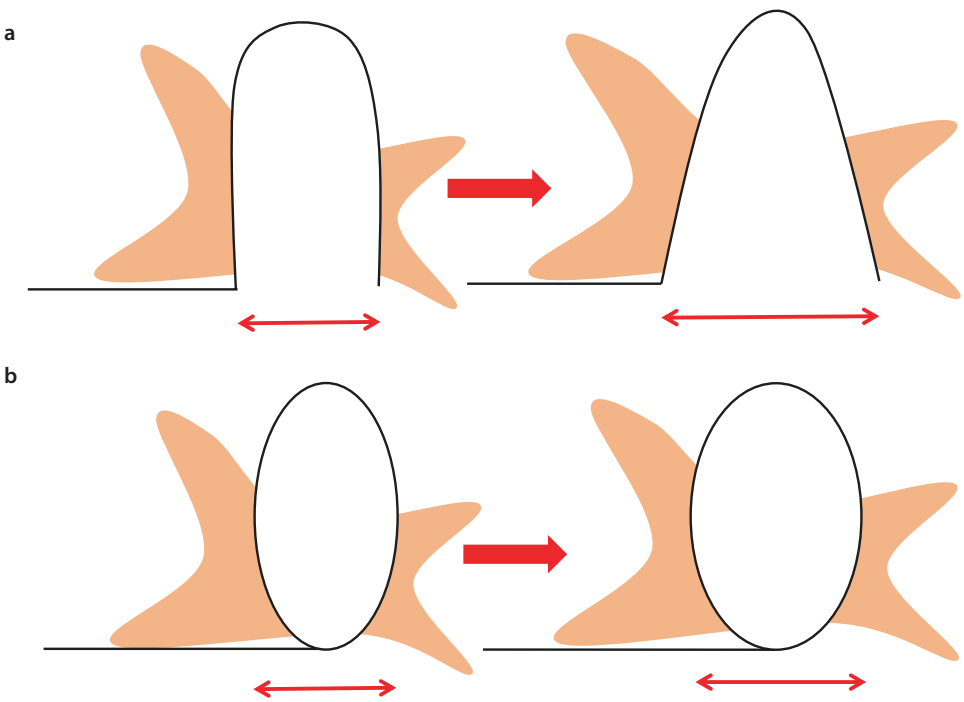

Fig. 35.1 Comparison of skin-pedicled and island flaps in terms of extensibility. **a** Skin-pedicled flap. **b** Island flap. Skin-pedicled flaps have a greater extension rate than island flaps because they include healthy skin, which can expand after surgery. By contrast, the inelastic scar tissue all around the island flap limits its extensibility

case of scar contracture release [3]. This greater extensibility is probably because the entire perimeter of the island flap is surrounded by new scar, whereas the skin-pedicled flap maintains a connection with normal skin. Since normal skin is highly elastic (much more elastic than scar tissue), it may promote the elongation and enlargement of the skin-pedicled flap. Moreover, at a theoretical level, the circular shape of the island flap also limits its extensibility. However, it should be noted that island flaps have technical advantages over skin-pedicled flaps: they are relatively simple to transfer to the recipient site, and they can employ the remaining healthy skin around the scars without any waste.

35.3 Transposition Flaps

The transposition flap is one of the classical and most representative of the local flaps. Its contracture-releasing effect is very high because the flap has a skin pedicle. The healthy skin of the flap expands over time after surgery; as a result, the rectangular shape of the flap becomes triangular (Figs. 35.2, 35.3, 35.4, and 35.5). This effect reflects the release of tension via the skin pedicle.

If the flap has to be large, perforators can be attached, and a supercharged transposition flap can be designed [4]. The perforator is then anastomosed to the recipient site. This perforator-supercharged transposition flap is

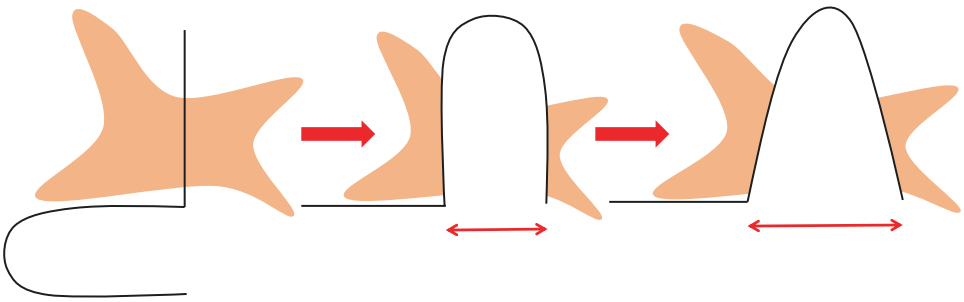

Fig. 35.2 Transposition flap. Transposition flaps should be designed parallel to the contracture line. After surgery, the skin pedicle can expand over time

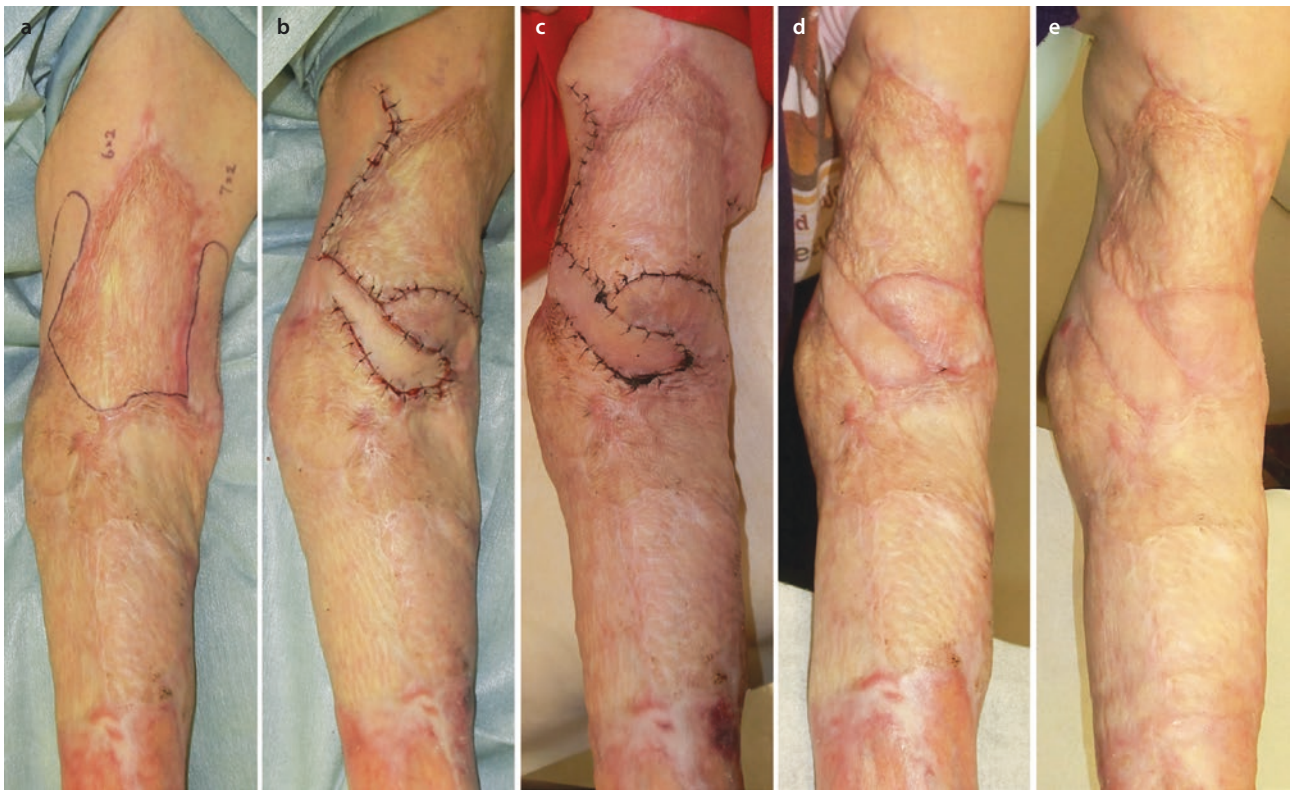

Fig. 35.3 Reconstruction of a scar contracture on the cubital fossa. **a** Preoperative view. **b** View immediately after the operation. **c** Two weeks after the operation. **d** Two months after the operation. **e** Ten months after the operation. Bilateral transposition flaps were harvested. No flap ischemia was observed. The contracture was released by about 10 cm

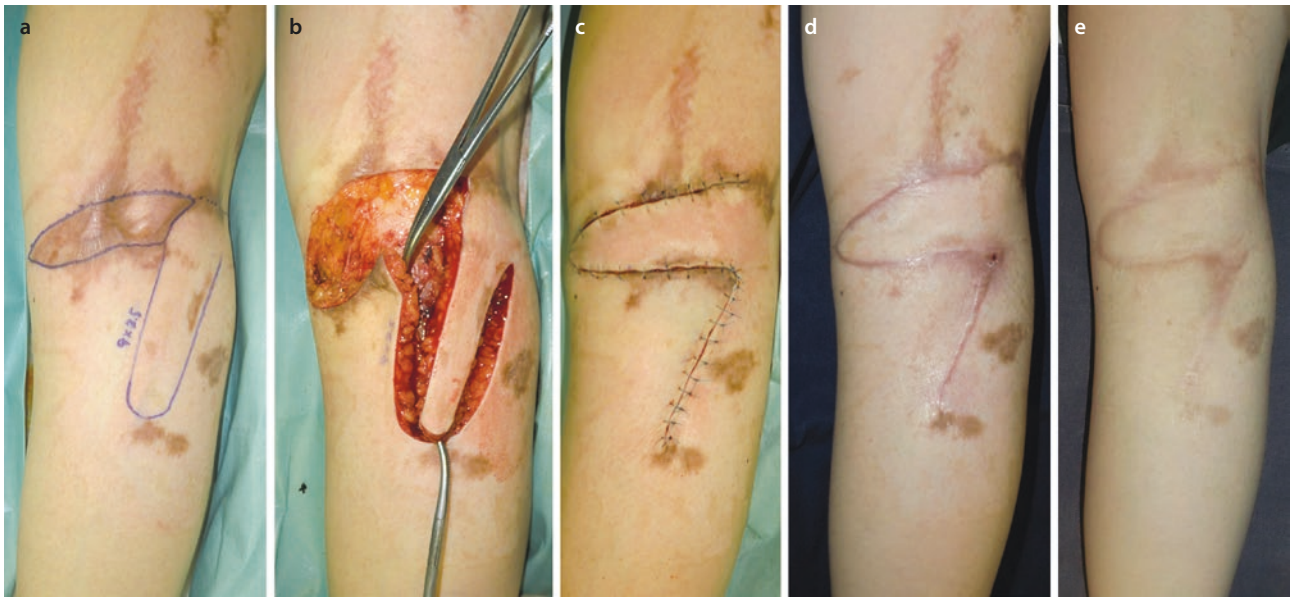

Fig. 35.4 Reconstruction of a scar contracture behind the knee. **a** Preoperative view. **b** Intraoperative view. **c** View immediately after the operation. **d** One year after the operation. **e** Two years after the operation. A transposition flap was designed next to the scar contracture behind the knee. The contracture was released completely

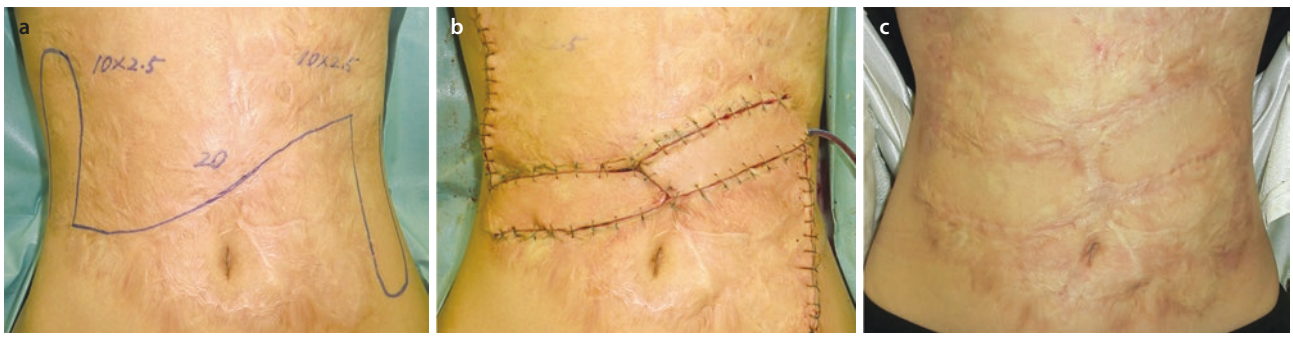

Fig. 35.5 Reconstruction of a scar contracture on the abdomen. **a** Preoperative view. **b** View immediately after the operation. **c** One year after the operation. A bilateral transposition flap was designed. The contracture sensation on the abdomen was relieved by the operation

especially useful for reconstructing anterior neck contractures (Fig. 35.6).

35.4 The Square Flap Method

The square flap method was reported previously by Hyakusoku et al. [5] and is an effective way of elongating the skin, especially for scar contracture release (Fig. 35.7). This method consists of a combination of a square flap, one 45° triangular flap, and one 90° triangular flap. The angle of the triangular flaps of Limberg's original method is 30° [6]. However, in the case of scar surgery, the 30° triangular flap can lead to blood flow failure because, in some cases, part of the scar must be included in the flap. Thus, the angles of the triangular flaps in the square flap method should be wider: the combination of a 45° triangular flap and a 90° triangular flap is ideal. One option is to design a four-flap z-plasty and a five-flap z-plasty. However, it is safer to include one square flap. Moreover, the biggest advantage of the square flap method is that one of the flaps has a square shape. This square flap can advance downward and can make a suitably large and pliable floor over the joints and web space. Thus, the method results in three-dimensional reconstruction [7]. In addition, the skin pedicle of the square flap can effectively release tension over time after the operation. This method is particularly indicated for scars on the joints, the neck, the axilla, the digital web, and the mouth commissure (Figs. 35.8, 35.9, and 35.10). Theoretically, this method increases the original scar length by 2.8-fold [7].

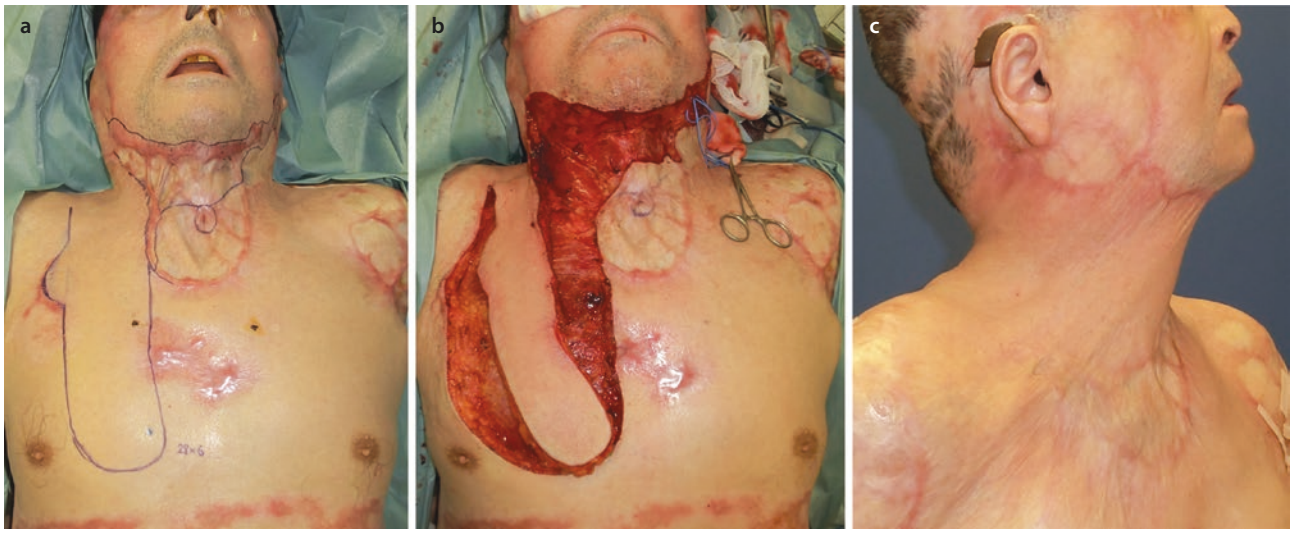

Fig. 35.6 Reconstruction of a scar contracture on the anterior neck by using a supercharged transposition flap. **a** Preoperative view. **b** Intraoperative view. **c** Two years after the operation. An anterior neck contracture of a 71-year-old man was reconstructed with a supercharged transposition flap. A perforator of the internal mammary artery in the first intercostal space was attached to the flap and anastomosed with the facial artery and vein. The flap allowed full extension of the neck

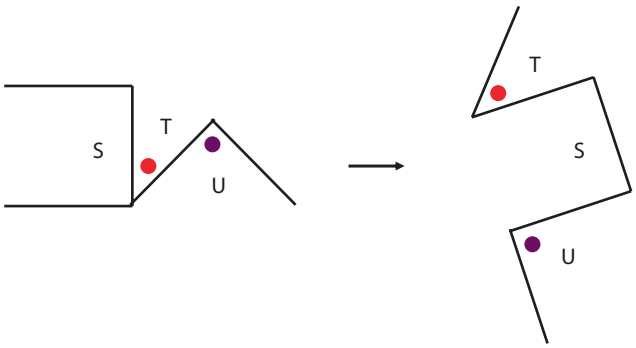

Fig. 35.7 The square flap method. Theoretically, the method lengthens the original scar length by 2.8-fold

35.5 Propeller Flaps

It has been reported that an island flap that can be rotated 90° like a propeller is suitable for the reconstruction of the axilla and cubitus [8] (Fig. 35.11). That was the first time this flap type was described. This original propeller flap was made by using the intact skin in a cubital fossa as a subcutaneous-pedicled island flap to release post-burn linear scar contractures that adjoined the fossa. The subcutaneous pedicle was located in the center of the flap. In the 20 years following this seminal advance, propeller flaps have been refined and modified, and various types of propeller flaps have been reported [9–13]. The most sophisticated of these is the perforator-pedicled propeller (PPP) flap [9]. This type of flap can be harvested from any site on the body that bears a perforator. It employs a skeletonized vascular pedicle that allows the flap to be rotated by up to 180°. Moreover, if the perforator pedicle is located at the edge of the flap, the flap can cover a defect that is a long distance away from the flap donor site. Depending on the case, the flap can be rotated in a clockwise or counterclockwise direction.

The PPP flap is now considered by many plastic surgeons to be a highly viable and particularly sophisticated perforator flap option. This largely reflects the fact that the human body has over 400 perforators whose diameters exceed 0.5 mm. Thus, at least 400 types of propeller flaps can theoretically be harvested. This broad availability means that custom-made PPP flaps can be used to reconstruct defects on many parts of the body. Indeed, PPP flaps are particularly suitable for scars on the trunk and limbs. However, donor site limitations may reduce the suitability of this method for reconstructing the head and neck region.

Since the course and territory of perforators differ for each region, it is advisable to perform a careful preoperative assessment with Doppler ultrasound, color Doppler ultrasonography, or multi-detector low computed tomography (MD-CT). This greatly facilitates the operation, thereby reducing the operative time [14].

It should be noted, however, that propeller flaps have one significant disadvantage: they are always island flaps. Thus, their contracture-releasing effect is lower than that of skin-pedicled flaps. Consequently, propeller flaps are generally only chosen when the available healthy skin adjacent to the defect is limited and a skin-pedicled flap is not possible (Fig. 35.12).

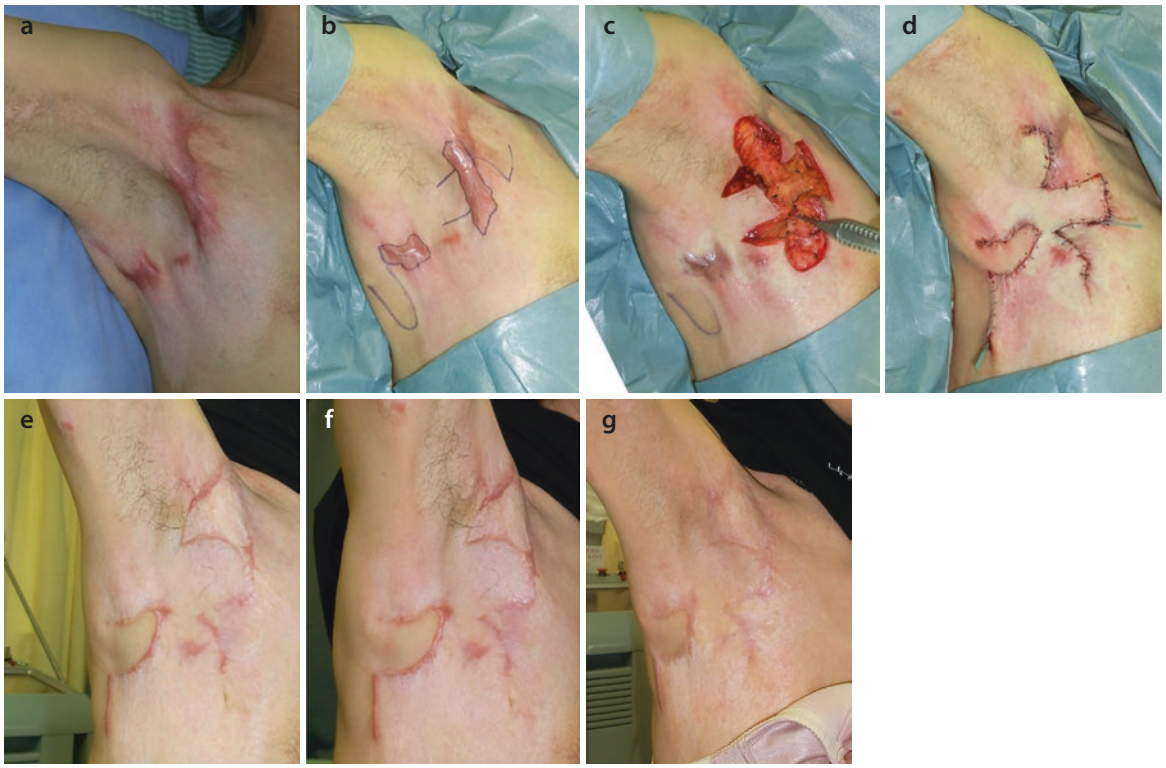

Fig. 35.8 Reconstruction of a scar contracture on the axilla. **a** Preoperative view. **b** Design of the flap. **c** Intraoperative view. **d** View immediately after the operation. **e** Three months after the operation. **f** Six months after the operation. **g** One year after the operation. The square flap method was used to reconstruct an axillary scar contracture. The square flap gained a triangular shape one year after operation. This indicates that the skin pedicle of the flap extended, thus effectively releasing the tension

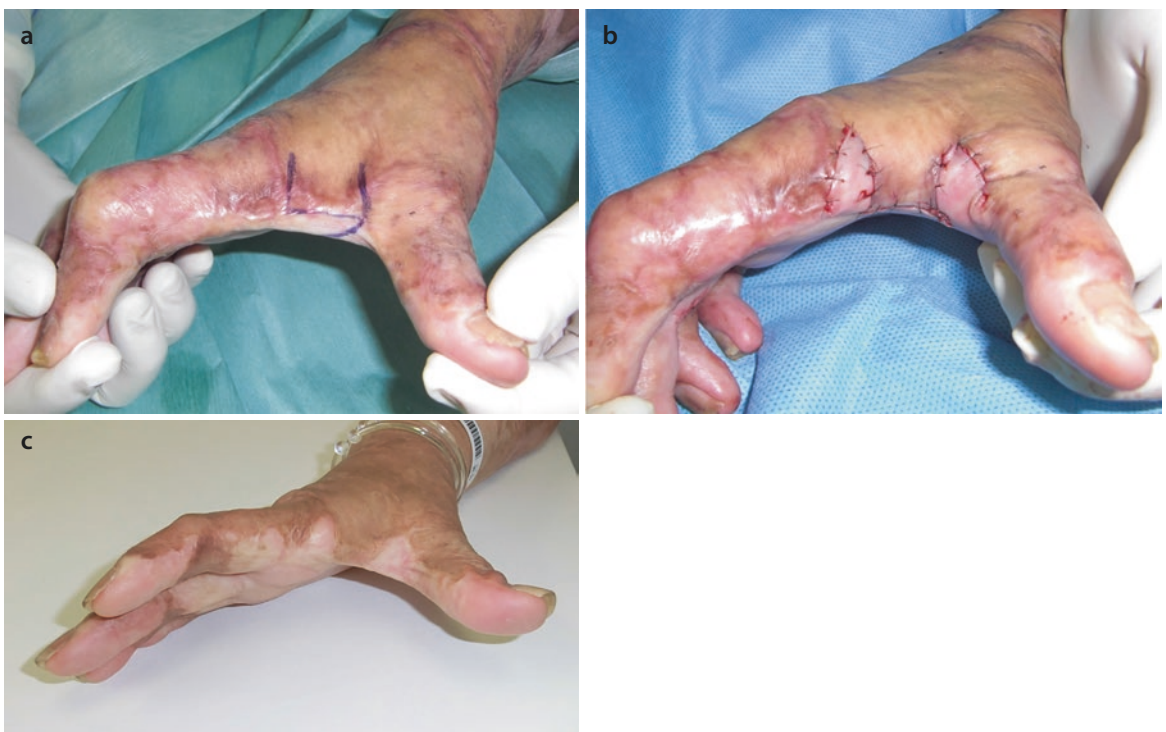

Fig. 35.9 Reconstruction of a scar contracture on the digital web. **a** Design of the flap. **b** View immediately after the operation. **c** Two years after the operation. The square flap method was used to reconstruct a digital web scar contracture. The skin pedicle of the flap extended, thereby effectively releasing the tension

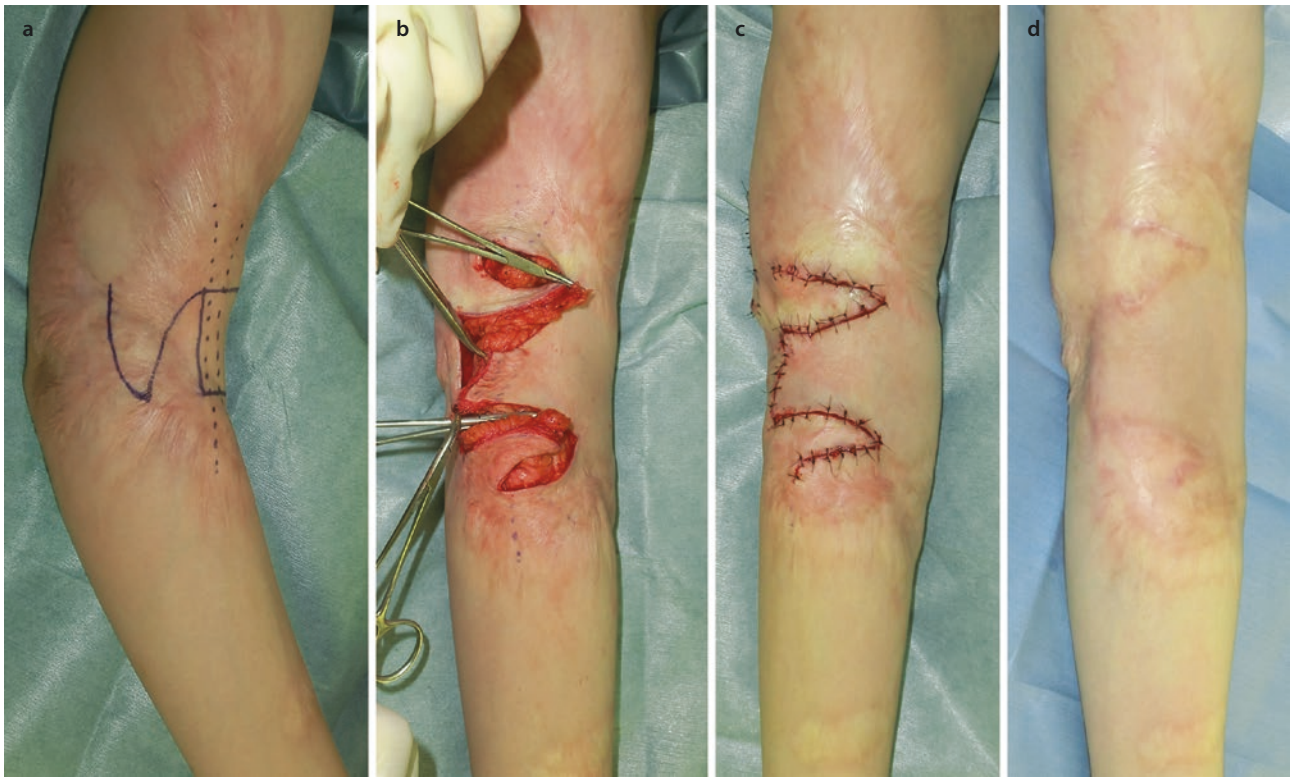

Fig. 35.10 Reconstruction of a scar contracture on the cubital fossa. **a** Design of the flap. **b** Intraoperative view. **c** View immediately after the operation. **d** Eighteen months after the operation. The square flap method was used to reconstruct a cubital fossa scar contracture. The skin pedicle of the flap extended, thereby effectively releasing the tension

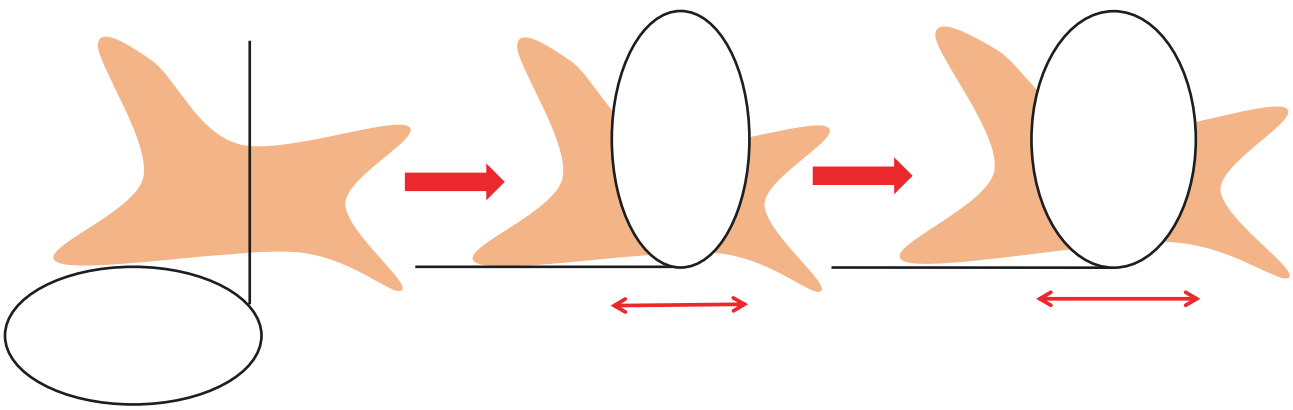

Fig. 35.11 Propeller flap. The most sophisticated of the propeller flaps is the perforator-pedicled propeller (PPP) flap. However, its contracture-releasing effect is lower than that of skin-pedicled flaps. Thus, propeller flaps are most useful when the available healthy skin adjacent to the scar is limited and a skin-pedicled flap cannot be performed

35.6 Conclusion

Local flaps generally provide superior functional and aesthetic outcomes. In terms of local flap selection, it is necessary to choose between a skin-pedicled flap and an island flap. It was suggeested that skin-pedicled flaps associate with greater scar extension rates than island flaps. Moreover, it should be noted that if the scar is large, it is effective only by dividing the scar with the local flap.

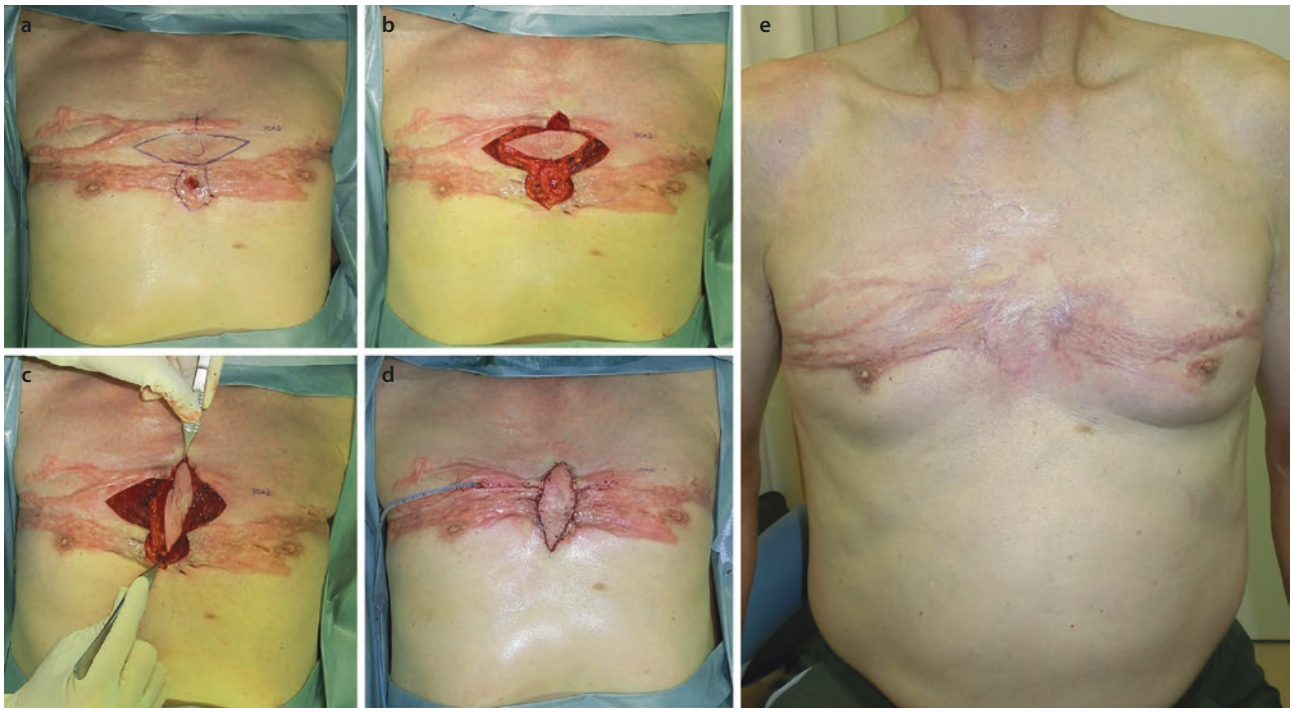

Fig. 35.12 Reconstruction of a scar contracture on the anterior chest wall. **a** Design of the flap. **b**, **c** Intraoperative view. **d** View immediately after the operation. **e** Eighteen months after the operation. The propeller flap was designed on the limited space between a scar contracture and an ulcer. Both open wounds were reconstructed by using a 90° rotated propeller flap

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Take Home Messages

- Local flaps are superior to skin grafts because the latter can contract, thereby leading to secondary contractures.
- The color and texture match of local flaps is better than that of grafted skin.
- Local flaps, especially skin-pedicled flaps, elongate the scar as effectively as z-plasty.
- It should be noted that if the scar is large, it is effective only by dividing the scar with the local flap.

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Scar Resurfacing

Fiona M. Wood

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_36

36.1 Overview

Established scarring can have an impact on the function and aesthetics of the skin related to the volume of the fibrous tissue, the vascularity of the area, the colour mismatch with the adjacent normal skin and disruption of the skin adnexal structures. Resurfacing is a technique which involves the disruption of the epidermal surface of a scarred area with removal of a varying volume of the underlying scarred dermal element, followed by a controlled repair of the surface.

The aim of resurfacing is to improve the character of the scarred area with a resulting scar more closely matching the surrounding uninjured skin. This can be focused on improving the texture of the surface, the pigment match or reduction of the volume of scar. Resurfacing will not address scar contracture or the absence of skin adnexal structures, with the exception of full-thickness excision and reconstruction with full-thickness skin graft or flap repair. The character of the skin varies across body sites such that the specialist nature of the skin site must be considered when planning any intervention. A complex scar reconstruction may be undertaken as a combined procedure with strategies designed to address the range of issues including resurfacing.

The timing and technique of the procedure are guided by the preceding clinical situation and specifically by the understanding of the conditions at the time of wound healing and subsequent scar development [1]. It is essential to understand that the opportunity to improve the scar depends upon the opportunity to better control the wound healing at the time of the resurfacing intervention.

There are a number of considerations to be taken into account when planning the interventions to improve the scar quality by control of the secondary wound healing:

- The mechanism of the initial skin injury and clinical pathway of healing, with specific reference to the initial techniques of wound repair, the time to healing and the presence of infection and other comorbidities influencing wound healing
- The time from the initial insult, considering if the scar is fully mature or there are symptoms of the scar, or epithelial stability compromise, such that early intervention is being driven in an immature active scar
- The techniques available for the intervention in terms of the scar intervention and subsequent wound repair and post-intervention scar management
- Counselling that it is possible to improve the scar but not to eradicate the scar with the current stage of knowledge of wound healing

For the scar resurfacing intervention to translate into an improved scar outcome, it is important to understand the clinical opportunities which offer an improvement on the initial treatments which have resulted in the unacceptable scar. For example, if the plan is to repeat the same procedure, such as a surgical shave and split-thickness skin graft, then there has to be a significant difference in the clinical situation to advise that such a strategy offers the opportunity of scar reduction. This may be appropriate as in a mature scar there is control over the timing of the intervention such that it is not associated with the inflammation of the acute episode. Alternatively, there may be the use of a new method of scar reduction such as laser or a method to reduce the time to healing such as a cell-based therapies.

The chapter aims to outline strategies for scar improvement by disruption of the scar surface and control of the secondary healing process. In the context of this discussion, it is essential to articulate clearly the potential gains on a risk matrix that is realistic for the patient. The more severe a scar is, the greater the potential for improvement, as compared to a good-quality scar when the risk of worsening the scar may sensibly limit the interventions.

36.2 The Mechanism of the Initial Skin Injury and Clinical Pathway of Healing

It is well known that scar outcome is related to the mechanism of injury such that burn injury is frequently associated with an aggressive scar outcome. The surface area of the body involved in the injury is also a driver of the outcome with the challenges in healing large surface areas in a timely fashion. Further, the body site of the injury is also influential with areas such as the presternal and deltoid regions and areas of skin tension being associated with poor scar outcome.

The time to healing is a key element in the scarring process and can be affected by local and [1] systemic factors, infection, necrotic tissue, haematoma and comorbidities such as diabetes, nutritional deficiency, drugs such as steroids and retinoid in acne treatment. The clinical history is key in understanding what can be optimised to improve the quality of healing and what factors may have been influential in the scar quality. Resurfacing is an elective procedure, and therefore, the preoperative optimisation of the patient's condition is possible and needs attention. The history of infection is of importance in ensuring the intervention is covered by the appropriate antibiotics or the risk of triggering secondary problems such as herpes is considered with the appropriate prophylaxis.

The knowledge of the initial intervention will also assist in the understanding of how resurfacing can be used in the post-acute phase to rehabilitate the scarred area [2]. Sharp dissection and haemostasis followed by careful approximation of the opposing surfaces with a suture designed to minimise inflammation are setting up the healing for the best outcome possible. In a wound such as a burn requiring cover of surface area, matching the repair to the defect in depth and body site with a focus on time to healing will again set up the best possible outcome. The concept of scar minimisation by meticulous attention to detail at the time of the initial intervention is covered in detail in ▶ Chap. 23.

Despite the best efforts, the post-intervention period has influence on the outcome with infection control and techniques of wound support and post-healing scar management having an ongoing role.

The knowledge of the clinical pathway, both initially and the proposed interventions, is essential when considering the following question:

- Is it possible to re-wound the scar and control the healing in such a way as to significantly reduce the risk of scar recurrence?

36.3 The Timing of the Intervention

The natural history of scarring is such that in the majority of cases, the scar severity will plateau between 6 and 12 weeks with subsequent remodelling leading to a mature scar construct by 52 weeks. However, the scar will continue to improve over the subsequent years. In order to have control over the extent of scar re-excision, it may be prudent to wait until the scar is mature prior to intervention. The scar may well improve over time to the point that it is acceptable. The progress towards maturation can be influenced by a range of non-invasive strategies highlighted in the chapters in section VIII. When considering resurfacing interventions, it is important to consider what aspects of the scar are of concern and how this could be influenced by time and conservative strategies.

However, there may be indications such as unstable epithelial surface, unsightly mismatched skin surfaces, or symptoms related to the scar such as itching which drives the decision for earlier intervention.

On the other hand, concern that a scar may be too old to consider treatment is unfounded, with improvement in the quality being achieved after many years.

Timing is an element in the risk matrix that needs to be considered in the context of the patient's symptoms and concerns. Early intervention may be explored related to specific techniques such as the re-suture a scar mismatch in height or laser to reduce pruritus, whereas in a florid vascular scar, more aggressive early intervention may add to the overall scarring pruritus, whereas in a florid vascular scar, more aggressive early intervention may add to the overall scarring [3]. The discussion with the patient needs to include the options such as time with the risks and benefits. It is useful to have a scar assessment tool which assists in understanding the character of a scar and facilitates the discussion and clinical decision-making.

The assessment of the scar can be done in a number of ways, e.g. surface scanning focusing on specific aspects such as stiffness or colour [4], subjective standard assessment systems, validated questions [5] and clinical photography. When embarking on scar revision, the documentation of the scars is essential in tracking progress over time; the options are explored in detail in section VII.

36.4 The Techniques for Preparing the Scar Wound Bed for Resurfacing

The prerequisite to prepare the scar for resurfacing is the removal or disruption of the epithelial layer by techniques including chemical, laser, dermabrasion and sharp dissection [6].

Chemical peels have been widely used aiming to remove the surface epithelium to a limited depth such that rapid healing by secondary intention is achieved with limited improved scar outcome.

There has been an expansion of the laser techniques used to remove or to disrupt the epithelial surface as explored in the chapters in section IX. Again, laser in isolation can be used with surface damage limited to a superficial level such that the healing by secondary intention is rapidly achieved. The use of fractional laser with discrete microthermal zones has been shown to initiate scar remodelling within the dermis. Further, the ablative lasers can be a tool used to prepare the wound bed for secondary interventions as described below.

Dermabrasion can be achieved with manually using abrasive sand papers, or mechanically with rotating brush or burr. The depth of tissue removal can be controlled, and the contour can be guided using adjuncts such as injection or surface coating with agents such as methylene blue. Surface irrigation is necessary to mitigate against heat damage and to remove the debris from the surface.

The sharp dissection tools range from freehand scalpels to mechanised guarded blades allowing serial shaving of the scar surface. Again, the depth of the tissue excision is dictated by the strategy of consequent wound healing [7]. In situations of superficial shave, the aim may be controlled healing by secondary intention. However, the use of sharp dissection lends itself to de-

bulking of the scar volume such that the wound bed does not retain the capacity to heal within a timeframe that would limit the secondary scar risk [8].

The extent of the excision of the fibrotic dermal layer can range from total scar excision to minimal removal of the tissue. With the retention of the scarred bed, the overall scar result relies on the remodelling, driven by the interaction of the cells of the new epidermal layer and those in the retained scar construct.

36.5 The Techniques of Wound Repair for Resurfacing

In the situation of total scar excision, a full-thickness skin replacement is the ideal reconstruction and is considered in ► Chap. 37, using flap repair, and ► Chap. 39 exploring the use of skin substitutes.

In some instances, an appropriate donor site for a full-thickness skin graft may allow full-thickness reconstruction, or the use of tissue expansion can facilitate local flap repair with the most similar skin characteristics. In complex scar reconstruction, the functional restriction may require the introduction of tissue from a remote uninjured body site using local or free tissue transfer explored in ► Chaps. 37 and 40.

In a scar which has been prepared using limited removal of the epidermal surface, healing by secondary intention may be appropriate. In these cases, specific attention to detail is required to protect the healing wound surface [9]. The key to limiting the risk of worsening the scar is the time to healing. There are many strategies employed to facilitate healing with advanced technology dressing systems, both synthetic and biologically based.

When the scar has been de-bulked, then secondary repair of the surface should be considered as prolonged healing by secondary intention will be associated with an increased scar risk. The use of thin split-thickness skin graft can result in an improvement of the scar in terms of contour and colour. However, this can be unpredictable with some split-thickness skin grafts associated with abnormal pigmentation. There is also the drawback of the donor site availability in terms of area and site specificity.

Matching the donor and recipient site is a key element in improving the potential outcome from scar resurfacing. For example, the use of full-thickness skin grafts to release scar contractures of the palm of the hand will frequently afford an excellent functional release but is associated with significant mismatch in terms of the skin characteristics. The ability to match donor site is most frequently limited by the surface area required. The donor site itself can be resurfaced such that a thick split-thickness or full-thickness harvested area is secondarily covered by a thin split-thickness skin graft aiming to reduce the overall donor site morbidity.

The use of tissue expansion techniques may also be used to address the donor site limitation. The concept of tissue expansion can be extended beyond the full-thickness skin construct, to the cells essential for re-epithelisation. The development of the processes of cultured epithelial autograft was specifically to address the need of large surface area skin cover in major burn injuries. The techniques of laboratory-based tissue expansion can provide epithelial cells as sheets or suspension from a limited donor site which will retain the epithelial characteristics of the donor site. The drawback of such cell-based therapies is the reliance on the laboratory environment and the time taken to achieve the expansion via the tissue culture process.

The first steps of the cell-based expansion process have been incorporated into a medical device as a lab in a box, ReCell™. The technique of harvesting at the point of care of the cells of the dermal-epidermal junction, for delivery as a cellular suspension, provides a method with an expansion ratio of up to 1–80. The technique uses the wound bed as the tissue culture environment with the cellular suspension adhering to the prepared wound surface and the cells migrating and differentiating into an intact epithelium. The use of the cell suspension from the dermal-epidermal junction allows the transfer of keratinocytes, melanocytes and papillary dermal fibroblasts in their normal ratio [10]. The use of such a cellular suspension in resurfacing is particularly useful in treating hypopigmentation. The melanocytes within the suspension will re-establish in the prepared wound, and re-pigmentation is seen over the subsequent 6–12 weeks. The introduction of the cell suspension facilitates the epithelial repair reducing the time to healing and therefore the risk of secondary scarring.

There is also interesting basic science evidence that the interaction between the keratinocytes and fibroblasts has influence on the phenotype of the fibroblasts impacting on collagen deposition [11].

The use of cell-based therapies is an opportunity to expand the surface area of wound cover possible for a given donor site with the appropriate cell phenotype. The seeding of the cells onto a de-bulked scarred wound bed reduces the time to achieve an intact epithelial surface with the potential to introduce melanocyte and keratinocyte characteristics to match the area. The introduction of an uninjured cell phenotype has a theo-

retical impact on the scar remodelling as the scar matures.

Whatever method of scar resurfacing is used, the objective remains constant, to improve the area of scar such that the scar blends better into the surrounding skin.

36.6 Post-Intervention Scar Management

The wound healing is only the first phase in the process of scar remodelling post resurfacing, and attention to detail at all stages is essential. The post-intervention dressing systems may involve a range of products focused on providing an environment of healing with infection control and protection of the fragile wound surface.

Further, the protection of the healed epithelial surface and control of the environment are important as the dressings are removed and the surface exposed. At this stage, it may be prudent to consider the non-invasive conservative strategies for scar minimisation such as silicones and massage as explored in the chapters of section VIII. At all stages, hygiene is an essential element to prevent secondary infection and breakdown whilst the cell surface is fragile and immature.

For decades, pressure garments have been used in the attempt to control scar progression particularly post burn injury. The mechanism of action is debated, but it remains a widespread practise. The fabrics used vary in terms of the pressure delivery and the moisture wicking characteristics. A light pressure fabric can be used to protect the area in the early stages post healing if well designed to avoid trauma and sheering.

Sun protection is also important not only to prevent sunburn of course but also to avoid the overstimulation of the melanocytes with the risk of hyperpigmentation in the resurfaced area. Simple advice such as wearing a hat and topical sunblock needs to be considered as part of the post-intervention information given to the patient. The advice will need to be tailored to the patient in relation to their environment.

36.7 Conclusion

The clinical decision to undertake a scar resurfacing procedure needs to bring together the needs of the patient and the characteristics and history of the scar, along with the tool box of potential interventions (Table 36.1).

The choice of the specific resurfacing technique will then consider the triangle of care to specifically address the patient's needs in the context of the clinician's knowledge and experience along with the technology environment available (Fig. 36.1). The diagnosis of the scar with the inclusion of an assessment tool will give clarity to the clinical discussion with the focus on the aspects of the scar causing the concern.

Understanding the natural history of the scarring process will help in giving advice to the patient, explaining the opportunities of conservative therapies and time to improve the scar. Then, choosing the technique that will give most benefit for least risk is the key to safely improving the scar. There are many ways of resurfacing, but understanding the need for bulk reduction, re-pigmentation or stabilising the epithelium of the scar will drive the clinical decision.

In the clinical counselling, being realistic that the scar may be reduced and blended to the surrounding skin rather than eradicated facilitates decision-making for the patient.

Table 36.1 Understanding the clinical details of the scar and the impact of the symptoms on the patient to drive the most appropriate clinical intervention for the individual

a

Scar Assessment to guide intervention

Clinical history	Scar symptoms
• Mechanism of original scar process	• Itching
• Timeframe of scar development	• Pain
• Time to healing	• Stiffness
• Technique used to achieve healing	• Dryness
• Presence of infection	• Epithelial instability
• Systemic health and nutrition	• Thickness
	• Vascularity
	• Colour

b

Scar Resurfacing

Techniques to prepare the scar for resurfacing	Techniques to control secondary wound healing
• Sharp dissection	• Cell based therapies
• Dermabrasion	• Advanced dressing systems
• Laser techniques	• Infection control
• Chemical preparation	• Systemic optimisation

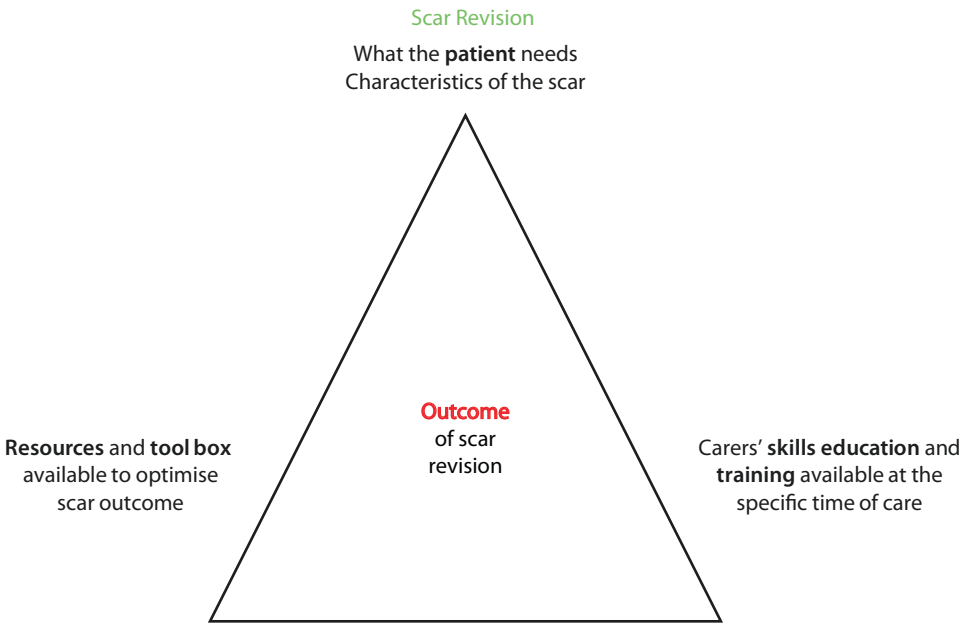

Fig. 36.1 The triangle of care bringing together essential considerations for clinical decision making

Take-Home Messages

- Clinical history of the patient and the scar is pivotal in the decision-making process.
- Scar assessment is key in tracking the impact of the scar intervention over time.
- Be clear on what elements of the scar need to be treated.
- Focus the intervention on the outcome required.
- The time to healing is a key element driving scar outcome.
- Meticulous attention to detail needs to be continued to the time of scar maturity.
- Education of the patient along the clinical journey is essential for a successful outcome.

36

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Invasive Techniques in Scar Management: Skin Substitutes

F. W. Timmermans and E. Middelkoop

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_37

37.1 Background

Modern wound care demands a high focus on quality of healing. Skin substitutes can play an important role in achieving the best possible outcome for each patient. Although skin substitutes were primarily developed for use in acute wound care, they have since then started to play an important role in secondary scar revision surgery. Initially, epidermal cell cultures were developed with a focus on efficient wound closure of large wound surfaces. Long-term results, however, indicated that several structures that played a role in stabilizing the connection between epidermis and dermis did not fully regenerate [1]. Thus the role and importance of the dermal component of skin regeneration became more apparent. This eventually led to the development of dermal substitutes. Various biomaterials were tested for their capacity to stimulate dermal regeneration, with various degrees of success. Synthetic as well as biological materials were extensively tested. Where synthetic materials demonstrated to actively stimulate wound healing in chronic circumstances such as diabetic wounds, biological biomaterials proved to be more beneficial for treating acute wounds. These biological materials were mainly composed of purified extracellular skin matrix components such as collagen, elastin, and/or proteoglycans. Long-term clinical results of several of these materials have since then become available. Further development of the field resulted in the addition of cells to these synthetic and biomaterial constructs. Various cell sources were investigated, with specific attention to different sources of stem cells, as well as allogeneic versus autologous cell sources [2–4]. Alongside the clinical studies, outcome analysis on different skin and scar parameters was further developed. This provided insight into the different skin characteristics that were influenced by the use of skin substitutes. Besides acute wound treatment, scar treatment using fat-derived mesenchymal stem cells is also subject of further research. Initial studies have demonstrated beneficial effects on scar maturation after lipofilling. This technique aims at regeneration of the subcutaneous fat layer underneath the dermal layer of the skin. Nowadays, all these developments allow us to use these different biomaterials as acellular dermal substitutes in state-of-the-art reconstructive surgery and acute wound treatment. New advancements are found in the development of full skin constructs, using autologous epidermal as well as dermal cell sources. At present, autologous (i.e., from the patient) cells are still the mainstay in the successful use of cellular substitutes. This is an advantage in terms of the absence of potential immunological reactions, but at the same time, the long culture times needed to prepare these constructs are definitely a disadvantage of using cellular substitutes in the acute trauma setting. Furthermore, the long-term regenerative capacity of these cellular skin constructs still remains to be fully established.

37.2 Permanent Wound Coverage

Wound closure normally proceeds by migrating epidermal cells from both wound edges and skin appendages such as sebaceous glands and hair follicles. As wounds grow deeper and larger, the skin loses its ability to provide enough epidermal cells to close the wounds in a reasonable time frame. This time frame of healing is considered to be adequate if the wound is closed within 3–4 weeks. Prolonged exposure to pathogens and fluid loss represent immediate dangers in delayed healing and might potentially lead to bacterial contamination, sepsis, and death in the worst cases. Biological processes such as wound contraction are initiated that aimed at speeding up wound closure. This is paradoxically an undesired action in terms of the final quality of the wound-healing process. Therefore, most large and deep wounds require surgical assistance to promote timely wound healing and adequate wound closure. The main purpose of surgery is to bring a new source of viable epidermal cells to the wound in order to speed up the wound closure. Skin grafts are the most well-known and most used methods for epidermal transfer and permanent wound coverage.

37.2.1 Epidermal Cells/Cultured Epidermal Autografts CEA

The keratinocytes in the epidermal layer of the skin form the first barrier of the skin. A standard technique for closure of large wounds is transplantation of skin using a split-thickness skin graft (STSG). The protective properties of the epidermal layer are best conserved in the form of split-thickness skin grafts, which usually comprise the whole of the epidermis and a very thin layer of dermis (approximately 0.1–0.2 mm). Coverage of larger wound areas is possible using meshed STSGs, where expansion rates up to 1:6 are possible (◘ Fig. 37.1). However, scar formation in the mesh interstices is apparent, and therefore larger expansions with fewer donor sites were needed. This pushed Rheinwald and Green, as early as 1975, into being the first to show that keratinocytes could be extracted, in vitro cultured into sheets, and that they were suitable for grafting [5]. This can easily be considered the first step in the tissue engineering of the skin. The usage of cultured cells marked a leap forward in the treatment

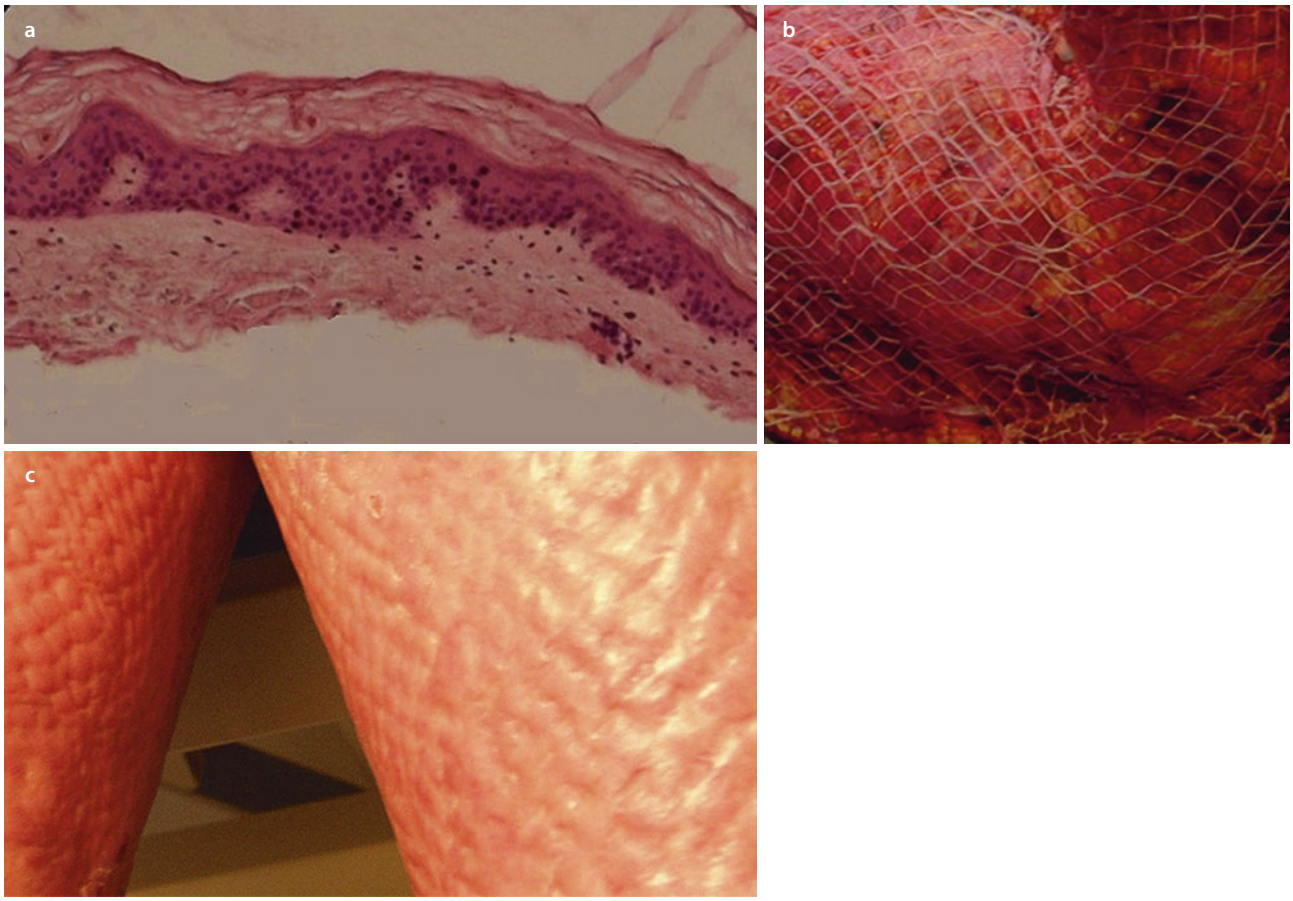

Fig. 37.1 **a** Microscopic image of hematoxylin eosin staining of human split skin. Note that only a very thin layer of dermis is present. **b** Split-skin mesh graft with wide expansion to cover larger wound area. **c** Typical scar pattern showing mesh pattern of the graft in the scar

of burn patients as larger areas of wounds could be covered with very small donor sites of healthy skin.

The development of cell culture techniques opened up the possibility to maintain viable cells outside of the human body. Initially, cultured keratinocyte layers (cultured epithelial autografts or CEA) opened opportunities to cover large parts of the body without the necessity for substantial donor sites. This greatly improved the survival chances of severely burned patients. However, early studies of CEAs on wound beds showed insufficient regeneration of dermal–epidermal junctions between the epidermis and the underlying tissue, which even after many years resulted in a vulnerable and weak skin barrier [1]. Thus, it was discovered that substitution of dermal tissue is also of great importance in creating and maintaining a well-functioning new skin. These insights sparked the development of more complex skin substitutes.

Although CEAs have been used for over 40 years now, they did not provide the definitive solution for the treatment of large wounds. Specific downsides such as variable graft-take rates, high manufacturing costs, production and transportation logistics, insufficient dermal–epidermal junction regeneration, and often having to compete with readily available split-skin grafts have limited most of the further development of CEAs [6].

A more recent development in the application of epidermal cells is in the form of in situ cell therapy, called the ReCell® system (Avita Medical, Cambridge, UK). With only a small donor site of split skin (approximately 1 cm^2), this device allows the isolation of a single-cell suspension that can be sprayed on a wound bed. The cell suspension consists of approximately 65% keratinocytes, 30% fibroblasts, and 3–5% melanocytes. This system avoids the time-consuming and costly cell culture step. The cells in the cell suspension can adhere to the wound bed and promote tissue regeneration by both cell proliferation and growth factor stimulation. This technique is sometimes used in combination with expanded meshed autografts to accelerate wound healing. The combination of these two treatment options has shown to improve cosmetic outcomes of scars and pigment abnormalities. In situ cell therapy can also be used as a means to promote repigmentation of depigmented skin in patients with vitiligo and congenital melanocytic naevi [7]. Whether these effects are due to actual cell

survival and proliferation or to growth factor and cytokine secretion is presently still unclear.

37.2.2 Dermal Substitutes

Skin substitutes aiming at dermal regeneration are dermal constructs designed to either temporarily or permanently replace dermal defects. In all cases, the aim of skin substitutes is to provide protection against microorganisms, reduce pain, promote wound healing, and assist in recreating the barrier function of the skin [8]. This method has become increasingly important for the treatment of burns, open wounds, chronic wounds, and deep tissue donor sites, as it has been shown to improve and accelerate skin regeneration, reduce scar contracture, and minimize donor site morbidity. All these different treatment indications resulted in the development of a wide range of skin substitutes with different characteristics such as mono- or bilayered compositions, temporary or permanent fixture, and cellular or acellular skin substitutes.

37.2.2.1 Tissues

A biological approach used in the design of permanent skin substitutes was to start with real human tissue. One of the early developed acellular allogeneic skin substitutes is Alloderm®. Alloderm® is harvested from cadaver donors as skin grafts, which are then washed with hypertonic saline to remove cell remnants. After removal of the epithelial layer, the remaining dermal layer is treated to inactivate viruses and then freeze-dried to be used on demand. This provides a nonantigenic dermal scaffold with basement membrane proteins, which are known to promote wound healing and angiogenesis. After rehydration of the Alloderm®, coverage with an ultrathin split skin would suffice as a full coverage treatment option. Recently, Alloderm® has seen a rise in its use for breast reconstructive surgery, whereas the use of Alloderm® on wounds and burns remains limited. Glyaderm® is a similar product based on allogeneic dermis preserved in glycerol instead of freeze-drying. Initial studies on burn patients have been performed with favorable results [9].

37.2.2.2 Dermal Scaffolds

Some of the most well-known and most used dermal scaffolds are Integra® and Matriderm®. Although both materials consist of bovine collagen combined with extracellular matrix components, their mode of application is generally different. Integra® was the first dermal substitute of its kind in the early 1980s and was created with the apparent goal of minimizing fluid loss and bacterial contamination and promoting cell migration into the wound bed. It does so through its two-layered composition and its two-stage procedure. The deeper layer of Integra® is made out of a combination of bovine collagen and glycosaminoglycan chondroitin-6-sulfate, whereas the top is made with a 0.2-mm-thick polysiloxamine polymer membrane with vapor-transmitting characteristics similar to normal epithelium. This membrane is intended to be placed on the full-thickness wound, and the outer silicone membrane will function as a temporary epidermal replacement and will need to be replaced by a split-skin graft after 2–3 weeks of sufficient ingrowth of vasculature into the deeper dermal scaffold. Due to the combination with a silicone layer as temporary epidermal coverage, Integra® can immediately function as a barrier to limit fluid loss and protect from microbial contamination of the wound, while providing the required extracellular scaffolding for cell ingrowth and proliferation of fibroblasts and endothelial cells. In the second stage, after vascular ingrowth, the silicone layer is replaced by a thin split-skin graft. This product has gained widespread use in the clinical treatment of deep partial-thickness and full-thickness burn wounds, full-thickness skin defects of other etiologies, chronic wounds, and soft tissue defects. The results of Integra® within burn care have been generally favorable and have shown improved quality of healing. However, the staged procedure leaves the wound open for a prolonged period of time and thus bears a risk of submembranous bacterial infections resulting in loss of the biomaterial. Other similar bilayered substitutes are Renoskin®, Pelnac™, and Hyalomatrix® [10].

Matriderm® is usually applied in a one-step procedure as this dermal scaffold allows immediate coverage with a thin split-skin graft. It consists of an extracellular matrix scaffold made out of purified, freeze-dried bovine collagen mixed with 3% elastin hydrolysate. An autologous split-skin graft can be applied directly onto the Matriderm®. Clinical research showed a somewhat slower take of the graft, which reflects the interpositioning of the unvascularized scaffold between the wound bed and the split-skin graft. Nevertheless, the outcome in terms of scar quality was shown to be superior over split-skin graft treatment even after a 12-year follow-up [11].

Both Matriderm® and Integra® have been used for acute and reconstructive purposes and as a means to improve scar quality. These dermal scaffolds initially lack cellular compounds and do require the body to incorporate the exogenous matrix into the wound environment through cell migration and remodeling, which is mediated by macrophages and fibroblasts. Fibroblasts, similar to keratinocytes, also secrete various cytokines and growth factors. But besides promoting cell proliferation, inducing angiogenesis, and modulating the inflammatory process, they also produce a new extracellular matrix, which helps to reconstruct the three-dimensional dermal structure of

the skin. Other one-layered scaffolds are Novomaix® (freeze-dried collagen with elastin fibers) and Permacol® (a porcine collagen matrix which is now primarily used in hernia and abdominal wall surgery) [10].

37.2.3 Cellular Dermal Substitutes

Cellular dermal and composite skin substitutes are the most recent products of skin substitute research. Dermal skin substitutes are primarily created to guide dermal regeneration and are used in combination with autologous split-skin transplants. This treatment is aimed at providing an underlying layer of dermal tissue where normally fibrotic scar tissue would be formed. One of the disadvantages of an acellular dermal scaffold is the relatively slow ingrowth of blood vessels and other cells into the scaffold, which can hamper the take and even minimize the survival of the covering split-skin autograft. The general understanding is that the inclusion of dermal cells in the scaffolds improves these outcomes and at the same time promotes the wound-healing process. DenovoDerm™, Hyalograft 3D®, Dermagraft®, and TransCyte® are a few of these known cellular dermal skin substitutes. The first two are, respectively, made of autologous fibroblast seeded in bovine collagen and hyaluronic acid scaffolds, and the latter two are respectively made of allogeneic fibroblasts seeded in a polyglactin and nylon scaffold. Other experimental studies have looked into using adipose-derived regenerative cells in combination with Integra®, and some attempts have been made to create skin substitutes with nanotechnology. However, the effectiveness and safety of these methods still need to be demonstrated outside of the experimental stages of development.

Most of the cellular dermal substitutes are produced using living neonatal fibroblasts. Examples include TransCyte® and Dermagraft®. TransCyte is produced by culturing neonatal fibroblasts on a nylon mesh, where the cells deposit collagen, other matrix proteins, and growth factors. After freezing, the cells are no longer alive, but the matrix proteins and growth factors remain and can actively promote healing, e.g., for deep partial thickness acute wounds. Dermagraft®, however, is composed of living allogeneic neonatal fibroblasts cultured on a polyglactin scaffold. The neonatal cells provide the extracellular matrix compounds and growth factors needed for efficient tissue regeneration. The allogeneic compounds in the skin substitute will subsequently stimulate granulation tissue formation that enables secondary closure or eventual coverage with a split-skin graft. Compared to the autologous counterparts, allogenic skin substitutes have thus far predominantly been successfully used for the treatment of chronic diabetic ulcers.

37.3 Full-Skin Substitutes

Several research groups have developed full biological skin substitutes comprising of both dermis and epidermis, while containing either allogeneic or autologous fibroblasts and keratinocytes. Apligraf® was the first of this kind to become commercially available. Apligraf® consists of cultured allogenic human foreskin-derived neonatal fibroblasts in a bovine type I collagen matrix over which allogenic human foreskin-derived neonatal epidermal keratinocytes are then cultured and allowed to stratify. The allogeneic character of this skin substitute ultimately results in the rejection of the keratinocytes, which eventually requires an autologous split-skin coverage for definite would closure. Therefore, Apligraf® is less suitable for large acute wounds but has found its main use in the treatment of chronic wounds. Orcel® is a similar product with a similar composition. The allogenic cells are considered to survive up to 2–3 weeks in the wound bed, and the overall effectiveness of these composite skin substitutes is thought to be based on the excretion of a mix of growth factors and cytokines.

Some novel autologous composite skin substitutes are DenovoSkin™ and Permaderm®. Both of these composite skin substitutes are made with a bovine collagen scaffold. Another described full-skin substitute is the TissueTech Autograft System™, which is essentially the combination of a dermal skin substitute (Hyalograft 3D®) with a CEA (Laserskin®). A major advantage of autologous composite skin substitutes is its one-stage character. Except for the initial skin biopsy from which the autologous cells are harvested and cultured, no secondary procedures such as split-skin transplantations are required. Most of these are newly developed skin constructs, which are still undergoing trials, and none are commercially available at present. Besides regulatory obstacles (see below), other downsides to the further development of autologous composite skin substitutes are the high production costs, long preparation time, and the necessity for a well-organized production-to-clinic transfer. Nevertheless, these are important developments, since in the end, these advancements may lead to clinically applicable regenerative full-skin substitutes, comprising of not only dermal and epidermal structures but also vasculature, skin appendages, and even nerves.

37.4 Subcutaneous Fat

In recent years, there has been an apparent shift from merely thinking about reconstructing the dermis and epidermis, to the inclusion of the subcutis. It has become more clear that the subcutaneous fat layer plays an essential role in the gliding and mobile functions of the

skin. This characteristic is especially important in anatomical locations where the skin is relatively thin, such as the back of the hand or the tibia. Scars in these areas can easily fuse to underlying tendons or bones if subcutaneous fat is missing. Recent studies have noted beneficial effects on scar quality of lipo-injection with the patient's own fat, harvested by liposuction. Lipofilling of these scars showed an increase of elastic fibers at the dermopapillary layer, which could account for the improvement of scar quality [4, 12–14]. The sustainability of a mere single treatment of autologous fat grafting in mature adherent scars showed to promote a lasting improvement in scar elasticity and tactile pliability [15]. Although there is not enough solid clinical evidence yet, the data gathered so far indicate that fat grafting could become a new treatment modality in improving scar quality and outcome after burns. Further research should aim at elucidating the best indications, timing, and techniques as well as frequencies of application.

37.5 Regulatory/Safety Issues

Further development of cell therapy and tissue engineering for better clinical outcomes with regard to wound healing and the reduction of scar formation is a common recommendation in studies on the use and development of skin substitutes. However, new regulations have become effective during the last decade, which designate cell-based therapy as advanced therapy medicinal products (ATMPs). Practically, this means that cell-based therapies in Europe are under direct assessment of the European Medicines Agency (EMA, a monitoring institute of the European Union), which is dedicated to the scientific evaluation and supervision of market access of medicinal products. In the USA, the Food and Drug Administration (FDA) is the relevant authority, where the Office of Cellular, Tissue, and Gene Therapies (OCTGT) exerts the tasks to evaluate and supervise market access of ATMP products.

The European Regulation (EC) No. 1394/2007 provides the overall framework on production and use of ATMPs within the European Union. According to this regulation, an ATMP is a "medicine for human use that is based on genes, cells or tissue engineering." When elaborating on the definition of tissue-engineered products, such products may contain or consist of engineered cells or tissues, with the purpose to regenerate, repair, or replace a human tissue, and it may contain viable or nonviable cells or tissues of human or animal origin. This means that most of the skin substitutes with living cells (both autologous and allogeneic), adipose tissue, and matrices containing human and/or xenogeneic material fall under the regulatory issues associated with this regulation. Scaffolds made of isolated and/or purified animal or human-derived proteins, however, are classified as medical devices. One of the main features of these regulations is that the production of ATMPs for human use must take place under *Good Manufacturing Practice* (GMP) conditions. This is translated into high standards of production facilities, which is only possible in a select few centers and represent a considerable administrative burden for importing and exporting ATMPs across international borders. These strict regulatory and production requirements imply intensive collaboration between centers for the further development of ATMP' and for successful commercial exploitation of these novel treatment options.

37.6 Conclusion

Acellular skin substitutes have gained a solid position in the treatment options for acute and chronic wounds as well as scar revisions, with improved outcomes in skin quality over standard split-skin graft treatment. Autologous cellular skin substitutes still hold a promise for the future. Tissue repair and regeneration through the use of autologous cells promote superior healing over the known methods. There are still some drawbacks in the production and application of tissue-engineered skin constructs, but further research, automated production process, and harmonizing our treatment practices will bring us closer toward a scarless future.

Take Home Messages

- Acellular dermal substitutes have proven their efficacy in reaching better scar quality compared to split-skin grafting for acute and reconstructive treatment.
- Acellular dermal substitutes can be used in a one-step procedure, providing immediate wound coverage, or two-step approach, which allows prevascularization of the dermal component prior to epithelial grafting.
- Epidermal cell sprays can be used to treat pigment disorders in scars and/or to increase epithelialization rate during acute wound healing
- Fat grafting is used successfully on adherent scars as autologous fat injection to improve scar elasticity and regenerate a gliding layer underneath a scar.
- Cellular dermal and full-skin substitutes are in clinical trials for treatment of acute and reconstructive wounds.

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Facial Scars Reconstruction

Luc Téot

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_38

38.1 Objectives of the Chapter

The objective of the chapter is to present the different reconstruction techniques, distinctly describing the ones recruiting autologous skin and subcutaneous tissues, transferred from surrounding color-matching donor site areas as well as techniques suitable for a complete face transplantation from a living human donor, with this homologous transfer being realized using microsurgical revascularization.

The aim is to minimize as far as possible the consequences of facial scars, which induce a loss of the dynamic aspect of the face and loss of the specific mimics of each human character to express different emotions. Consequences of the different surgical strategies are described, including local, regional, and systemic potential complications.

38.2 Techniques

1. Skin Resurfacing

   Used in postburns scars involving retractions and loss of skin capacity, the resurfacing using dermal substitute and partial thickness skin grafts is the easiest technique to perform. Excision of the scars is done via a long meticulous surgical debridement, preventing to severe venous and arterial pedicles, resecting the hard thick scar tissue, which may be strongly adherent to the muscular and aponeurotic structures of the face around the orifices, mouth, nose, and ears. The neck is extensively freed from retracting scars, allowing a restauration of the movements up and down and laterally on each side. Covering using dermal substitute has become more and more popular in burns surgery since the initial works on Integra [1].

2. Pedicled-Expanded Deltopectoral Flaps

   Among the commonly used donor sites, the deltopectoral site was conceived as one of the most suitable donor tissues for the reconstruction in the face and neck for its adjacent site and match in color and texture [2]. This technique uses an island flap, which is prepared and expanded to the size of the surface to be covered over the face and the distance of the flap pedicle to the distal end of the flap. This is a two-staged procedure. The size and projection of the silicone expander should precisely be determined before the first surgical step. Thanks to a limited incision outside the future face flap which will be drawn over the dorsal skin, a large expander will be inserted in a cavity created subcutaneously between the subcutaneous fat and the underlying muscle aponeurosis. The expander is chosen based on its capacity of inducing a predetermined skin projection, surface of the projected area, and length and width. The expander is connected via a silicone tubing to a valve which is also inserted under the skin at a limited distance from the expander edges. After a period of 2 weeks, the expander filling will start, and the amount of liquid determined on the rate of filling and the needed projection to obtain the desired skin expansion. Usually the skin expander is overexpanded to 1.5 of its volume, in order to obtain an even skin expansion. Possible complications may include extravasation of the expander (in case of rigid silicone angle), a too rapid expansion inducing a local devascularization and stretch marks, the long distance from the back to the face and the postop edema sometimes causing flap tip necrosis

   But a good skin compliance, normal contours, and emotional expression are usually noted after the reconstruction.

3. Prefabrication

   In 2000, the main author proposed the neofabrication of a cervico-deltopectoral flap used as an island flap after skin perfusion boosting. This technique, called prefabrication, was developed on the principle that when a vascular carrier (a fascia including an artery and a vein) is inserted between the expanded skin and the silicone balloon, the expanded skin territory can be extended and its neovascularization amplified. The technique was published in 2000 in *The Lancet*, opening the way to the creation of flaps larger than the normal anatomy allows it [3].

   Technically, the radial forearm facial flap (20 cm × 6 cm) is harvested with the radial artery and the vein, which are microsurgically branched on the facial vessels artery and vein using a limited incision. The fascia is inserted subcutaneously over the clavicular bone anteriorly, the trapeze muscles posteriorly, and the deltoid muscle laterally. A transfixient suture is needed at the distal end of the fascia in order to prevent any gliding possibility.

   Depending on the surface to cover, the amount of expansion and size and capacity of the expander may vary. When the complete face should be covered, a 2-liter skin expander will be inserted between the vascularized fascia and the underlying structures. The valve and tubing are positioned posteriorly on the back.

   A progressive filling of the skin expander is realized twice a week, with a regimen allowing to get the surface of the face (25 cm × 30 cm) on the shoulder after 3–4 months. An arteriogram is realized before the second stage in order to confirm the viability of the fascia and its capacity to revascularize the extra skin obtained thanks to the skin expansion. This arteriogram shows all the new arterial ramifications emerging from the radial transplanted artery, a sign which was interpreted by the radiologists as a certi-

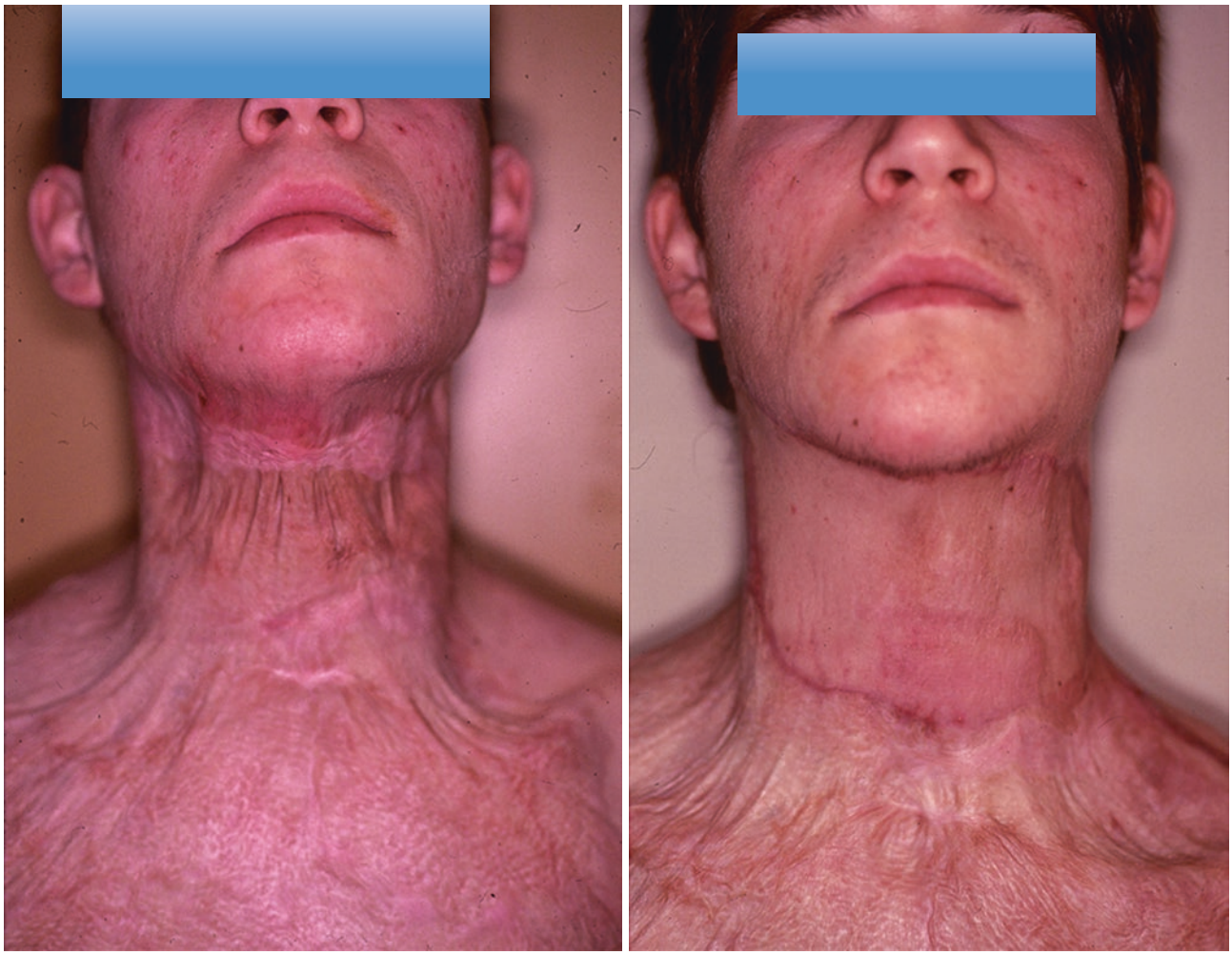

Fig. 38.1 Before and after prefabricated flap on the neck of a young male presenting a contractile postburn scar

tude that the fascial vessels were inducing the new flap vascularization.

During the second step, a flap large enough to cover the entire face (if needed) is designed over the expanded skin. The dissection starts from lateral to medial over the shoulder, with a particular attention not to harm the vascular pedicle. Once the flap is harvested and the flap pedicled on the arteriovenous pedicle, all facial scars are removed deep to the fascia, in order to get a maximum surface covered by the new flap. Orifices (mouth, eyes, nostrils) are opened in front of the anatomical corresponding zones.

Long-term results are good, with the transplanted skin depth remaining adapted to the volume of the face, thanks to the precompression realized during the skin expansion (Figs. 38.1, 38.2, 38.3, 38.4, 38.5, 38.6, and 38.7).

This technique allows to get a precompressed large piece of skin, well vascularized and conformable. The whole face can be covered with a large viable piece of skin. There is no need for complementary drugs.

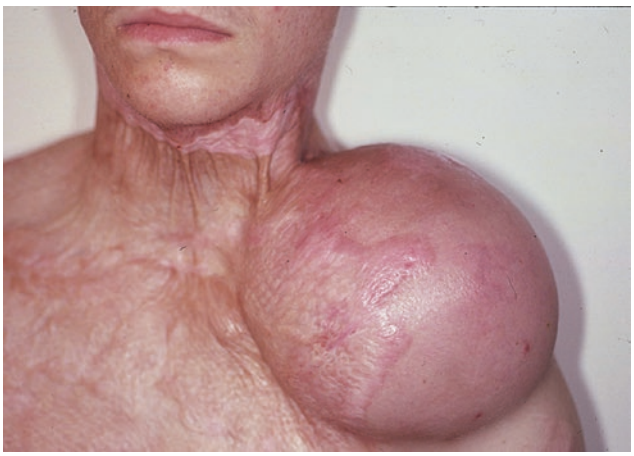

Fig. 38.2 Aspect of the expanded skin flap before the second procedure

4. Superthin Flaps

The "superthin flap" concept was introduced by Ogawa et al. in 1994 [4], based on the subdermal vascular network (SVN).

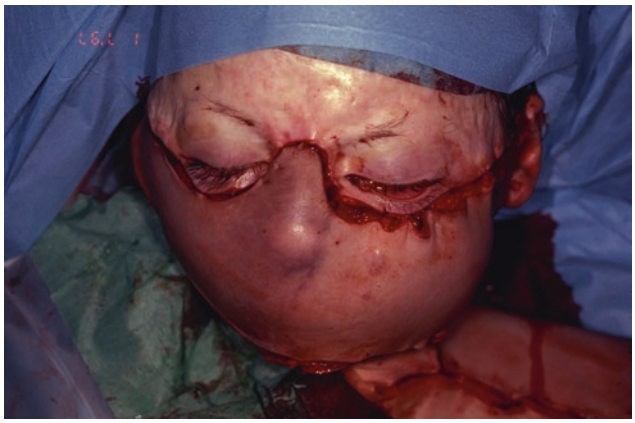

Fig. 38.3 During the second procedure, the orifices (mouth, nose,) must be reopened adequately

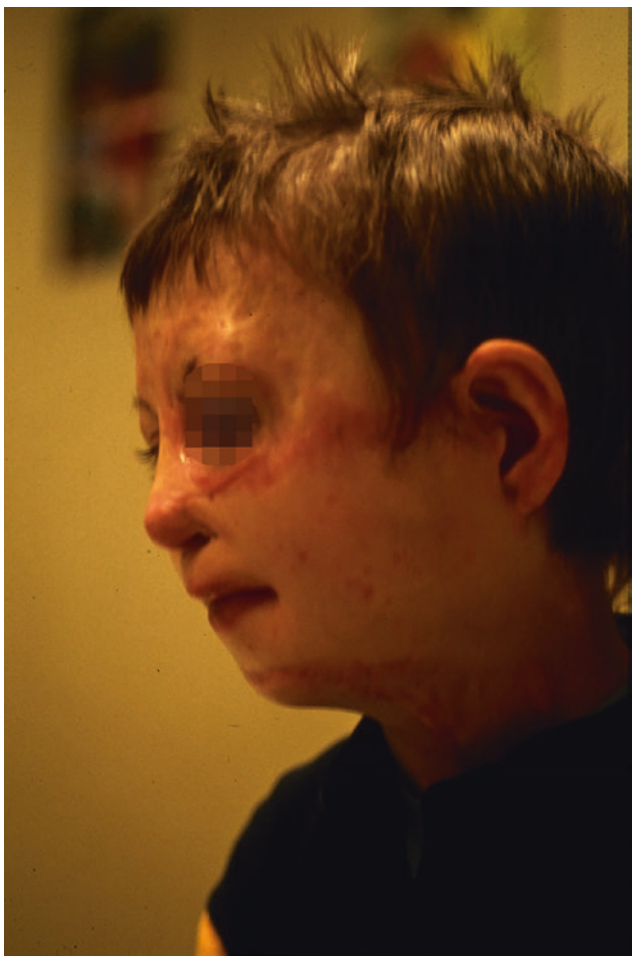

Fig. 38.4 One year postoperative aspect

Superthin flaps were used in different clinical situations. Twenty-one expanded flaps were used to reconstruct 21 face or neck scar cases in 9 males and 12 females. In the first operation, an expander was inserted on the fascia of the pectoralis major muscle, and then about 1000 cc of saline was injected during a 2-month period. In the second operation, the flap was thinned primarily and applied to the recipient site. Three weeks after the second operation, the pedicle of the flap was cut down and sutured.

In 2007, the authors reported an expanded "superthin flap" for reconstruction of the face and neck for the first time in a patient.

In their series the authors reported different flap sizes, ranging from 4 cm × 14 cm to 10 cm × 22 cm. Expanded volume ranged from 800 cc to 1200 cc. All flaps survived completely, and scar tissues were replaced with normal skin. Flaps did not shrink after the operations, and contractures did not recur. The main advantages of the expanded flaps are the potential to create large thin flaps with a texture and color matching with the recipient area. The donor site can be closed primarily; and microsurgery is not required. However, the disadvantage of the method is the requirement for two or three operations.

The advantages and limits of the techniques are using skin expansion with or without microsurgery. This technique may be considered safe in terms of skin manipulations, the obtained tissue being conformable enough to redrape the whole face without lymphatic accumulation. Edema can be maintained at a low level, especially when using complementary compressive techniques comparable to the ones used in postburn-grafted faces. However, the second stage (flap positioning) after skin expansion is crucial in order to prevent distal regions of the flap to be partially devascularized and become distally necrosed, a complication issuing to a potential tissue loss. The transferred tissues are coming from areas where the dermal component is thicker than desired for facial tissues like the eyebrows or lips, but the global aspect of the transplanted face is compatible with a normal life, thanks to a daily adapted makeup and some retouching on the eyebrows and the lips. The skin has been submitted during skin expansion to a pressure which limits the depth and gives a thin texture. However, in most of the cases, complementary surgical retouches will be needed for refining the red lips, nasal skin depth and nostrils, columella, and eyebrows, reshaped using liposuction, fat transfer, and mucosal surgery

5. Facial Allotransplantations

Historical Aspects

The Pioneers

The first clinical case was realized in November 27, 2005, in Amiens (France); the patient presented a disfiguration after a severe dog bite. She was submitted to the world's first partial face transplant This disruptive approach established loss of quality of

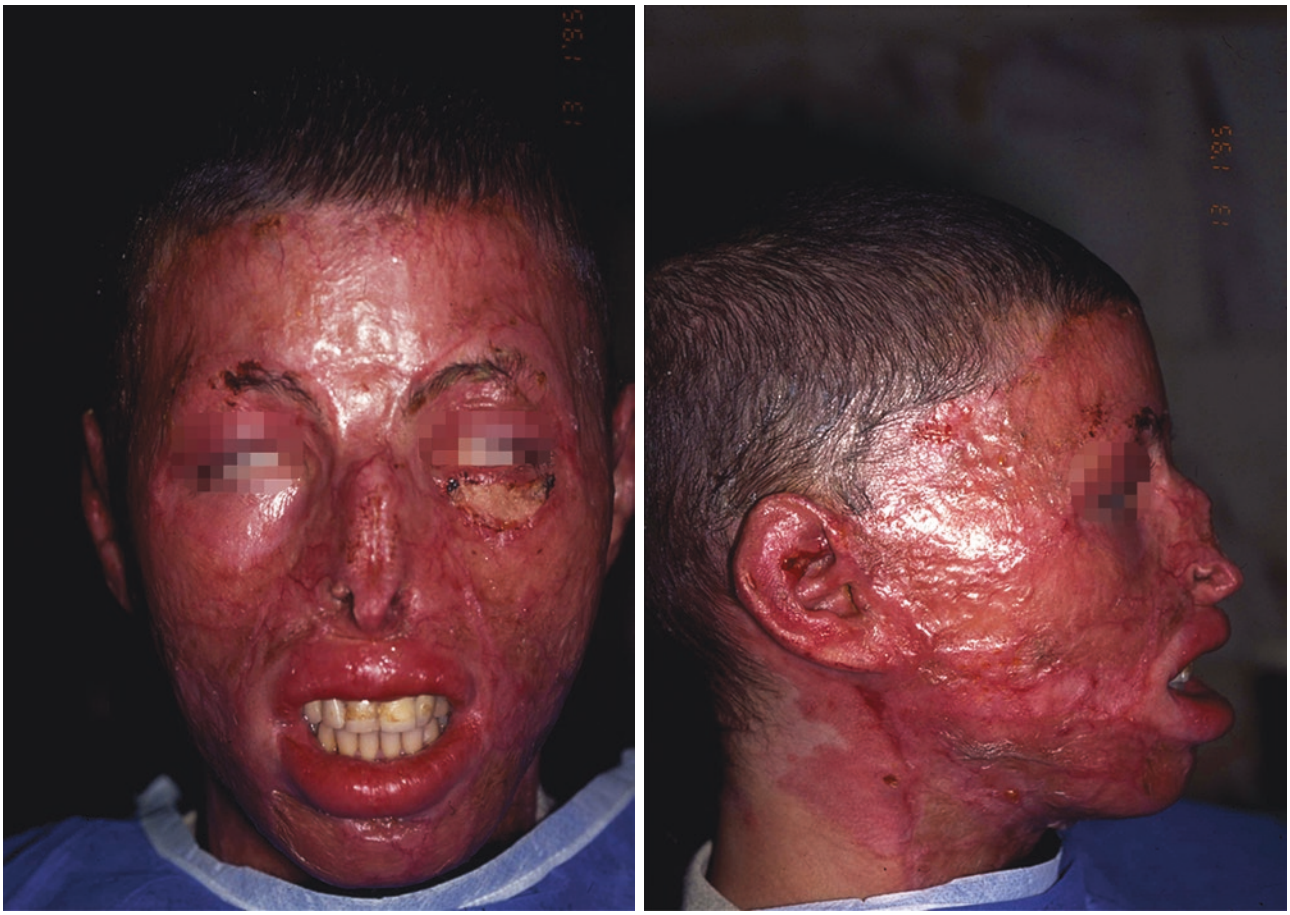

Fig. 38.5 Preoperative aspect face and profile female 28 years old

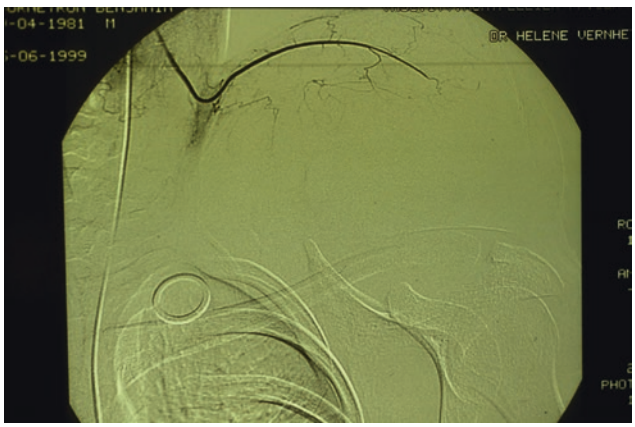

Fig. 38.6 Arteriogram before the second procedure. Note the good vascularization of the pedicle and the branches covering the freshly expanded skin area

life and social exclusion due to scarring as a medical consideration comparable to a life-threatening situation, as it imposed an immunosuppression for life.

In 2015, 12 partial and 5 full facial transplants were recorded in the literature. Procedures included partial and near-total facial myocutaneous flaps and complex osteomyocutaneous grafts [5]. Fifteen patients received fully vascularized grafts, and 2 patients died of transplant-related and infectious complications

Facial transplantation was proposed to restore quality of life and enable social reintegration. Results publishing the first facial transplants created some polemics all over the world. The main discussions were concerning the long-term aesthetic and functional outcomes where more precisely defined outcomes are expected. In addition, significant technical, medical, and ethical issues remain to be solved, such as the secondary late failure and need for a second transplantation, recently reported by two authors [6, 7].

In 2018, Ozkan et al. [8] presented their long-term experiences with a series of five face-transplanted patients in terms of surgical aspects and postoperative outcomes. Possible salvage strategies in case of difficulties were also described. Five patients, four receiving full-face transplantation and one undergoing partial transplantation were included. The

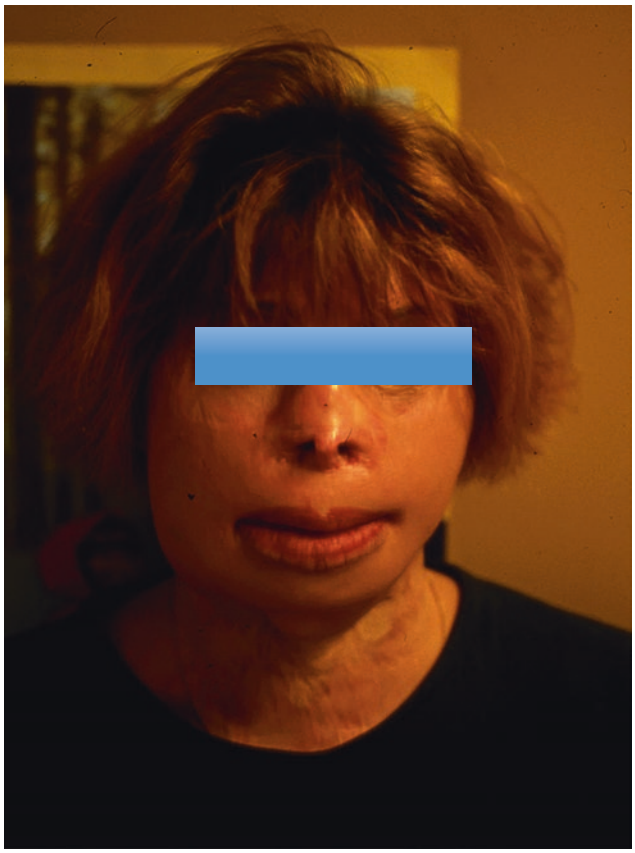

Fig. 38.7 Four years postoperative, the quality of life has strongly improved. This young woman married, had a child, and returned to work

patients were aged between 19 and 54 years. Two had extensive burn scars to the face, and three had suffered gunshot injuries. The posttransplant induction immunosuppressive regimen included ATG plus tacrolimus, mycophenolate mofetil, and prednisone.

Patient files included their etiologies, preoperative preparations, surgical techniques, immunosuppressive regimen, postoperative courses, revisional surgeries, together with challenges including acute rejection episodes, and immunosuppressive drug complications.

No re-surgery due to vascular compromise was required in any case. One of the five patients was eventually lost due to complicated infectious and metabolic events 11 months posttransplantation. The other four patients were still alive, with a mean follow-up time of 53 months, and had satisfactory functional transplants and cosmetic appearance.

Potential complications may be linked to compliance and psychological maturity of the patients, the risk of opportunistic infections, and malignancies.

These situations need be resolved for it to be accepted as a safe procedure.

Advantages and Limits of the Homologous Transplantation

After more than 50 transplants, the concept of "face transplantation" has emerged even if several considerations should be mentioned: the immunological science used for these transplantations is derived from the ones used in organ transplantation, and the antirejection regimen should be adapted to the rejection levels of the transferred tissues, their rejection capacities depending on their structure and vascularization (skin, muscle, aponeurosis), etc. The number of cases already realized all over the world is limited, and each case has his/her own multifactorial problems, linked to their own medical history, the preoperative difficulties during transplantation, the rate of opportunistic infections, and the compliance of the patient [9].

The ethical discussions ended with a mandatory preliminary authorization for transplantation in most of the countries where they were realized. This frame has limited the number of cases but opened a disruption in the "no-harm" principle, due to the risk of potential complications induced by immunosuppression in a non-vital medical situation. However, the intense need for more social inclusion of these abandoned patients has transformed the conservative approaches into more progressive possibilities.

38.3 Critical Analysis of the Literature

The scarce literature concerning large face reconstruction is the reflection of the limited number of patients presenting a scar incompatible with a minimal social life or the difficulty to find surgical teams able to sustain a complex program including microsurgery, multiple actors, and adapted rehabilitation and care. The choice between the two strategies may be led by other considerations, like the ethical problem of submitting the patient to immunosuppression for the rest of his/her life. Several authors have considered this as a progress opening the way to a large diffusion; others have simply refused to consider that facial tissues would be compared to any organ transplant performed on a daily basis all over the world like the kidney, pancreas, lung, or heart.

In conclusion, extensive facial scars remain a difficult challenge for reconstruction. Even in highly sophisticated teams, the capacity of a homologous facial transplantation needs to be prepared. The technique demands

a permanent immunosuppression, and even if the ethical problem was more or less solved, the opportunistic infections remain a risk, and the long-term consequences are unknown in terms of life-threatening issues. The techniques imposing a long-term preparation like skin expansion plus or minus microsurgical revascularization are more usual. The specificity of the transferred tissues is less fine than with a complete homologous transfer and will need complementary techniques (fatty tissue removal or fat injections, makeup, etc.). A more EBM-based approach is needed to compare the results and mainly quality of life after allotransplantation versus auto transfers.

Take Home Message

Face disfiguration represent difficult cases where the technical capacities of restoring a normal face using long and complex surgical techniques have to be weighed to the motivation and understanding of the patient. Psychological testing should be realized before proposing surgery, in order to prevent disillusions and bad feelings afterward and to drive the patient toward the right choice to do. All potential complications have to be explained, as well as the length and risks of each procedure, keeping in mind that some strategies will need several procedures and that the final result will only be visible a long time after the last procedure.

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Invasive Techniques in Scar Management: Fat Injections

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Background

Since the end of the nineteenth century, fat grafting has become one of the most promising treatments for aesthetic and reconstructive purposes. Its very first application dates back to 1889 when Van der Mullen used fat grafting to treat a diaphragmatic hernia; some years later, in 1893, Neuber A. treated posttraumatic depressed facial scars with a small-dimension autologous fat graft taken from the forearm. Neuber, indeed, noticed that the application of small pearls of fat, compared with the bigger ones, could bring to better aesthetic results. Later, in 1910, Lexer reported the application of the autologous fat grafting for facial rejuvenation; in fact, he uses the fat as a filler for periorbital and facial wrinkles. During his experience, Lexer noted that, in order to obtain a good aesthetic results, the fat should not be damaged during the taking procedure.

In the same period, authors reported their experience with the engraftment of fat tissue, and in 1911 Brunning noticed that fat graft could be reabsorbed.

From 1912 to the Second World War, many studies have reported on the application of lipofilling for "aesthetic purpose" as treatment of the scars; but in the meantime, researchers such as Wasserman in 1926, and later Neuhof, Shapiro, and others, demonstrated that the fat grafting was a "living tissue" in which there were present preadipocytes which could later become mature adipocytes. They also noted that even if there were a degenerative process for the first months after the implantation, later there was the presence of a regenerative process with a full transformation of the preadipocytes in mature adipocytes after 5 months.

But it has been only during the end of the twentieth century that the real features and potentiality of the autologous fat graft started to become clear. In fact, it was only during that period that researchers started to demonstrate the presence of stem cells, the adipose-derived stem cells, which could survive after the transplantation and regenerate the adipose tissue. Nowadays, it is a common opinion that there are three zones that arrange the autologous fat grafting: (1) the outer one called "surviving zone," (2) the intermediate one called the "regenerating zone," and(3) the inner one called the "necrotic zone."

As the name suggests, the intermediate zone or regenerating zone can replace the dead adipocytes in necrotic/center area; this process is allowed by the presence of the so-called stromal vascular fraction (SVF). The SVF indeed consists in a multiple cellular lineage composed by fibroblasts, pericytes, endothelial cells, and mesenchymal stem cells which composed the "adipose-derived stem cells" (ADSCs) and which can promote wound healing stimulating the reepithelization and neo-angiogenesis.

But how can ADSCs do this?

39.1 Adipose-Derived Stem Cells: Their Biological Properties

Obtained by a lipo-aspiration procedure, ADSCs can be found in large quantities, representing a fraction of 1/500–1/1500 cells for a total of 5000 per cell each gram of fatty tissue taken, with stem potential 500 times higher than the medullary equivalent.

The adipose-derived stem cells have both a regenerative and a volumetric effect due to multiple mechanisms:

1. They produce a sort of filler effect because of the direct differentiation of the preadipocytes to mature adipocytes. This differentiation is promoted by an auto-paracrine stimulation too.
2. They have an antioxidant effect and protect against damage due to ischemia reperfusion, reactive oxygen species (ROS), and hypoxia.
3. They induce angiogenesis promoting the perfusion of the treated area, supporting existing vascular structures, and having a paracrine promotion of angiogenesis.
4. They modulate inflammation suppressing the T- and B-cell proliferation via NFkB-mediated mechanism; they also produce IL6 and IL8. These cytokines can recruit monocytes and macrophages in the site of injury because of their chemoattractive role.
5. They modulate the granulation tissue and other processes as fibrosis and/or reepithelization. In fact, they upregulate type I procollagen a1mRna, and they stimulate the migration of keratinocytes and fibroblasts.
6. They secrete lymphangiogenic factors.
7. They recruit systemic endogenous stem cells via a home chemokine gradient to the area of injury.

39.2 The Guidelines

As every procedure, the free fat grafting also has to follow some guidelines. From 2007 to 2014, the US Food and Drug Administration and the American Society of Plastic Surgeons (ASPS) and American Society for Aesthetic Plastic Surgery (ASAPS) proposed many guidelines [1, 2], but it has been only in 2016 that there have been clear guidelines. In fact, FDA defined the adipose tissue as a "structural tissue" because it is a "connective tissue that stores energy in the form of lipids, insulates the body, and provides cushioning and support for subcutaneous tissues and internal organs"; but this definition restricted its use. Nowadays, the guidelines can be summarized as follows:

1. *The graft should be taken and used in the same patient at the same session. Delayed grafting is not allowed.*
2. *The graft should be minimally manipulated.* Based on the definition given by FDA, the minimal manipulation is "a process that doesn't alter the original features of the tissue, which maintains its utilities." *The graft shouldn't be sizing*. Even if centrifugation is consid-

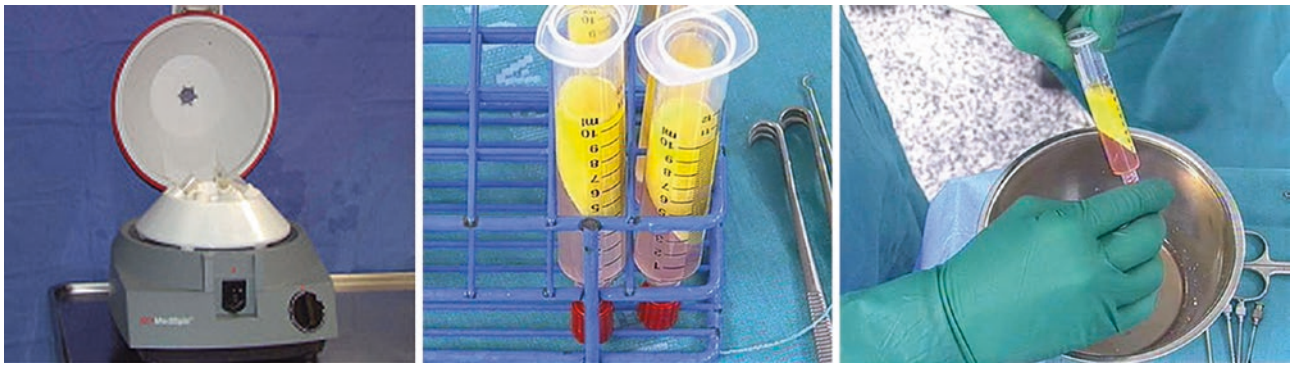


Fig. 39.1 Centrifugation

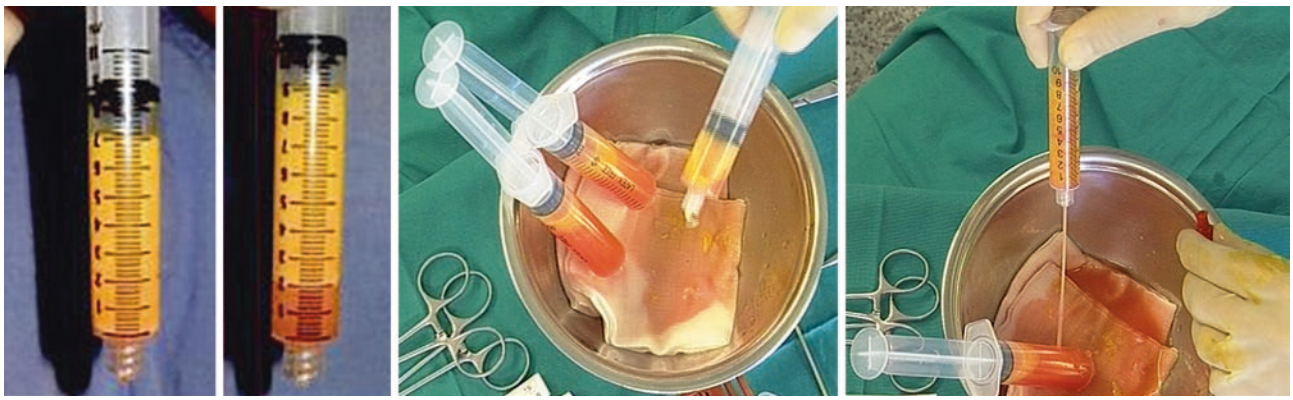


Fig. 39.2 Decantation

ered a sizing procedure, nowadays the immediate centrifugation at low speed (3000 rpm for 3–5 minutes) is allowed, but decantation and mechanical purification are preferable, because they don't alter any features of the tissue (Figs. 39.1 and 39.2).

3. *The manufacturing of the graft may not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent. Enzymatic process is not allowed. Separation and reinjection of the stromal vascular fraction are not allowed.* Till some years ago, enzymes were permitted to be used as collagenase in order to "upgrade" an adipose stem cell (ASC)-poor fat. In fact, the collagenase could disrupt the link between the ASC permitting to add some freshly isolated stromal vascular fraction in order to obtain a so-called ASC-enriched fat. Nowadays, this enzymatic process is considered manipulation, so it cannot be allowed. Also, today it is possible to prepare the adipose tissue with a tumescent solution, and the lipoaspirate obtained can be added with sterile saline without altering the tissue. This process guarantees the keeping of the original features of the tissue, but it doesn't help us in increasing the engraftment of the free fat graft; so, as we will see later, we can use some ancillary procedures to increase the survival of the fat grafting, as plasma-rich platelet.
4. *The graft has to be harvested with sterile technique; the contact with air has to be minimal*. In order to perform this process, a so-called closed system has to be used that is featured by a sterile disposable canister for collecting, separating, concentrating, and transferring the fat graft (Fig. 39.3).
5. *The graft has to be taken with small cannulas (3–4 mm) and injected with 2–2.5 mm cannulas in a retrograde way (retrograde fat distribution)*. Actually this is not a new guideline; indeed it was there already in 1893 when Neuber A. treated scars noticing that small-dimension fat graft could be more effective than bigger one (Fig. 39.4).

39.3 The Procedure

Set up by Coleman in 1925, in order to improve overall adipose cell survival, the procedure is featured by a tumescent technique lipo-aspiration with cannulas or micro cannulas from regions as, for example, the abdomen, medial thighs, hips, and trochanteric region. The fat taken can be centrifuged for 3000 rpm for 3–5 minutes or decanted in order to separate the oily part, which can be calcified if injected, from the seric part and the "real" fat. After being separated, the adipose tissues are injected, with small cannulas, in other regions as, for example, the face. The lipofilling

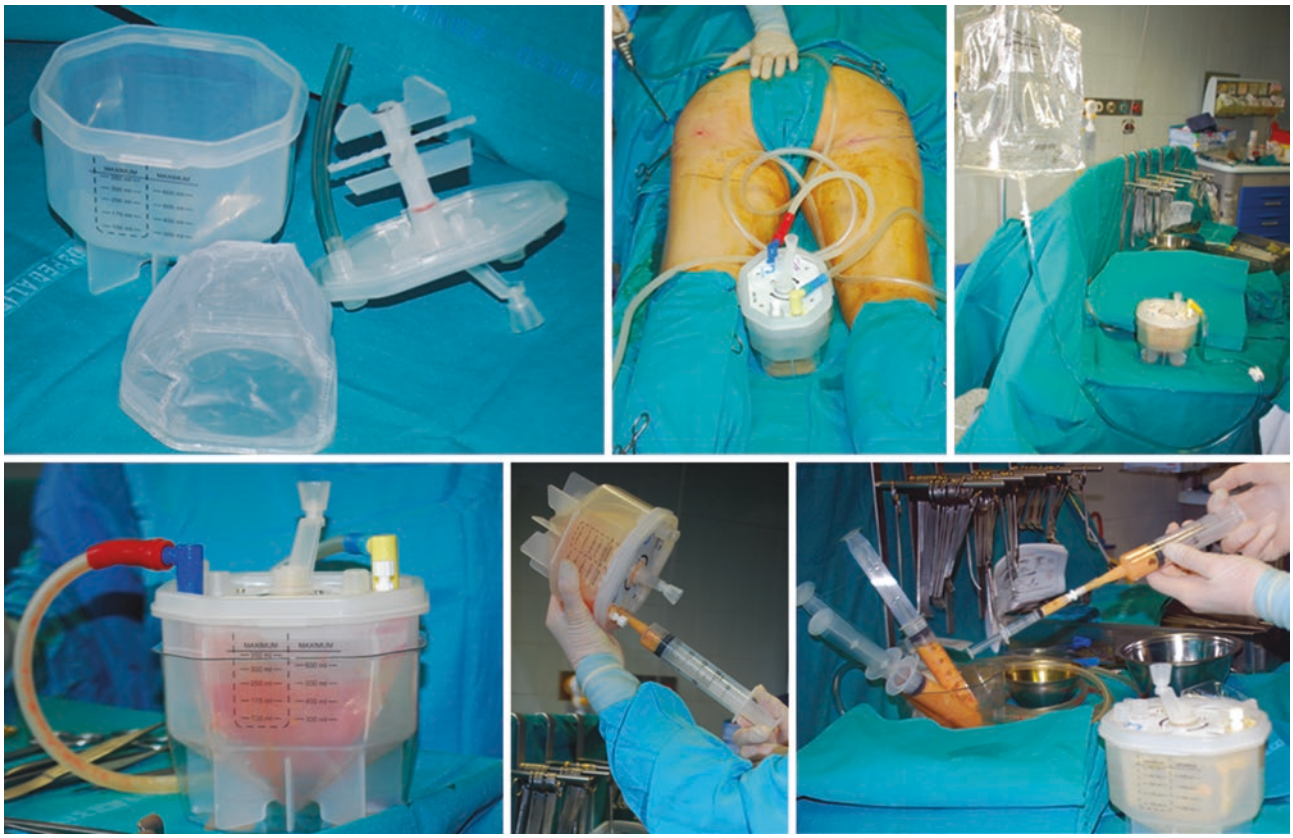
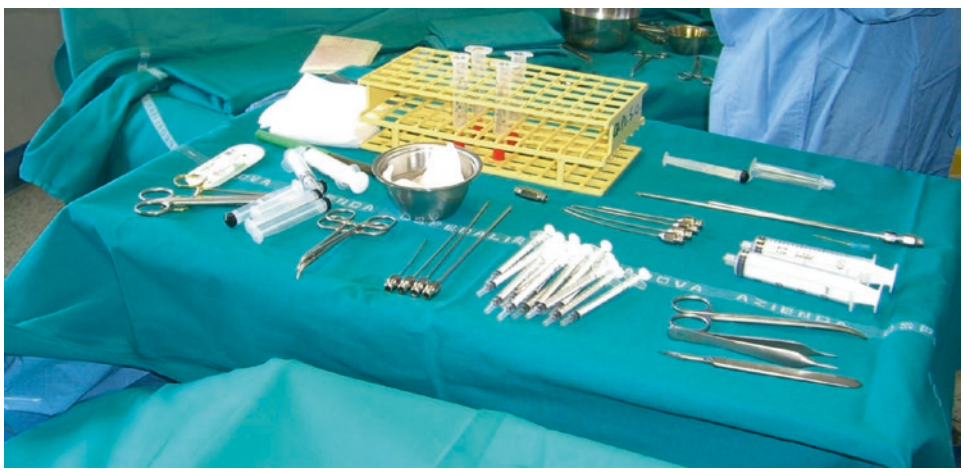


Fig. 39.3 Closed system

Fig. 39.4 The cannulas



procedure can be executed under general or locoregional anesthesia; it depends on the volume of adipose tissue that we have to take and on the area that has to be injected. The procedure is not free of peri- and postoperative complications such as infection, hematoma, or calcifications.

It also has to be also considered that the free fat grafting can be physiologically reabsorbed. Unfortunately, the engraftment percentage is a subjective parameter, and it varies from 10% to 70% and in some comes till a total reabsorption. This feature can be brought to multiple sessions in order to obtain the correct volume.

39.4 The Free Fat Grafting and Scars [3–9] (Figs. 39.5, 39.6, 39.7, and 39.8)

Considering its biological properties, we can propose the free fat grafting both to stimulate wound healing and to treat or prevent scarring, because it can act and improve more than one feature of a scar:

1. *The skin texture, thickness, and pliability*
2. *The volume and contour*
3. *The fibrosis*
4. *The pain*

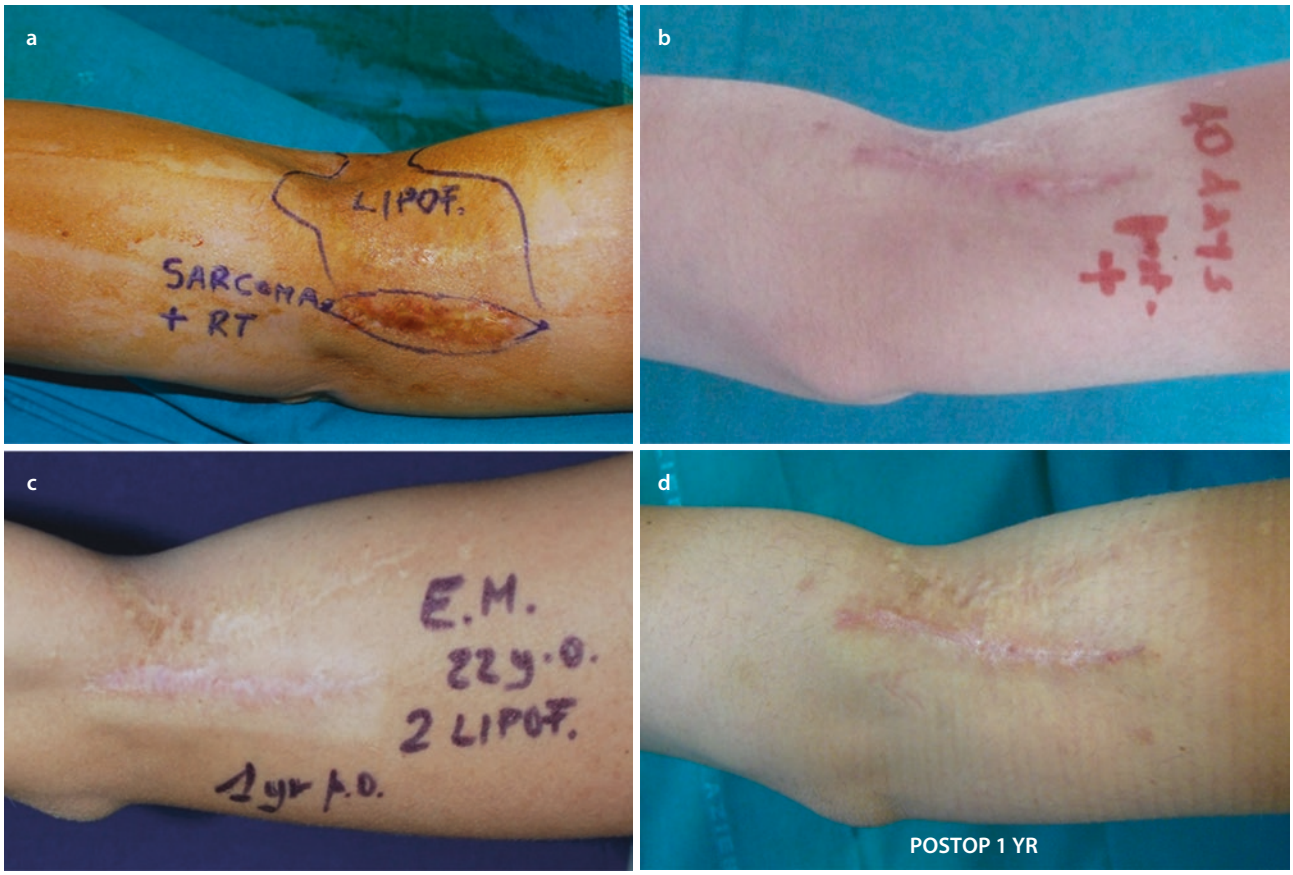


Fig. 39.5 Skin texture and color: **a** Pre-lipofilling after radiotherapy for sarcoma; **b** 40 days postop; **c** preop second lipofilling; **d** post-second lipofilling at 1 year

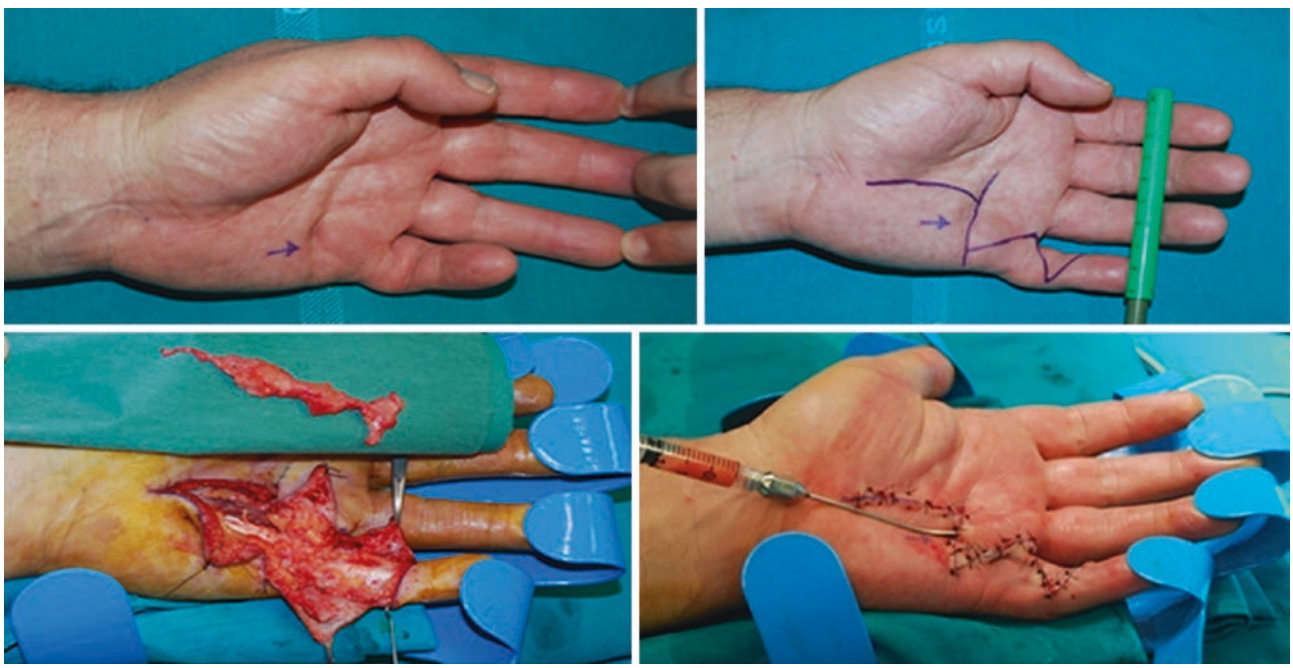


Fig. 39.6 Fibrosis control in Dupuytren's disease

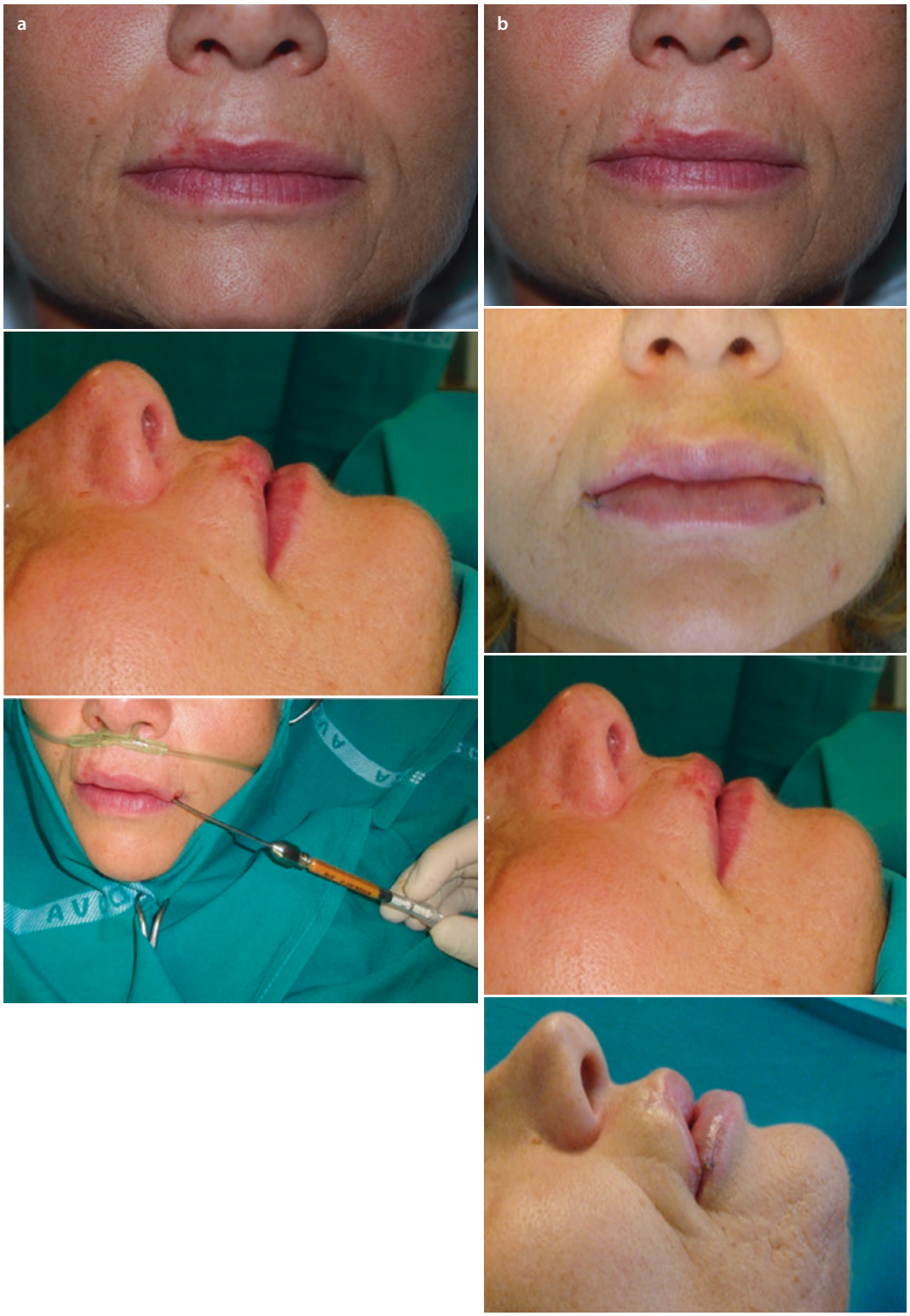


Fig. 39.7 **a** Volume and contour: dog bite scar; pre-lipofilling; interoperative. **b** Volume and contour: postoperative results

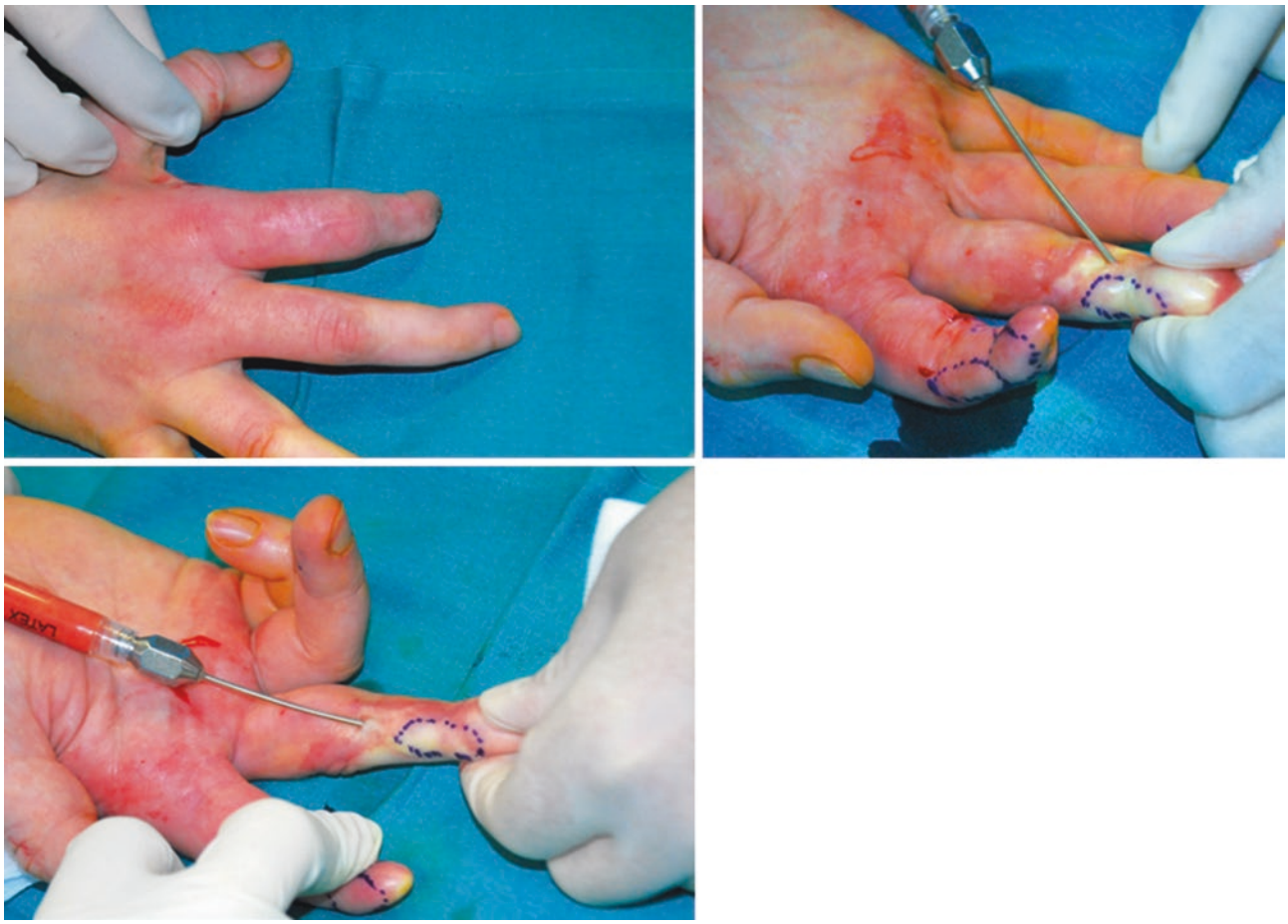


Fig. 39.8 Pain and nerve release: posttraumatic nerve entrapment

39.4.1 The Skin Texture, Thickness, and Pliability

As demonstrated in 2009 by Mojallal et al. in an experimental mouse model, the transplantation of human adipose tissue to nude mice brought to an improving in the thickness of dermis. These results were obtained, thanks to a stimulated neosynthesis of type I collagen fibers, with a consequent composition of a denser extracellular dermal matrix. This skin feature improved its texture, thickness, and pliability.

Some years later, in 2013, Klinger M. et al. performed a study on humans, and they noted that the areas treated with free fat grafting assumed features that were similar to normal skin in terms of elasticity and softness. In order to demonstrate these features, they also used a durometer evaluation that demonstrated a significant reduction of skin hardness.

But why do ADSCs behave this way? As we said earlier, ADSCs can modulate and reduce inflammation; studies demonstrated that there is also an improvement in melanin secretion. These last utilities can also modify the skin color, thereby reducing the erythema and improving normal color of the skin.

39.4.2 The Fibrosis

Related to skin thickness, fibrosis can be due to diseases as, for example, connective tissue diseases or Dupuytren's disease or treatment such as radiotherapy. We used lipofilling in the treatment of a specific connective tissue disease called scleroderma or systemic sclerosis. This systemic connective tissue disease is featured by a progressive skin fibrosis especially on the face and in particular in the perioral region which brings to the so-called microstomia. The patients affected (usually female) report a bad lips sensation and progressive mouth dryness, difficulty in speaking, oral hygiene, and feeding. In our experience, the application of fat grafting

in perioral region has improved the symptoms reducing skin stiffness and improving opening the mouth.

Regarding the use of lipofilling in Dupuytren's disease, this pathology is due to a fibrotic degeneration of the longitudinal fibers of palmar aponeurosis, with the consequent involvement of subcutaneous septa, the loss of subcutaneous fat, and the adherence of dermis to palmar aponeurosis. In this case the autologous adipose tissue is used as adjuvant therapy to prevent the formation of new fibrotic tissue (Fig. 39.7).

Finally, regarding radiotherapy, the fibrosis is a sort of adverse event that rises years after the end of radiotherapy treatment and that it is due to the presence of an important post irradiated fibro-necrotic tissue featured by local dystrophic fat lobules, smaller but thicker vessels, and a perivascular fibrosis. In this case the fat grafting reduces the necrotic areas and improves neoangiogenesis with a consequent increasing in skin quality. It is supposed that these results are due to the intrinsic ability of the ADSCs to secrete growth factors, as angiogenic ones, as we said earlier.

39.4.3 The Volume and Contour

As we said earlier, the free fat grafting has a trophic/volumetric effect. As Mojallal noticed the autologous free fat grafting has to be considered as a *dynamic filler*. In fact, the "fat filler" doesn't have only an immediate effect of restoring volume, but it has the ability to produce adipogenesis with the consequent transformation of the preadipocytes in mature adipocytes. This can bring to an increased volume of the soft adipose tissue. The plasticity that features the adipose tissue makes it a good filler to restore the contour too, not only in posttraumatic scars but also in postoperative deformities and/or congenital malformation or adult progressive and self-limited deformation as, for example, in Parry-Romberg syndrome (the adult hemifacial atrophy).

39.4.4 Pain: The Analgesic Effect

According to Coleman who demonstrated the positive effect of free tissue transfer on neuralgias, Riyat et al. published in 2017 a review in which they noticed as the lipofilling had an analgesic effect, demonstrated with tests as, for example, POSAS or McGill Pain Questionnaire, on 966 patients. This effect seems to be due to multiple aspects: first of all, there is a mechanical release. To perform the injection, we have to insert the cannula under the scar in the space of the dermo-hypodermal junction, and then we proceed to distribute the fat in a retrograde way to reproduce a sort of a weblike matrix. This procedure can mechanically release fibrotic adherence and nerve entrapment, but most of all, the presence of the adipose stem cells can stimulate the nerve repair mediated by the brain-derived neurotrophic factor (BDNF), an adipose-derived neurotrophin which is fundamental in nerve growth and repair. But this is not the only mechanism to improve analgesic effect: as we said earlier, fat tissues are featured by an anti-inflammatory effect which is mediated both by the TGFβ production that can modulate and suppress T-cell function and by the production of IL 10 a cytokine which is abundantly produced by ADSCs and is known to inhibit Cd4 and CD8 lymphocytes reducing the inflammation response.

39.4.5 The Possible Applications

Based on the aforementioned effects, we can propose the free fat grafting for the treatment and prevention of multiple kinds of scars such as the following:

1. The treatment of atrophic and/or depressed scar, for example, in case of acne or previous removal of bulky neoformations. In case of atrophic and/or depressed scar, the free fat grating can be used both for a volumetric effect, indeed it fills the empty spaces, and for regenerative effect, indeed it can improve the skin texture.
2. The treatment of retracting scars which can limit not only the aesthetic point of view but also many functions as the flexor extension of the neck or of the elbow. In this case we can associate fat grafting with surgery as z-/w-plasty or flaps.
3. Unstable posttraumatic scars in order to obtain both scar stabilization and to improve wound healing.
4. Fibrotic diseases such as Dupuytren's disease and connective tissue diseases such as scleroderma, as we said previously.
5. Fibrotic irradiated tissue.
6. Fibrotic response to foreign bodies named periprosthetic fibrotic and, often, contracted capsule: this response can be described as a pathological and excessive deposition of collagen fibers around a mammary implant, in this case, the lipofilling.
7. Postsurgical deformities.
8. Nerve release in case of neuromas or posttraumatic pain.

39.5 The Ancillary Procedures to Increase the Overall Survival of Adipose Cells

39.5.1 The Plasma-Rich Platelet [10]

Known as PRP, it is a product obtainable by a blood draw of at least 20 cc. It is featured by a high concentration of platelet >300–350 × 10^3 platelets/μL, (three to five times than normal) and the production of growth factors, including *PDGF*, *TGF β*, *VEGF*, *IGF-1*, *FGF*, and *EGF*, released by the α granules of the activated

platelets. These factors promote tissue repair, modulate inflammatory processes and neoangiogenesis, and ultimately regulate homeostasis of tissue and regenerative process. The PRP is easily obtainable without morbidity for the patient, and it can be associated to free fat grafting during the same session, in order to increase the percentage of engraftment and to improve the overall adipose cell survival.

39.5.2 The External Volume Expansion [11]

In order to improve on-site adipogenesis and overall adipose cell survival, a new technique called external volume expansion (EVE) is being used in these years. This procedure is based on tissue expansion combined with the mechanobiology principles which explain how mechanical forces, such as the ones produced by the application of the negative pressure therapy, can be transduced in the cells in order to stimulate processes as cellular shaping, proliferation, and differentiation. In fact, studies demonstrated that the EVE application can increase cell proliferation, deep dermis capillary density, and adipogenesis due to the edema and inflammation response which are proadipogenic factors.

39.5.3 The Future

Recently the fat graft has been proposed for the treatment of keloids or hypertrophic scars. Keloid is a fibroproliferative disorder which is known as pathological scar, and it is featured by an excessive production and deposition of extracellular dermal matrix due to prolonged inflammatory and proliferative phases of wound healing. Nowadays, there is not a gold standard treatment for pathological scars; it is actually based both on prevention with compressive garments or silicone gel or sheets both on topical injection of keloid with anti-inflammatory drugs as corticosteroids. Based on the anti-inflammatory properties of the free fat grafting and on its ability to stimulate neoangiogenesis and a better skin quality, it has been proposed to use it in the treatment of hypertrophic/keloid scars, for example, in postburn patient. Even if the first impressions are absolutely positive, unfortunately, as Lee G et al. noted in 2017, there is a lack of high-level literature about this field, so further studies are required.

39.6 Something to Discuss: The Oncological Point of View

Even if the adipose tissue transfer has multiple benefit effects, recently it has been supposed that the pluripotent adipose-derived stem cells and the neoangiogenesis stimulated by growth factors can bring to the onset of a new neoplasia or a recurrence if the free fat graft is injected in a recipient site which is recently affected by a cancer, especially in a breast that has undergone a nipple-sparing mastectomy or a partial mastectomy (quadrantectomy). Many studies have been performed in order to demonstrate the safety of the fat grafting in such patients, but nowadays, even if a correlation between lipofilling and neoplasm or its recurrence has not been demonstrated, it is preferable to propose the free fat transfer after 2 years free of disease.

39.7 Conclusion

In light of our experience, the free fat grafting is considered an effective and promising treatment for scars. The biological properties of ADSCs combined with an easy and quick procedure, a low morbidity for the patients, and a high compliance make lipofilling an ideal treatment to propose. Unfortunately, the treatment has some limitations. First of all it cannot be proposed to a very slim patients; in fact we need fatty areas to obtain ADSCs; secondly, as we said earlier, the percentage of reabsorption of fat grafting subjectively varies from 10% to 70% till the complete reabsorption in extreme cases. This negative feature can result in multiple treatment sessions in order to obtain the right volume, but unfortunately it is not possible to set the number of sessions required since the beginning.

Fortunately, new studies and new research on cell therapy help us to avoid or reduce this problem, as we saw that the use of the external negative pressure therapy and/or the combination of free fat grafting with the plasma-rich platelet can improve the fat engraftment and the overall adipose cell survival with consequent better morpho-functional results.

Take Home Messages

- The fat grafting contains stem cells called adipose-derived stem cells.
- The adipose-derived stem cells are pluripotent cells.
- The fat grafting is an easy procedure with low morbidity rate.
- The fat injection has both a volumetric and a regenerative effect.
- The fat injection stimulates neo-adipogenesis and neoangiogenesis, and it modulates inflammation and fibrosis.
- The fat grafting can be reabsorbed.
- We can use external volume expansion and/or the combination with plasma-rich platelet to improve engraftment and overall adipose cell survival.

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Additional Invasive Techniques in Scar Management

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40.1 Background

Soon after the discovery of radiation, radiotherapy was recognized as a treatment technique for tissue overgrowth. Also, hypertrophic scars and keloid disorder were treated both therapeutically and for prevention of recurrent growth following surgery.

Both patients and care providers might hesitate about radiation treatment considering the associated ominous reputation and tissue burden. While radiation treatment represents a significant burden, for the patient as well as financially and logistically, it is also safe and characterized by low recurrence rates, high patient satisfaction, and, in combination with excision, excellent aesthetic results. Therefore, when other techniques fail in preventing keloid disorder recurrence, radiation treatment is a valid option and should be considered.

This chapter will provide an overview of the history of radiation treatment for keloid disorder. The available techniques and suggested dosages, as well as the authors' experiences and vision on indications and biological working mechanisms, are described.

40.2 Introduction

Soon after the discovery of X-ray technology, radiation was recognized as a possible treatment modality for excessive tissue growth. Like malignant tumors, aberrant scars are proliferative tissue overgrowths and were therefore also considered valid targets for treatment with radiation. L. Freund first described the positive effect of roentgen treatment on a hypertrophic scar in 1898. Harris then described the same effect on a keloid disorder in 1901, whereas Wickham recommended radium for the treatment of keloid scars. Already in 1909, Freund combined surgical excision of the keloid with postoperative radiation, where he left the wound open and waited 2–3 days before starting radiation treatment [1]. In the following period, various treatment protocols were described using external radiation with relatively good results. Folke Jacobsson described in 1948 that in 625 cases treated, a total regression of 73.6% was achieved, most of which with radiation alone (*The Treatment of Keloids at Radiumhemmet*, 1921–1941).

External beam radiation therapy uses a radiation source which emits energy onto the target area. The disadvantage of this technique is that it gives a relatively high dose to the adjacent healthy tissue due to the large distance between the radiation source and the target.

Brachytherapy, where the radiation source is placed inside or adjacent to the area requiring treatment, was pioneered in medicine soon after the discovery of radioactivity in 1896 and was widely used in the 1930s to treat various sorts of tumors. The benefit of brachytherapy over external radiation therapy is the ability to deliver radiation as very localized and enabling a higher dose with fewer side effects and fewer treatments needed for the same effect. Brachytherapy for the treatment of keloid scars is nowadays always combined with excision.

After an enthusiastic start, the usage of brachytherapy declined due to the problematic radiation exposure for staff and patients while handling the radioactive materials. The advent of novel radiation delivery methods and the use of new radioactive sources in the 1950s and 1960s caused a renewed interest in brachytherapy. Current remote afterloading devices provide safety by manually placing a hollow catheter (◘ Fig. 40.1b) first and then loading the radioactive source later through the catheter. It was not until 1976 that Malaker et al. introduced this technique for keloid treatment. Current methods focus on excision of the lesion followed by adjuvant radiation therapy. Although this method offers total scar eradication with an optimal aesthetic and low recurrence rates (mean, 10.5%), its use is limited due to significantly higher costs in comparison with other treatment options, as well as availability of the technique in the hospital and the need for more advanced specialist care (e.g., plastic surgeon/dermatologist/radiation oncologist with interest in keloid scar treatment).

40.3 Types of Radiation Therapy

40.3.1 External Beam Radiation Therapy (EBRT)

The classic form of radiation therapy uses a radiation source which emits energy onto the target area. Regular X-ray radiation is probably the most widely available and least expensive radiation option. It does not penetrate too deep, so underlying structures remain undamaged. Due to the inaccuracy of the technique, however, more skin side effects are seen. In superficial radiation therapy (SRT), low-energy X-rays (the same range as diagnostic X-rays) emit photons at 20–150 kV reaching an effective depth of 3.5–16 mm. At higher energy of 200–500 kV, an effective depth of 2 cm is reached (orthovoltage radiation). Electron beam radiotherapy uses a linear accelerator to create β-rays. It reaches a depth of 2–6 cm and can be more accurately delivered.

40.3.2 Brachytherapy (Internal Radiation)

In brachytherapy, a hollow catheter is placed either interstitially during closure or superficially on the desired target area (see ◘ Fig. 40.1a–c). After this procedure,

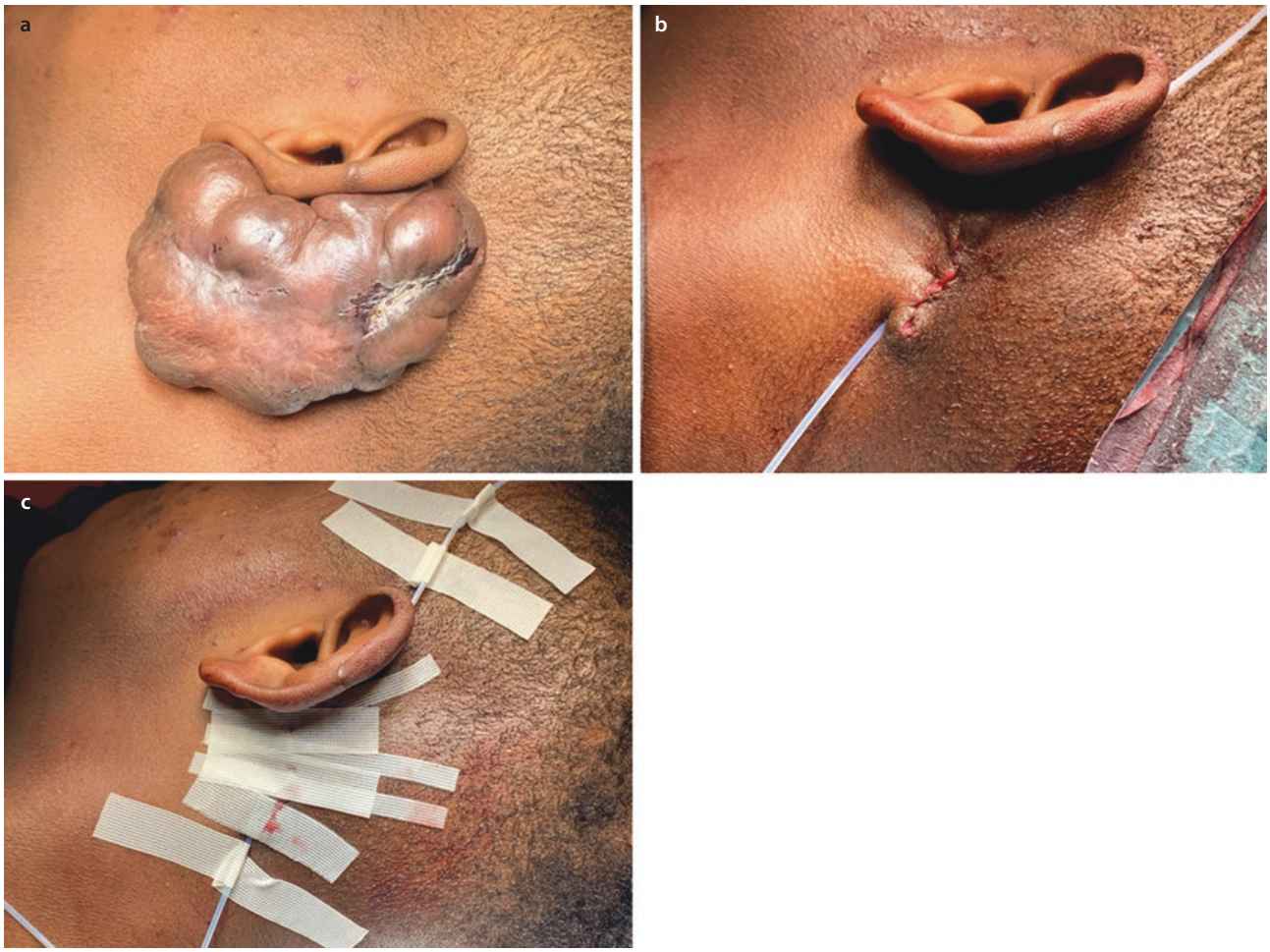

Fig. 40.1 **a** Keloid of the earlobe. After excision, a hollow catheter is placed before closing the wound **b**. The catheter is fixed into place to ensure precise radiotherapy delivery **c**

the catheter is loaded with a radioactive source. The treatment regimen can either be low-dose rate (LDR) or high-dose rate (HDR). In LDR a low-dose-rate radioactive source is used to treat for a longer time frame (20–72 hours). It requires hospitalization in a lightly shielded chamber. In HDR the patient is transferred to a shielded chamber after the excision. Here, a high-dose-rate radioactive source is loaded into the catheter remotely by personnel in a separate area for a short exposure (5–10 minutes). Because of the short treatment duration, HDR can effectively be used as an outpatient treatment option and is therefore preferred over LDR. The main advantage of brachytherapy to external beam radiotherapy is the diminished exposure of surrounding tissue, which also provides the possibility to administer a higher dose in a shorter time frame. Additionally, because the applicator can be shaped to fit the desired area, uneven surfaces will receive the same dose, and deeper structures can be avoided. The most commonly used radioactive source is Iridium-192 which emits γ-rays.

40.4 Excision and Radiation Type

Radiotherapy should be reserved for recurrent keloid scars because of its invasive characteristic and significant cost. It should be noted that both excision-only and radiation-only have higher recurrence rates compared to excision followed by radiation [2]. The keloid is preferably excised in an extralesional fashion [2] and closed primarily. If this is not an option due to the size of the scar or high tension on the wound edges, skin grafts can be used, or excision of the core of the keloid can be performed.

Close cooperation with the local radiotherapy department is necessary to facilitate radiation therapy for keloids. Radiation equipment usually represents a significant cost to any hospital, and keloid treatment with radiation therapy will most likely only be performed in a small fraction of treatments. This means physicians will probably be bound to techniques that are already available in their hospital. Usually, a form of

external radiation will be available, while brachytherapy may be more common in larger medical centers in developed countries.

When planning the procedure, two main considerations should be timing and adequate dosage of the radiation therapy. The first dose should be administered as soon as possible after excision. A clear decrease in recurrence rate was seen in external radiation if treated within 7 hours as opposed to the first 24 hours. HDR brachytherapy should be administered in the first 24 hours after surgery and is also likely more effective in the first 7 hours [3]. Many protocols, therefore, opt to transfer the patient to the radiation department immediately after excision [2]. Choosing the right dosage is important and there is no "gold standard" (yet). The concept of biological effective dose (BED) is important in the radiation regimen to be formed. BED is the measure used to quantitatively indicate the biological effect of any radiotherapy treatment. Because it corrects for the dose per fraction given and the fraction number, it will allow comparison of all kinds of treatments and modalities. In keloid treatment, it would appear that administering less than a BED of 10–12 Gy is correlated with a higher recurrence rate [2]. Literature suggests there seems to be a strict threshold because doses of less than 10 Gy repeatedly report higher recurrence rates. This would also mean that a single fraction could be enough, possibly preventing an overnight stay and/or additional hospital visits. At present, there are not enough studies yet in support of this, and a recent study even found a higher recurrence rate in a 13 Gy single-faction protocol [4]. In a multicenter comparison of HDR brachytherapy, 2 × 6 Gy (BED of 19) treatment gave an equally low recurrence and lower complication rates than using 2 × 9 and 3 × 6 Gy [4]. Administering more than a BED of 20 Gy seems unnecessary in HDR brachytherapy [4]. In the treatment of earlobe keloids with EBRT, a BED of 15–22.5 over two fractions (2 × 10 Gy) was found to be sufficient [5]. In a recent systematic review, HDR brachytherapy achieved the lowest mean recurrence rate, followed by LDR brachytherapy and external radiation therapy (HDR, 10.5 ± 15%; range, 0–44; LDR, 21.3 ± 2.1%; range, 19.4–23.6; external, 22.2 ± 16%; range, 0–72) [2].

40.5 Recurrence

When reviewing the literature, it should be kept in mind that recurrence is often defined differently. It can be described as any regrowth of tissue, mild or total relapse, or even regrowth extending beyond the borders of the original lesion. Symptoms like pain or itching or any other complaint in the operated area not related to radiation may be counted as recurrence. With respect to radiation therapy, recurrence is usually correlated to the administered BED; the higher the BED, the lower the recurrence and vice versa. Since the opposite can be said of complications, a balanced approach should be made toward BED. Recurrence rate is also influenced by location; in a recent meta-analysis, Mankowski et al. found the chest and trunk to have higher recurrence rates (34%) as opposed to the ears (12%) [5]. Furthermore, to properly assess recurrence, a follow-up of at least 1 or 2 years posttreatment should be considered to avoid bias by missing recurrences.

40.5.1 Complications

Complications following radiotherapy of the skin are scored with the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [6]; see Table 40.1. Since radiotherapy influences wound healing, wound-related complications like wound dehiscence, infection, and the failure of the wound to close (chronic wound) are additional entities to consider. The most commonly seen complications are erythema, temporary and permanent pigmentation disturbances, and telangiectasia. Wound-related complications are rarely seen when administering doses as

Table 40.1 Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [6]

Grade	1	2	3	4
Acute	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Late	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration

discussed earlier. Reported recurrence and complication rates vary. A recent retrospective study comparing 2 × 9 Gy, 3 × 6 Gy, and 2 × 6 Gy reported minor complications in 57%, 40%, and 33.7%, respectively, and 18.6%, 13.8%, and 3.3% major complications, respectively. Recurrence was the same for all groups (25%) [4]. Pigmentation complications are more commonly seen in people with a darker skin (Fitzpatrick V–VI) who seem to benefit from brachytherapy in which the irradiated area is greatly reduced [7]. It should be noted that pigmentation differences are less prevalent in brachytherapy in comparison with cryotherapy [8]. Furthermore, HDR brachytherapy yields good results in patient-reported outcomes such as the Patient and Observer Scar Assessment Scale [7].

40.6 Safety Concerns

When administering radiotherapy for benign diseases, concerns will arise about the risk of inducing secondary malignancy in the treated area. As of now, only a few cases have been described in external radiotherapy, and Ogawa et al. found the risk to be very low, with an estimated incidence of 0.1–0.0335% [3]. No cases of late malignancy have been described while using brachytherapy. Of course, the possibility should be mentioned when discussing therapeutic options with the patient [3].

40.7 Additional Thoughts on the Biomechanisms of Radiotherapy in Keloid Treatment

The working mechanism of radiation therapy to prevent the recurrence of the keloid scar is still the subject of research. Initially, the application was based on the principle that radiation inhibits tissue growth, and since both keloid disorder and hypertrophic scars are considered tissue overgrowth reactions, they were treated as such. Early irradiation, within 7 hours of surgery, has been shown to result in lower recurrence rates as opposed to a later moment [2]. This suggests that interfering in the early stages of wound healing is paramount in preventing recurrence of the disorder. Radiation is especially harmful to dividing cells; the fact that particularly the most proliferative cells are vulnerable explains its effectiveness in treating cell overgrowth.

Fibroblasts have been linked to keloid disorder for a long time, and ionizing radiation has been proven to influence keloid fibroblast proliferation [9]. Current theories consider keloids to be an immunological problem where endothelial cells and neovascularization may play a pivotal role as well [10]. During surgery or trauma, the tissue is damaged, and blood vessels are severed. To provide the upcoming immune cells and fibroblasts with enough nutrients and oxygen, new blood vessels are formed along the wound edges, while the surroundings of the wound show redness as a sign of vasodilation. This process starts during the first hours following wounding [11]. Endothelial dysfunction has been linked to abnormal wound healing [10, 12, 13], so by suppressing endothelial cells and therefore angiogenesis due to radiation, the formation of dysfunctional blood vessels could be prevented and inflammation decreased, ultimately potentially suppressing keloid formation and preventing recurrence [1, 10].

In the classic definition, hypertrophic scarring is confined within the boundaries of the original lesion, whereas a keloid scar grows beyond its boundaries. However, in close visual inspection of hypertrophic scars, we see that they also can extend beyond the borders of the original lesion. The extension beyond the scar borders is less compared to keloid disorder, and the ongoing process of scar formation stops earlier. In the case of keloid disorder, the vascularity is the highest just around the keloid as may be observed clinically during excision (◘ Fig. 40.2).

40.8 Conclusions

Radiotherapy is a last resort option for recurrent and therapy-resistant keloids and hypertrophic scars. It represents a significant burden, both financially and logistically as well as to the patient. On the other hand, It is a very efficacious treatment option (in preventing recurrence) while obtaining the most optimal esthetic result. It is a safe procedure and most patients experience no or minor side effects. The therapeutic goal should be to try and excise the entire keloid (extralesionally) and start radiation treatment as soon as possible, preferably within 7 hours. Between external radiation and LDR and HDR brachytherapy, the most preferable option is high-dose-rate (HDR) brachytherapy because of the

- Ability to customize the device per treatment area, therefore only radiating the target area while minimizing radiation damage to the healthy surrounding tissue
- Lower total BED compared to external radiation to achieve the same effect
- Ability to deliver the desired BED in a short period of time, allowing an outpatient setting

The optimal dose appears to be around a BED of 20–30 Gy; however, more research works are needed to determine treatment protocols. Physicians should adjust their therapies on the merit of experience and existing

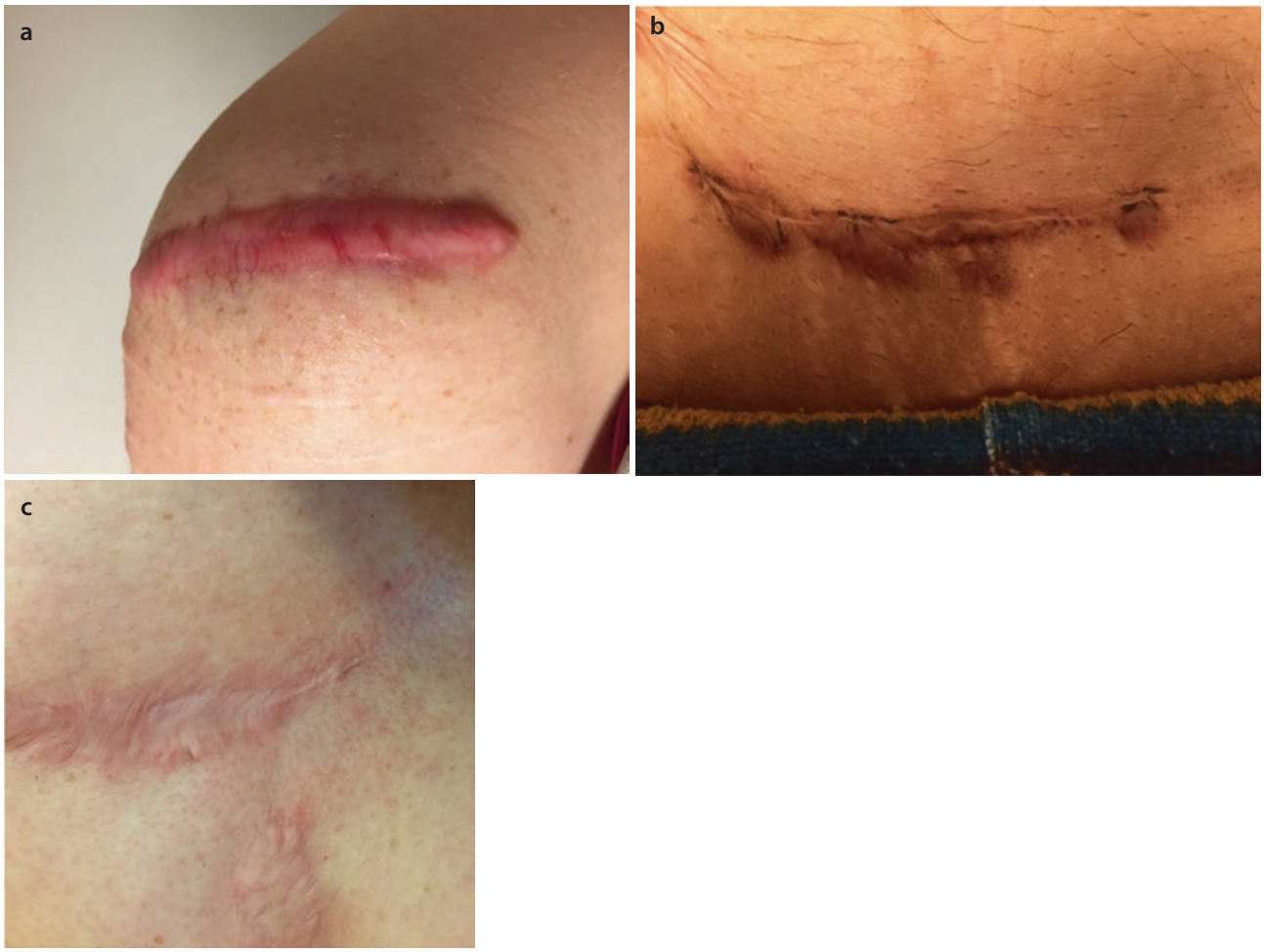

Fig. 40.2 **a** Hypertrophic scar on the shoulder (age 18 months) with apparent vascular involvement. **b** Hypertrophic scar after cesarean section (age 5 years) extending beyond its borders. **c** Hypertrophic scar after breast reduction surgery (age 2 years) extending beyond its borders

literature in collaboration with the local radiotherapy department and in accordance with the wishes of the patient.

40

Take Home Message

- Consider excision and radiotherapy as a last resort for therapy-resistant keloids.
- HDR brachytherapy started <7 hours after surgery and a BED of ±20 is recommended.
- The chance of secondary malignancy seems very low.

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Specific Attention Areas in Scar Management

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Specific Attention Areas in Scar Management: Management of Atrophic Scars

Matteo Tretti Clementoni and Ernest Azzopardi

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41.1 Background

Atrophic scars represent some of the most difficult and insidious pathologies confronting the reconstructive surgeon. Deriving from the ancient Greek "a-trophos" (wasted), the term presents a vivid representation of the clinical picture and an area of scar management particularly worthy of specific attention.

The atrophic scars typically develop as a result of an intracutaneous inflammatory process. Rather than exuberant inflammation, the process results in reduced matrix regeneration and focally reduced collagen production. Focal contraction of the scar tissue will result in uneven soft tissue defects. Clinically, these result in contour defects on the surface of the skin [1].

Several pathologies may result in atrophic scars [2], This chapter is intended for the experienced laser practitioner tackling three clinical conditions presenting to the reconstructive specialties, often as a last resort after exhaustive traditional management: acne, striae albae, and burns. It explores common principles, followed by state-of-the-art management and evaluation of the senior author's experience.

41.1.1 Common Principles

These atrophic conditions wound both tissue and psyche. They tend to be underestimated causes of significant morbidity for the individual patient who often either loses all hope of amelioration or presents with unrealistic expectation. Therefore, its appropriate management entails identification of their concern, their attitude toward the risk/benefit of the management proposed, and setting their expectations at an appropriate and realistic level. It is important to emphasize that current treatment modalities can improve but cannot completely remove atrophic scars. Scarring from acne vulgaris and burns has been associated to a range of mental health issues including depression as well as embarrassment, poor self-esteem, and general social impairment. Early and appropriate involvement of multidisciplinary opinion is key [3, 4].

Appropriate clinical documentation not only helps set the baseline at presentation but also allows the patient to observe progress and build confidence. Both two-dimensional photography and three-dimensional photography are useful adjuncts in management, given reproducible conditions and serial repetition.

Further, an objective grading of the condition is key to identify appropriate therapeutic options in mind. While classification systems are extensively discussed elsewhere, it is our experience that the use of one over the other is not in itself as important as consistency, and familiarity with one system, geared toward a therapeutic solution.

41.2 Atrophic Acne Vulgaris Scarring

Atrophic scarring is substantially more common than hypertrophic [5]. Being able to deconstruct the presentation into the component symptoms is crucial. Often the components of the presenting complaint are a mixture of contour and dyschromia, which can be general or specific to particular areas or even single scars. It is important to enquire about the physical consequences which the patient perceives, such as the inability to apply makeup, which are key areas of concern, past treatment regimes, and the frequency of recrudescence. Tendency to hypertrophic, keloid, or poor scarring is asked. Enquiring about postoperative social commitments is important, considering the variation in recovery times with the various treatments while sun exposure without adequate protection may dramatically alter the result and incidence of complications. Examination establishes skin type and excludes residual active inflammation, extent, and grade of disease. Application of the Goodman and Baron classification imparts some degree of objectivity in concluding one's deliberations to focus on the appropriate therapeutic modalities (Table 41.1).

Management of atrophic acne scarring depends on the infrastructure and equipment available to the practitioner; therefore, a critical appraisal of traditional methods is presented first, followed by state-of-the-art methods and our experience thereafter. For ease of reference, these techniques are grouped by their main mode of action into resurfacing and tightening, dermal lifting techniques, and dermal volumization techniques.

41.2.1 Resurfacing and Tightening Techniques

41.2.1.1 Microdermabrasion

Microdermabrasion is a minimally invasive technique that improves texture but only addresses superficial scars, although its combination with aminolevulinic acid photodynamic therapy (ALA-PDT) is more effective, based on RCT evidence [7]. In principle, subsequent wound remodeling results in neocollagenesis and hence increased dermal thickness. Its main use is for well-defined superficial scars with distinct borders or broad-based scars with indistinct borders. Its main drawbacks are high operator dependence and a suboptimal safety profile. Further adverse effects may include dyschromia and scarring. For these reasons it has been largely replaced by laser.

Table 41.1 Post-acne scars, qualitative global grading system (Goodman and Baron) [6]

Grade	Disease level	Features and tests
I	Macular	These scars are erythematous, hyper- or hypopigmented macules They do not represent a problem of contour but that of color
II	Mild	Mild atrophic or hypertrophic scars that may not be obvious at social distances of 0.5 m or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair if extrafacial
III	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 0.5 m or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial. Can be flattened by manual stretching of the skin (if atrophic)
IV	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances greater than 0.5 m and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extrafacial. Cannot be flattened by manual stretching of the skin

41.2.1.2 Chemical Peels and Microneedling

Chemical peels can improve pigmentation and tone and texture. Bhargava et al. reported that glycolic acid (35%) peels and salicylic (20%) – mandelic acid (10%) peels were more effective for ice-pick than boxcar scars. Twice-weekly stronger strength peels seem to be more effective than daily low-strength creams. Trichloroacetic acid (35%) peels with a short downtime seemed to be particularly effective in darker skin types. Yet others combine needling with TCA peels to good effect. Caution needs to be taken in view of several potential adverse effects including prolonged erythema and post-inflammatory hyperpigmentation. These side effects are more prevalent but by no means limited to deep peels. Paradoxically, very high concentrations of TCA have demonstrated high efficacy in atrophic scars, and boxcar scars in particular, and have been rebranded as chemical reconstruction of skin scars (CROSS). Skin needling is another method, based on the principle of percutaneous induction of collagen, creating dermal microclefts, with collagenesis resulting from the cascade of growth factors unleashed by the wound-healing process. It appears to be more effective on rolling scars, and collagen deposition happens slowly, with the final result taking several repeat sessions and up to a year to be complete. Needling seems to confer added value as a method for transcutaneous drug delivery. Several such applications have been reported, such as combinations with TCA, platelet-rich plasma (PRP), and CROSS. Current best evidence suggests that results are operator-dependent, frequency-dependent, and concentration-dependent and that depth and degree of post-inflammatory hyperpigmentation are unpredictable, requiring experience and expertise; for this reason, the authors have moved away from these techniques toward light and laser therapy.

41.2.2 Dermal Lift Techniques

41.2.2.1 Punch Excision

Punch excision is a simple and quick technique that converts a discrete atrophic scar into a well-apposed, well-oriented surgical "healthy scar" which is easier to manage by both surgeon and patient. An appropriately sized punch biopsy is used to perform *full-thickness* excision. The wound is then sutured along relaxed skin tension lines (RSTLs). Observing the elongation of the circle into an ellipse with tension allows the practitioner to choose the optimal orientation for closure. It is also useful to avoid closely spaced defects and thus excess traction. Punch excision is replaced by sharp elliptical excision to avoid standing cone formation, when the defect is larger than 3 mm. Once healed, the resulting surgical wounds can be incorporated into laser remodeling.

Punch grafting replaces the punch excision with a similarly sized graft, of better quality in principle, but is laborious and often results in suboptimal color and textural mismatch. Punch elevation is another less commonly practiced technique reserved for boxcar scars with sharp edges and normal bases. The punch biopsy tool is used to excise the scar and its walls down to fat. This is followed by careful tissue elevation for the surface to sit slightly proud of surrounding skin to allow for subsequent retraction. The punched base is then secured. While both techniques are described in the literature, a clear advantage of either compared to punch excision and suturing, or our preferred techniques illustrated hereunder, is not immediately evident.

41.2.2.2 Subcutaneous Incision

Subcutaneous incision (subcision) frees dermis tethered by fibrous bands causing rolling scars. This technique employs a needle (ideally tribevelled) by severing adherent bands in a subcutaneous plane. Given adequate infiltration with adrenaline-containing local anesthetic, risk of hematoma formation is minimized. The technique does, however, run the risk of subcutaneous nodule formation.

41.2.3 Volume-Imparting Techniques

41.2.3.1 Filling Techniques

Both autologous (lipotransfer) and alloplast (nonanimal, cross-linked hyaluronic acid, NAHA) have been described to improve the volume underneath atrophic scars. The technique mandates prior release of the tethered scarring, without which the defect may be exaggerated due to volumization surrounding a tethered defect. Additionally, the technique is prone to the same complications of the volumizing agent. There is some evidence that dermal fillers can be used to impart volume which can be useful for soft boxcar or rolling scars [8]. While this produces some improvement of the dermal volume to counter the atrophic nature of the scar itself, the results are dependent on the nature of the dermal filler. Injections of cross-linked hyaluronic acid stimulate collagen formation by dermal fibroblasts and ameliorate skin quality [9]. Several studies claim advantages of different fillers, and this is extensively discussed elsewhere [10]. However, the emerging consensus is that dermal fillers offer very little on their own in the management of atrophic acne scars and work best as combination therapy. Traditionally, fillers care combined with prior subcision [8]. The combination of dermal fillers with high-pressure blast-effect devices is discussed further in this section as part of our current regime.

41.2.3.2 Dermal and Fat Autografting

Two less common techniques used for correcting volume deficit in atrophic acne scarring are dermal grafting and fat autografting. They are included for completeness, as the practitioner may occasionally encounter patients having been on the receiving end of this technique. In dermal grafting, harvested dermis is processed and implanted into recipient areas. This traditional technique's limitations are that it is limited to atrophic scars at least 4 mm in diameter; necessitates pocket dissection for insetting the graft, which may simultaneously mean subcision; multiple incisions; and inclusion of epidermis may lead to inclusions and dermal cysts.

Lipotransfer involves harvesting, processing, and insetting adipose tissue, which then will be needed to survive by developing a blood supply from surrounding tissues. Evidence regarding its use in atrophic acne scarring is controversial. A combination of fat grafting and condensed nanofat has been successfully used to treat atrophic scars [11]. Other studies claim that this technique may improve atrophic acne scars and texture [12]. Azzam et al. claim that fat grafting proved to be more effective in the treatment of acne scars than ablative fractional CO2 laser treatment. However, it should be pointed out that this study's methodology suffered from limited validity. Follow-up was limited to 3 months after a single lesion of fractional CO_2 laser therapy. Relatively low energies were used as well as a limited number of treatments. Currently, there is no evidence on the long-term success of this modality in the management of atrophic acne scarring [10].

41.2.4 Isotretinoin Treatment

Exposure to isotretinoic acid within 6 months was often cited a contraindication to treatment with a second modality [13], although more recently this view has been challenged. Historically, a few case series reported adverse events (development of keloids and hypertrophic scars, delayed healing) when patients recently completing isotretinoin treatment received dermabrasion and laser. "Spontaneous" keloids were also described in patients on isotretinoin. More recently, literature describes successful treatment of atrophic acne scarring, including fractional laser and dermabrasion; chemical peels in patients on isotretinoin challenge the traditional view of withholding treatment for 6–12 months. Rather, these adverse events result from individual variations in immunologic and inflammatory pathways. Early treatment of acne scars is critical for improved quality of life. The risk/benefit implications of treating the patient early need to be considered in the light of informed consent.

41.2.5 State-of-the-Art and Combinatorial Approaches

Most of the studies published today attempt to perform head-to-head comparison between different treatment modalities, in the attempt to identify the better option. This is understandable from a cost–benefit perspective due to the prohibitive outlay of some therapeutic modalities (◘ Fig. 41.1).

Here we concentrate on combinatorial approach (◘ Table 41.2) for the more taxing Goodman type 3–4 acne scars. There is a clear trend in the literature that favors combination treatments, and trends are now starting to emerge about useful synergies especially for the more severe acne types [2, 14].

41.2.5.1 Fractional Radiofrequency (FRF)

Fractional radiofrequency (FRF) transmits bipolar currents through contact electrodes or paired microneedles. This results in controlled, loco-temporal thermal dermal injury, inducing a wound-healing response. Clinically, this results in improved texture, tightening, and some improvement of skin clarity. There is consensus in the literature that three to six treatments provide optimal effects, ranging from 25% to 75% improvement and

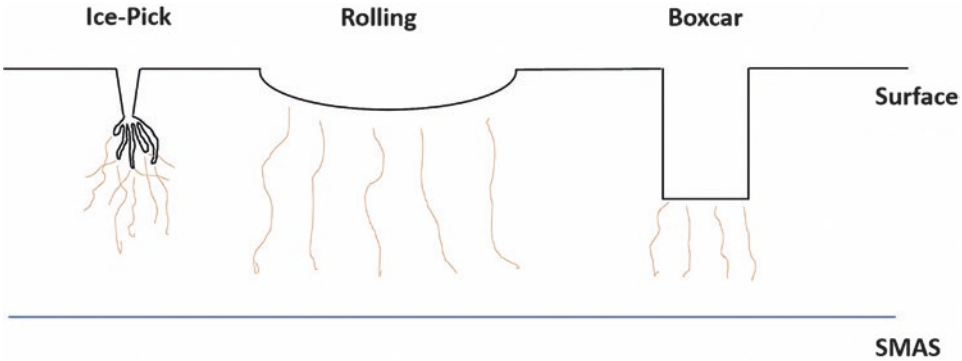

Fig. 41.1 Morphological classification of post-acne scarring [13]

Table 41.2 Proposed combinatorial approach and treatment schedule for treatment of atrophic acne scarring

Treatment	Effect	Repeats	Typical interval duration	Typical side effect duration
Bipolar radiofrequency	Regeneration	5	45–60 days	5–7 days
Hyaluronic acid/high pressure	Dermal revolumization	3	45–60 days	1–2 days
Fractional CO_2	Resurfacing/tightening	1/2	9–12 months	5–7 days

Schedule, temporal interval, and side effect duration are based on expert experience, using calibrated and maintained technology. Equipment settings vary between different manufacturers and versions

patient satisfaction. *Radiofrequency with microneedles* (RFM) delivers energy through microneedles (both insulated/non-insulated). The initial, mechanically induced microneedle wound-healing response [15] is followed by controlled thermal energy, up to 3.5 mm deep. This results in focal epidermal ablation, and controlled thermal damage to dermis, and, consequently, neocollagenesis, neoelastogenesis, and ground substance deposition [16]. Clinically, this results in textural amelioration, dermal density, and scar grading, whereas transepidermal water loss and sebum measurements did not change [17]. Some hybrid devices achieve this with a mixture of RF and galvanic energy. Transient posttreatment effects include pain, redness, mild swelling, and some crusting for up to 5 days. Track marks (<6%) and post-inflammatory hyperpigmentation (<3%) have been reported. Lesions arising from ice-pick and hypopigmented acne scars do not respond optimally to this treatment modality from a revolumization perspective, but there may be benefit from resulting skin tightening. Due to the risk of cross-infecting unaffected areas, RFM is contraindicated in patients with any areas of active acne.

Pre- and post-therapeutic regimes are integral to a positive outcome. Makeup removal, and adequate drying of the skin, is essential to avoid short-circuiting and epidermal injury. In contrast to other authors [18], we have achieved acceptability with topical anesthesia only (lignocaine/tetracaine cream 70 mg/g). The patient is advised a rigorous regime of UV protection (≥50%) and emollients to accelerate healing and decrease the risk of PIH.

41.2.5.2 High-Pressure Dermal Filler Deposition

More recently, low-viscosity NAHA dermal fillers have been employed to replenish volume loss associated to volume loss. Early studies were performed using microdroplet applicators [19]. Even though these limited studies did report a beneficial effect, with recent improvements in high pressure, needle-less transdermal delivery systems have allowed the development of high-pressure transdermal hyaluronic acid delivery. The latter leads to a controlled "blast effect," releasing tethered scars while improving delivery of the NAHA to a controlled surface area and depth. The combined physicochemical blast deposition effect is purported to be synergistic and promotes sustained neocollagenesis [19]. Limited level 4 evidence does not allow pooling of data, but consistent beneficial effects have been reported on difficult-to-treat anatomical areas and skin types. Patel et al. used jet volumetric remodeling (JVR) technology to deliver cross-linked hyaluronic acid, using 40–45% pressure vs. levels 4–5 filling, and demonstrated a beneficial effect on ice-pick and boxcar scars. Although level 4 evidence is based on small case series, remarkable results are reported, on

Table 41.3 Evidence summary for JVR on the face and neck, since 2011, in the literature (English language)

Ref.	Technique	Reported improvement – reduction in Goodman score (%)	Mean age (years)	Follow-up (months)	Area	Skin types (Fitzpatrick)	Areas (*n*)
[21]	JVR/Histo/SP	50	54.7	6	Neck	Korean (II–V)	12
[22]	JVR/SP	27.6 (face)/21.2 (neck)	53.2	3–18	Face/neck	I–IV	34

SP standard photography, *JVR* jet volumetric remodeling, *Histo* histological analysis. Search String "Pneumatic AND Hyaluronic"/ limits: English, human since 2010

a cohort of patients which are difficult to manage technically. Benefits include shortened procedure times and minimal downtime for a sustained improvement in the Goodman score. Murine model histological evidence supports the notion that the pneumatic injection of NAHA induces neocollagenesis and dermal thickening [20] (Table 41.3).

41.2.5.3 Laser

Laser now enjoys a solid evidence base in acne treatment. Traditional ablative laser therapy involved wholesale, partial thickness ablation of diseased dermis. While this produced impressive results, it was associated with significant and prolonged side effects. In our practice this has been entirely overtaken by ablative fractional laser (AFL). Several ablative and non-ablative lasers have been described for the treatment of acne and which are well-described elsewhere [10].

In fractional laser, the laser beam is split into multiple hundred columns, which create noncontiguous zones of thermal injury. These microthermal zones result in noncontiguous columns of epidermal and dermal ablation, resulting in epidermal regeneration and neocollagenesis. There is consensus in the literature that repeat treatment is necessary, when offered in monotherapy, but this may not always be the case when offered as part of a regime intended to address the separate aspects of atrophic acne scarring pathology. Fractional carbon dioxide laser addresses both scar elevation and recontouring (Fig. 41.2).

The skin stretch test of Goodman et al. [6] (Table 41.1) is a good indicator with which to assess the amenability of scars for laser. Scars not correcting with a simple stretch test indicates that it will likely not correct with laser therapy but may require prior treatment with either punch excision or high-pressure injection of hyaluronic acid or, in select cases, subcision.

In a first pass, a narrow size scanning pattern is targeted at the scar base, with the aim of achieving lift (Deep Fx). The second pass targets the edges of sharp-edged scar (such as boxcar scars), contouring it to a smoother scar edge (Deep Fx). In the third pass, active FX is performed to feather out the troughs and crests of the scars. This is typically done at a fixed distance from the skin using a spacer. However, the authors prefer to use a "spray painting" technique, by holding the handpiece still further away from the skin, on increased density, resulting in a more efficient and effective resurfacing (Table 41.4).

Using this technique, substantial improvement has been demonstrated histologically, and efficacy has been maintained for up to 3 years. The results appear to be more significant when compared to non-ablative modalities, albeit at the cost of increased downtime. It is important to advise patients appropriately regarding the importance of pre- and posttreatment regimes (Table 41.5).

Non-ablative laser can also be useful in the correction of acne scarring. This modality trades off minimal downtime, against slower, lower degrees of improvement, compared to ablative laser. Particularly useful is Erbium glass (1565 nm) fractioned laser which may be used to refine dermal texture and contour. In shallow atrophic depressions requiring low energy for adequate penetration, high density may stimulate neocollagenesis, while the corollary settings on elevations may induce flattening.

Picosecond laser may also be used to the same effect with some distinct advantages. Hyperpigmentation may be effectively treated on collimated beam settings, with the picosecond duration resulting in light-reduced inflammatory response. In fractionated mode, picosecond laser results in light-induced optical breakdown (LIOB) which stimulates gentle neocollagenesis.

41.3 Striae Albae

Lineae albae present another difficult challenge, especially in darker-skinned individuals. Myriad treatments have been described, none entirely satisfactory. Several eponymous terms are used interchangeably, but we prefer the one proposed by Nardelli's "striae atrophicae," as it embodies the current histopathologic understanding [23].

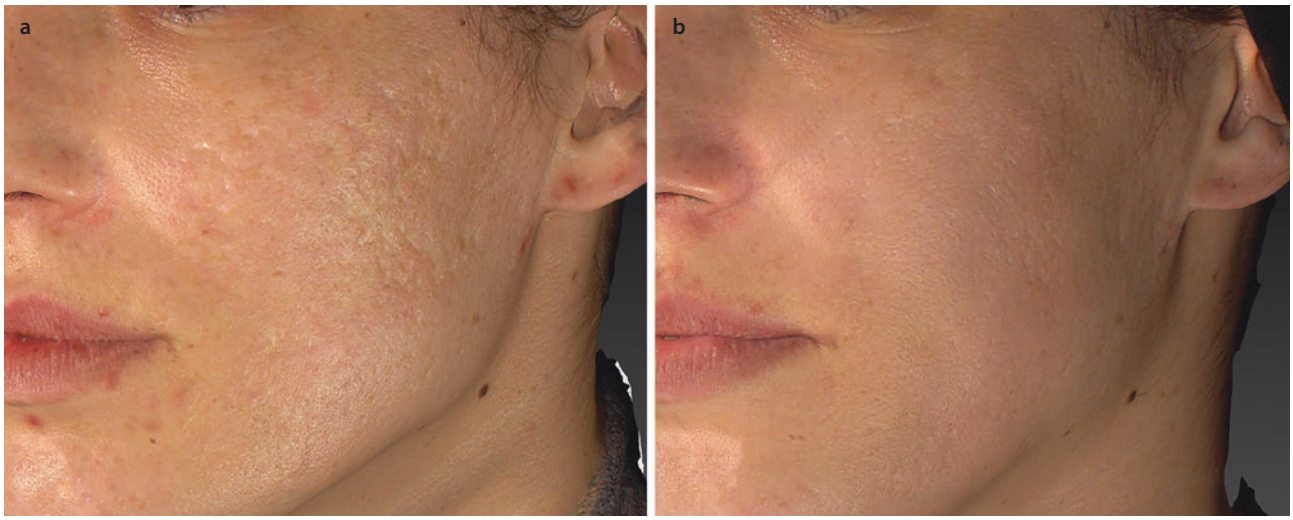

Fig. 41.2 Figure 1**a** repesents the face before fractional CO_2 procedure and **b** is the patient 6 months later

Table 41.4 Suggested typical settings for post-acne AFL protocol

Cycle	size	Pulses	Density (%)	Pattern cycle (Hz)	Energy (mJ)	Aim
1 DFX	2	1	5–10	300	15–20	Base of scar
2 AFX	2	1	9	350	40–60	Flange out Boxcar scars, Handpiece at 45°
3 DFX		1	15	300	17.5	Tighten surround[a]
4 AFX		1	3	125	100–	Re surface full face

DFX Deep Fx™, *AFX* Active FX™
[a]For severe scarring (optional)

Table 41.5 Suggested pre- and posttreatment considerations

Phase	Advice
Pretreatment	
All patients	Back to "normal shade" with complete loss of holiday tan
	SPF 50+ (every 2 h)
Fitzpatrick 3–6	Initiate Kligman regime from 8 weeks pretreatment, stop 2 weeks pre Rx
	tretinoin (0.02%); hydroquinone (4%); vitamin c (3%); hydrocortisone (1%)[a]
Posttreatment	
All patients	Emollients plus SPF 50+ (every 2 h)
	Antivirals PO
	Consider antimicrobials as per local protocols (antifungals, antibiotics)

[a]With particular attention to an airtight container, avoid mucosal, periocular, and perioral areas, and avoid pooling in nasolabial sulcus

Compared to adjacent unaffected skin, striae albae present histologic evidence of attenuated dermal papillae, with the latter nearly entirely substituted with collagen fibers running parallel to the skin.

Trofolastin demonstrates level 2 evidence of positive results for their prophylactic use in SD [24]. Tehranchinia et al. [25] observed some degree of improvement in 80% of patients after two treatment sessions within a 4-week interval. However, 76.7% of patients remained dissatisfied. The authors concluded that this modality resulted in minimal improvement with mild side effects. It also is apparent that Trofolastin's mode of action is related to the deposition of hyaluronic activity [26]. Additionally, it is well established that fractional laser treatments induce long-term clinical and histological improvement of mature atrophic scars [26], including increased architectural reorganization toward normalization, such as collagen structure (from thick surface paralleled hyalinized bundles to uniform dense interwoven fibers with higher vascularization), and decreased inflammation. Unlike Taudorf et al., we do not perform stack pulsing. First as unless there is complete immobility, true stacking is

impossible to achieve and, secondly, because stacking does increase risk of excessive thermal damage.

Clinical evidence supports the use of JVR with NAHA promoting sustained neocollagenesis and increased dermal depth, while the blast effect untethers the underlying scarring of lineae alba [27]. The combination of JVR to non-ablative fractional laser gives, in our opinion, a substantial improvement over both techniques used alone. NAFL then provides an effective tool to address dermal recontouring, by stimulating collagen synthesis in troughs and the opposite effect in surrounding areas. While effects of individual treatments appear to be long-lasting, we have also observed that one-off treatments are rarely as effective as repeated cycles spaced 6–8 weeks apart.

41.4 Burn Atrophic Scars

Great strides have been registered in acute burn management, resulting in increased burn survival, even with major and previously unsurvivable burns. As a result patients are presenting with increased requirements relating to morbidity and quality of life, arising both from the mechanism of injury and subsequent interventions required to safe life and limb. Atrophic burn scars form an important minority of burn scars. Often interspersed with hypertrophic counterparts, they result in wound instability and breakdown and contribute to poor cosmetic outcomes. The postoperative course of a burn scar is summarized symptomatically in Table 41.6.

A plethora of lasers have been described in the treatment of atrophic scars (Table 41.7), both non-ablative and ablative with an approximate cutoff of 200 nm. Fractional ablation, first described by Mannstein [28], produces arrays of microscopic thermal damage zones (MTZs) throughout the epidermis and dermis, affecting only a part of the surface area, with consequent remodeling and neocollagenesis for up to 6 months after treatment with permanent results [29]. Less energy is required to achieve the desired depth (≤2 mm) of penetration in atrophic or flat scars, allowing higher fractionated densities to be used, depending on the device, (≤10%).

Non-ablative fractional resurfacing (NAFR), in contrast, leaves the epidermis intact (ad dermis) whilst forming MTZs. A focused dermal injury instigates dermal remodeling and neocollagenesis [28]. The result is a bloodless cylindrical coagulation area within dermis. The clinical advantage is lower risk of infection and pigment alteration, as the epidermis is intact.

Post-procedure discomfort after AFR is surprisingly limited. Patients generally return to normal activity within 1 day, but downtime may be up to 7 days and requires several topical applications which may interfere with clothing and social activity. In contrast, NAFR requires far less downtime, dyschromia, PIH, with lower analgesia requirements, at the expense of more treatment sessions being required. In consideration of these reasons, for flat or atrophic scars, there is

Table 41.6 Therapeutic burn phases

Phase	Typical procedures	Aim
Immediate	Tracheostomy, escharotomy	Life/limb saving
Early	Burn wound excision and grafting	Excise dead tissue Reduce evaporative loss
Intermediate	Periorbital, perioral, address functional gain	Protect special senses Improve ROM deficit arising due to increasing mobility
Late	Incisional/ excisional release	Address functional deficit Improve range of movement Address pain, pruritus

Table 41.7 Wavelengths described from atrophic burn scars

Wavelength (nm)	Lasing medium	Modality	Effect
10,600	CO_2	Fractioned	Lower (×10) water affinity, more coagulation, less bleeding, favorable to LADD
2790	Er, Cr-YSGG	Fractioned	More water affinity, narrower rim of thermal coagulation around MTZs
2940	Er: YAG	Fractioned	
1540,1550,1565	Er: Glass	Fractionated	For scars with a thickness lower than 2 mm

CO_2 carbon dioxide, *Er YAG* erbium-doped yttrium aluminum garnet, *Er,Cr-YSGG* erbium, chromium-doped yttrium scandium-gallium-garnet, *LADD* laser-assisted drug delivery

emerging consensus in the literature that NAFR is the treatment of choice [30]. We also suspect that such wide variety of data exists in part from the prohibitive cost of each technology. Having access to the entire range of technologies in our center, we favor the use of NAFR Er:YAG to raise the base of atrophic scars on higher-density settings.

While the optimal timing of fractional laser therapy is not yet determined, current trends in the literature over the past 5 years favor earlier intervention. Scars of any age can be considered for fractional resurfacing. In practice, the contrast between postoperative regimes required by laser and complex burn surgery poses practical limits on how early a laser intervention may be successfully offered. Notwithstanding, younger scars are more susceptible to remodeling, and some studies now suggest that the ideal timeframe may be as early as 4–12 weeks post-injury, repeated every 1–2 months until response plateaus or the therapeutic aims are attained and may help in scar remodeling, reduce contracture rates, and expedite rehabilitation [31].

Vascular Laser Lasers targeting abnormal scar proliferation have the potential to improve scar characteristics. A number of wavelengths are often used for this purpose, including millisecond range potassium titanyl phosphate (KTP) 532 nm, pulse dye laser (PDL) 595 nm, and neodymium:yttrium aluminum garnet (Nd:YAG) 1064 nm. Although the primary target of PDL is hemoglobin, its mechanism of action is not fully understood. After multiple treatments, PDL results in some softening, flattening, and smoothening [32]. However, melanin acts as a potential competitor; therefore, conservative settings need to be used in darker individuals.

Fractioned picosecond modality laser has the potential to produce light-induced optical breakdown, limited to the dermis, which may stimulate dermal inflammation, remodeling, and neocollagenesis. There is still some controversy regarding the timing of appearance and significance of microscopic epidermal necrotic debris (MEND). In one such study, this phenomenon was noted as early as 3 h (post-pico-532 nm) and within 24 h (both 532 and 1064 nm wavelengths) [6].

Burn reconstruction really starts in the immediate postburn period with adequate first aid therapy that limits the zone of stasis and hyperemia and careful, multimodality management including judicious debridement and maximal attention to dermal sparing. Fractional laser resurfacing for atrophic wounds is an integral part of this armamentarium. Additionally, our recent experience suggests that JVR (NAHA) is a useful adjunct in achieving revolumization of selected atrophic burn wound reconstructions. In particular, resurfacing with split thickness skin grafts often leads to a honeycombed appearance, reduced elasticity, and a feeling of tightness, due to the minimal dermal component of a split-thickness skin graft. Our early experience with this technology has produced excellent results when used in tandem with fractional laser, where we have observed synergistic dermal "re-plumping" and substantial improvement of skin texture.

41.5 Conclusion

Atrophic scars present a significant challenge to the reconstructive specialist, with acne, linea albae, and burns being topics worthy of special consideration. Optimal treatment is not based on superiority of one particular treatment over another but rather by the specialist's ability to precisely identify the component parts of the presenting complaint and bringing his entire armamentarium to bear. We believe, based on experience and balance of current evidence, that combined, repeat treatment produces the best results and that these must be carefully balanced against the relative costs: physical, social, and economic, in consideration of each patient's individual needs.

Take Home Messages

- Atrophic scarring is the final common pathway resulting from reduced matrix regeneration and focally reduced collagen production.
- Addressing patient concerns, expectations, and attitude to risk/benefit is key.
- Techniques may be considered according to their principal mode of action: resurfacing and tightening, dermal lifting techniques, and dermal volumization techniques.
- Acne scars affect physical, psychological, and social well-being. Involvement of multiprofessional advice is important.
- In appropriately selected patients, combined RFM-JVR-AFL treatment, tailored to individual needs, is more likely to produce appropriate results.
- Repeat treatment is likely to be needed.
- Color laser may lead to substantial improvement in dyschromias.

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Specific Attention Areas in Scar Management: Specific Scar Management Depending on Anatomical Features (Face, Hair, Breast, Hand, Joints, Foot)

Julian Poetschke and Gerd G. Gauglitz

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_42

Background

Scarring can have a variety of different detrimental effects on the affected patients. While small scars are often little more than an aesthetically unpleasing blemish, scarring has the potential to drastically affect patients' lives.

Ultimately, not only the scar type but also the dimension of the affected areas and their location play a large role regarding the impairments they might cause.

Different aspects come into play when certain areas of the body are affected by severe scarring, and they should be taken into consideration when planning the treatment.

Severe facial scarring causes a multitude of issues. It is incredibly stigmatizing for affected patients and will likely cause significant psychological suffering. This oftentimes has detrimental effects on the patients' social life leading to isolation and thus further psychological problems. Facial scarring can have a variety of functional impairments, too. It can cause impaired closure of the eyelids leading to lagophthalmos or leading to ectropium or entropium, all of which can endanger the patients' vision and result in pain and unease.

Microstomia is another common consequence of facial scarring, leading to a reduction of the mouth opening, thus greatly impairing the intake of food and beverages as well as hindering speech or oral hygiene all the while causing significant discomfort.

On the head, scarring can lead to hair loss or cicatricial alopecia which, while problematic in men, too, can be downright devastating in women, where hair loss and baldness remain stigmatizing.

The chest is another aesthetically important area where scarring can lead to a significant psychosocial burden, especially in women.

While scarring of the hands can be aesthetically unpleasing, too, its most problematic consequence is the functional impairment it can cause. Especially in burn patients, the functional consequences of the scarring can be so severe that not only the patients' ability to work but to maintain their self-reliance throughout their daily lives is also at risk. Even with immediate physiotherapy and occupational therapy after surgical treatment, functional impairments often remain and are exacerbated by the incipient process of scarring thus leading to a lasting need for further treatment.

Similar problems arise with scarring on the feet. Since walking around throughout the day places a great load on the scars which are often less durable than healthy skin, instable scarring is a common problem around the feet. Scars can lead to deformities of the toes, too, like mallet, hammer, or claw toes which can lead to progressive joint damage and painful clavus.

In general, scarring around functionally important areas of the body like the hands, feet, and joints can cause dire impairments throughout the demands of the patient's everyday life. Problematically, if left untreated, joint damage, a permanent reduction of one's range of movement, and thus progressive worsening of the patient's condition long after the initial trauma are potential consequences.

Therefore, physicians need to make sure that their proposed treatment not only improves the scarring but that it is also suitable to reduce the risk of secondary damage.

In this chapter, we aim to provide an overview of therapeutical options for the treatment of scarring in different anatomical localizations.

42.1 Scar Treatment Options for Different Anatomical Localizations

42.1.1 Face

When planning treatment for facial scars, physicians need to take all the aspects of the scarring into consideration. If functional impairments like impaired opening or closure of the eyes and mouth are present, the initiation and success of suitable therapeutic options are required more promptly than it would be with merely aesthetic impairments so that permanent damage beyond the scarring itself can be avoided.

If swift therapeutic success is required, surgical intervention remains the gold standard. Common indications for surgical intervention in facial scarring include microstomia, which is often the result of facial burns, acid attacks, or the ingestion of caustic fluids. It hinders sustentation and oral hygiene and impairs speech. Techniques for commissuroplasty to widen the oral opening through the advancement of mucosal flaps after scar excision have been published as early as 1831 by Dieffenbach and have since been modified and refined by Converse in 1959, Friedlander in 1974, and others (Fig. 42.1). Often, commissuroplasty is aided postoperatively by splinting to avoid fresh scar contractures.

Lagophthalmos is another indication for swift surgical intervention. It, too, is often caused by thermal or chemical injuries. If left untreated, corneal ulcers, infections, and pain are common ailments associated with this affliction, and permanent damage to the patient's vision is a large risk.

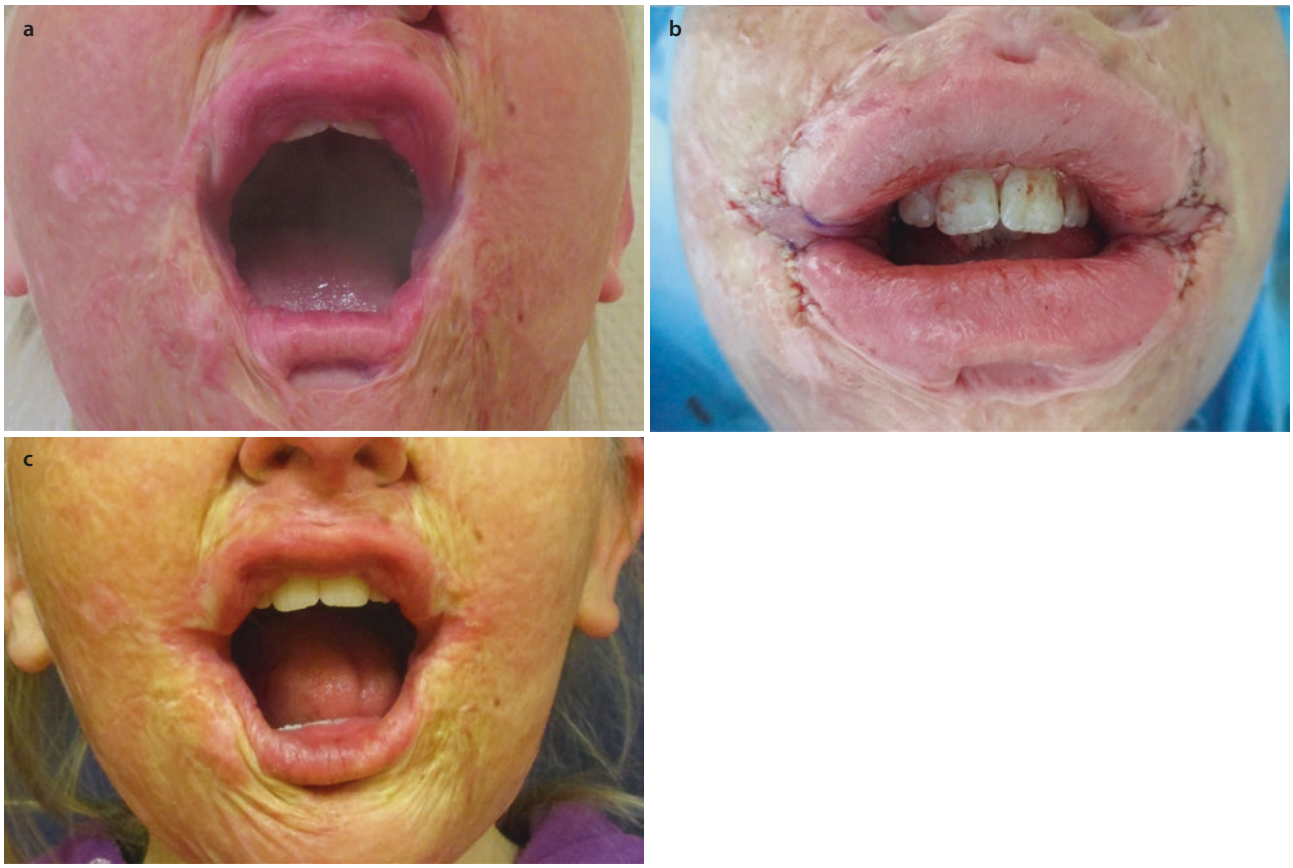


Fig. 42.1 A 7-year-old child with severe microstomia due to burn scarring. Scar revision was performed with bilateral commissuroplasty (Converse plasty). Images were taken before **a**, intraoperatively **b**, and 4 weeks after surgery **c**. As a result of the surgery, the teeth are visible again, when the mouth is opened, thus facilitating dental hygiene

Ensuring sufficient closure of the eye is therefore a priority. Consulting an ophthalmologist is important in determining if surgical intervention is necessary and when it is best performed as well as to assess the extent to which reconstructive surgery is necessary.

A variety of treatment options exist for the reconstruction of the eyelids. Where full-thickness defects that affect both the anterior and posterior lamella of the eyelids can require complex reconstructions based on local flaps, oftentimes, only the anterior lamella is affected. Here, reconstruction with full-thickness skin grafts remains the standard (Fig. 42.2). In lower eyelid reconstruction, lateral canthopexy is routinely performed to avoid sagging of the lateral corner of the eye, thus leading to ectropion. This technique often results in good function and cosmesis.

Lasers, too, play a vital role in the treatment of facial scarring. Ablative laser treatment has been used for years to treat atrophic acne scars and has proven reliable and effective. Since the advent of fractional lasers, side effects and after-treatment downtimes have been reduced significantly while maintaining a good treatment efficacy. In the treatment of acne scars, the fractional CO_2 laser has proven more effective than its Er:YAG counterpart [1]. Through the radiance of heat into the surrounding tissue, the CO2 laser stimulates heat shock proteins which trigger a cascade of molecular pathways leading to increased levels of scar remodeling factors like transforming growth factor beta 3 (TGF-β3) and matrix metalloproteases. Since treatment with the Er:YAG laser results in almost no heat transfer to the surrounding tissue, those effects are less pronounced.

Widespread hypertrophic scarring as the result of burns, scalds, or chemical agents is becoming a frequent indication for the use of fractional ablative lasers, too. Through its ability to penetrate deep into the scar tissue to stimulate remodeling within the deep dermis all the while being an effective tool for superficial ablation of the irregular, ropelike and tuberose scars that often result from the aforementioned trauma, the CO_2 laser has become an oft-used and reliable tool for facial scar revision. While studies have shown significant improvement of scar texture and firmness after just one session [2], commonly, repeated treatments are necessary to achieve satisfactory results. Furthermore, the scar remodeling stimulated through the treatment continues

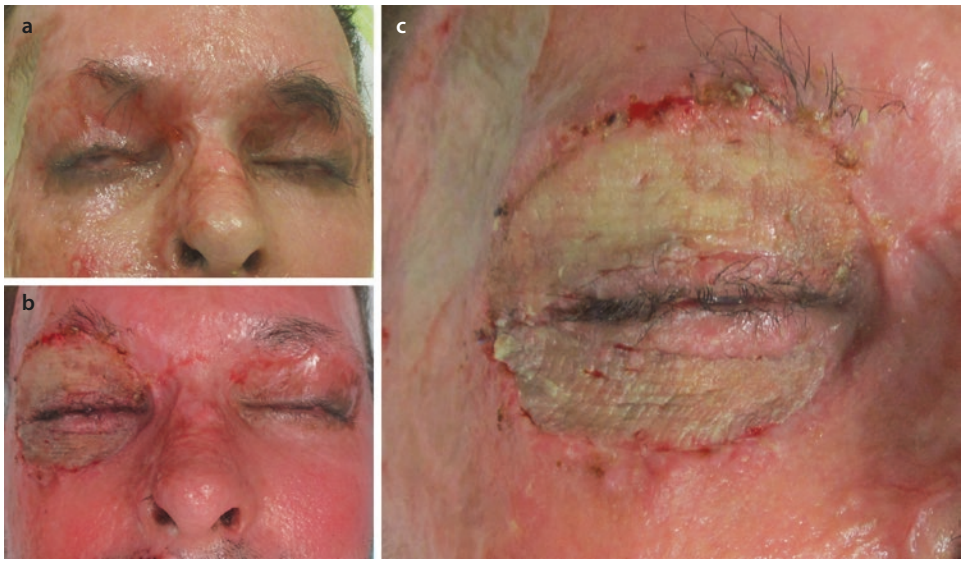


Fig. 42.2 A patient with pronounced facial scarring and lagophthalmos after sustaining burn injuries. Recurring conjunctivitis and a corneal ulcer led to the indication for surgical revision of the lagophthalmos. The scars were released, and the anterior lamella of the upper and lower eyelid were reconstructed using a full-thickness skin graft from the upper arm of the patient. Image **a** shows the preoperative site, while **b** and **c** show the postoperative results where full closure of the eyelids can be achieved

for months so that final results can only be expected after 6–9 months. Thus, while able to loosen contractures and greatly improve facial scarring, other tools should be chosen where immediate scar relief is required.

Medical needling is another option that aims to improve scarring through percutaneous collagen induction. It has been shown to significantly improve acne and burn scars in connection with a low-risk profile and minimal side effects [3]. Satisfactory scar treatment, however, often requires multiple sessions, and thus far, clinical studies have often relied solely on subjective means of evaluation thus leading to a continued demand for evidence.

Ultimately, it seems best to combine different therapeutic paths. While surgical intervention is paramount for the treatment of severe functional impairments, it is rarely able to improve pliability and texture of scars thus normalizing the look and feel of scarred skin. Here, the combination of surgical intervention with fractional ablative laser treatment might provide a more holistic approach to the treatment of severe facial scarring resulting in improved overall results and lasting patient comfort and satisfaction.

42.1.2 Hair

Scarring in areas of hairy skin will often result in hair loss. This is particularly problematic in widespread scarring. While small scars can easily be excised even on the immobile parts of the scalp, larger scars resulting in pronounced hair loss are often difficult to treat.

On the scalp, the scarred, hairless tissue is excised and replaced by healthy surrounding skin. Ideally, local flaps from the scalp can cover the wound defect after excision; sometimes though, pre-expansion through skin expanders is necessary to provide the required tissue. Side effects of this course of treatment are frequent and include expander malfunction, infection, and dehiscence or "breaking" of the skin over the expanders. If successful, however, the scarred tissue can be excised completely, and permanent hair loss of the scarred areas can be revised.

If neither local flaps, skin grafting, nor tissue expansion are an option after scar excision, free-flap reconstruction can be considered. Here, fasciocutaneous flaps should be considered since the healthy skin architecture seems preferable for receiving a hair transplant as opposed to muscle flaps that have been covered with split-thickness skin grafts. After successful reconstruction and consolidation, fasciocutaneous flaps can easily be thinned to provide a natural contour and integrate well into the surrounding tissue, and consequently, hair transplantation can be attempted to restore a natural appearance. Hair transplantation can also be performed on scars or skin grafts; however, this will require both sufficient thickness of the subcutaneous tissue and adequate tissue perfusion so that the hair grafts are likely to take.

Hair transplantation is the standard therapy for alopecia of the eyebrows or eyelashes, too. While surgical techniques for reconstruction of the eyebrows are available, too, local flaps or composite grafts from the scalp will look different than natural eyebrows. Furthermore, in composite grafts, less so in pedicled flaps, the risk of reduced perfusion might lead to renewed hair loss, thus compromising results. Overall, for this indication, hair transplantation might lead to more natural results.

If hair transplantation is considered, patients should be aware that multiple sessions are required to achieve a satisfactory hair density. Furthermore, it is paramount that sufficient donor sites are available [4].

42.1.3 Hands

Normalizing function in scarred hands is paramount to avoid lasting impairments. Scarring of the hands is common in burns and scalds and often leads to widespread scarring, either through the trauma itself or through the resultant surgical treatment and skin grafting. Oftentimes such scarring will lead to contractures of the web spaces, thus greatly affecting thumb or finger abduction and diminishing grip strength. Closure of the fist is commonly impaired, too, as contractures of the dorsum of the hand and fingers inhibit full flexion.

Such problems are often addressed surgically to allow for swift improvement of the functional impairments and to allow for early mobilization through physiotherapy and occupational therapy.

Loosening of contractures of the web spaces has been described through many different techniques such as single or multiple Z-plasty, butterfly, or jumping man flaps as described by Shaw or Trident flap plasty according to Glicenstein or Hirshowitz (◘ Fig. 42.3). Many other techniques have been described as well, but their common goal is to loosen the contracted linear scar and deepen the affected web space.

It is important when planning web space scar revision that adjacent web spaces are never treated at the same time, to avoid perfusion problems to the finger in between, should one of the neurovascular bundles get damaged during surgery. Therefore, when planning to operate on multiple web spaces on one hand, pairings of web space 1 and 3, 2 and 4, or 1 and 4 are possible, while other combinations should be avoided.

Postoperative regimens vary, but commonly, load-free assisted exercising can be started shortly after surgery. Ideally, compression gloves with silicone spreaders for the affected web spaces are prescribed for overnight use for a year after surgery.

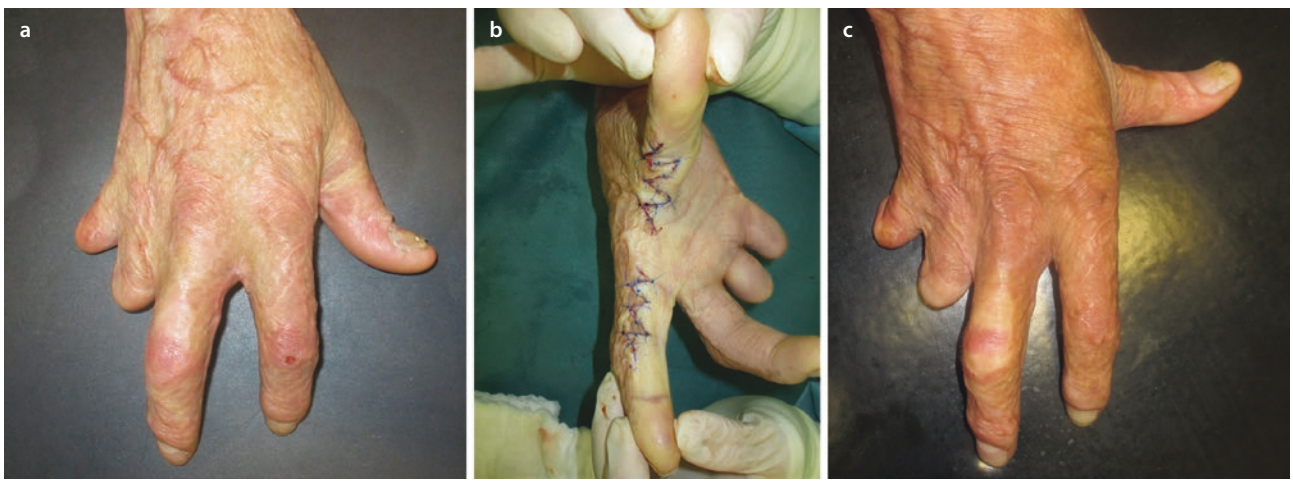
Volar flexion contractures are often treated through multiple Z-pasties, thus lengthening the scar and resolving the contracture.

Especially in widespread dorsal contractures, treatment remains difficult. Ensuring full closure of the fist is central to ensure good hand function; however, scarring is often rigid and restrictive.

To ameliorate these impairments, different techniques should be considered. One option is to replace the scarred tissue. After scar resection, full-thickness skin grafts or dermal substitutes like Integra® in combination with split-thickness skin grafts can be used to create a thicker, more flexible, and pliable skin in commonly stressed areas like the dorsum of the hand. Studies have shown that this might lead to improved pliability and functional results, both in acute and secondary burn reconstruction [5]. This, however, requires adequate coverage of functional structures like neurovascular bundles or tendons so that the grafts will take reliably. Otherwise, local or more likely free-flap coverage will be required. That course of action will, however, likely lead to multiple surgical revisions as flaps are often bulky and require subsequent thinning and contouring.

Laser therapy should be considered when improving the skin quality and rigidity is required. Fractional ablative CO_2 laser treatment has proven effective in releasing contractures and improving scar firmness, and different authors have described swift improvements in range of motion and scar quality in patients with burned hands [6, 7].

After scar revision on the hands, dedicated hand therapy is imperative to achieve lasting improvements regarding hand function and strength. After severe



◘ **Fig. 42.3** A patient with severe impairment of the abduction of the thumb following burn injuries to the right hand with consecutive scarring of the first web space **a**. After double opposing Z-plasty in the first web space and serial Z-plasty along the radial side of the index finger **b**, abduction of the thumb is drastically improved **c**

trauma and scarring, patients often require months of therapy to reach satisfactory results and to enable self-reliance throughout their daily lives.

The ideal time for scar revision should be carefully weighed, too. Especially in the pediatric patient population, where scar contractures might inhibit physical and functional development, timely intervention is indicated to avoid lasting damages that can be hard or even impossible to reverse.

In general, if possible, the conservative treatment of scarring through compression gloves, silicone finger spreaders, and hand-therapy should be exhausted, especially throughout the phase of scar maturation to avoid unnecessary surgery or even exacerbation of the scarring through stimulation of the scarring process.

42.1.4 Feet

Severe scarring of the feet can lead to a variety of problems for the affected patients. Common causes of scarring located on the feet include burns and scalds but also complex physical trauma.

Oftentimes such injuries cause contractures of the toes that will lead to painful malposition and toe deformities that can greatly impair walking.

Unstable scarring around the feet is a frequent problem, too, and chronic wounds and tears open under the daily stress those scars are exposed to.

These common problems results in a high urgency for scar therapy regarding the feet. The goal is to provide stable skin that is flexible and resistant to the daily strain the feet are exposed to.

Scars resulting from burns or scalds are commonly located on the dorsum of the foot, and resultant contractures of the toes can often be released through excision and Z-plasty or other local flaps, not unlike contractures on the dorsum of the hand. Similarly, though, more severe scarring or unstable scars might require excision of larger scarred areas and then skin grafts or a combination of a dermal substitute (like Integra® or Matriderm®) and skin grafts. Full-thickness scars that require excision onto the extensor tendons might even require free flaps for successful defect reconstruction.

Severely contracted joints might require capsulotomy for release, and sometimes, temporary Kirschner wire transfixation is indicated to achieve lasting rehabilitation of the affected joints [8].

The data on laser treatment for severe scarring of the feet is scarce. In light of the capabilities of fractional ablative lasers, however, it seems prudent to consider this line of therapy as an adjunct in more severe cases or as a primary therapy option in mild to moderate cases where its capabilities to loosen contractures and to soften the scarred skin might yield promising results or at least ease subsequent surgery.

Complications of surgery around the foot include hyperkeratosis, which is especially common around the load-bearing areas like the heel or the ball of the foot, where scarring can often result in this cumbersome problem, which is associated with significant pain, thus hindering walking and resulting in severe discomfort. Authors have noted that hyperkeratosis oftentimes forms protectively around a scarred area to minimize pressure on said area. Especially early on during the wound healing phase after local or free flaps to the heel or the sole of the foot, hyperkeratosis can often hinder the healing process by overgrowing the wound margins and thus inhibiting complete fusion of the wound margins. Therefore, after surgical treatment of the foot, medical foot care presents an important adjunct, not only to ensure patient comfort but also to facilitate wound healing and to minimize complications.

As with treating scarred hands, surgical or laser-based interventions should always go along with conservative means like compression garments, scar massages, and physiotherapy to optimize treatment results. This should be continued until the scar activity has subsided.

42.1.5 Joints

Scarring over joints can be particularly cumbersome to deal with. The constant tension that the healing tissue is exposed through the movement of the respective limb will encourage scar hypertrophy after trauma but also after scar revision. This should be taken into consideration when planning the treatment of scars that run over joints.

Plenty of treatment options are available, but ideally, a combination is chosen to avoid recidivism of problematic scarring.

Linear hypertrophic scarring can be released through Z-plasty or other comparable techniques relying on local flaps. While hypertrophic scars commonly show a great tendency for regress without treatment after an initial phase of growth activity and a consecutive constant phase so that invasive treatments are not considered a first-line treatment option, an exception can be made if hypertrophic scars are under constant tension.

As this stress can be considered a major cause of the scar hypertrophy, resolving it through surgery or fractional ablative laser treatment can result in

subsiding hypertrophy and symptoms thus constituting a causal therapy.

Supportive measures that should be considered to avoid renewed hypertrophy include intralesional triamcinolone acetonide or 5-fluorouracil injections, silicone gel or sheets, and pressure therapy.

Widespread scarring can be treated through serial excision. Here, the scar is excised in two to three consecutive operations every 3–4 months. This allows the remaining skin to stretch thus facilitating complete scar removal that would not have been possible in one single step. To avoid stretching of the scar, wound closure should be performed in a layered fashion. The subcutaneous and corium sutures should provide large tensile strength that remains over an extended period. Many studies, most recently by Gupta et al., have shown that superior scar appearance results can be achieved by using intradermal polydioxanone (PDS) sutures when compared to polyglactin 910 (Vicryl) sutures [9].

Alternatively like in other problematic areas, fractional ablative lasers have shown great potential to ameliorate scar contractures and should be considered a treatment option and be discussed with patients [10]. Successful treatment, however, will likely require repeated treatment sessions.

42.2 Conclusion

When treating pathological scarring, taking the anatomic location of the scar into account is imperative when choosing the right form of treatment.

Facial scarring can be extremely disfiguring and beyond the aesthetic implications often results in severe functional impairments like microstomia and lagophthalmos, among others. Treatment should be initiated quickly to avoid secondary damage to the affected organs. Commonly, surgical intervention remains the gold standard. Contractures are loosened through local flaps (e.g., Z-plasty), and skin defects after scar excision can be treated through split- or full-thickness skin grafting. Fractional laser treatment as an adjunct has become an important factor in improving facial scarring as they are able to improve scar firmness and smoothen their irregular surface. Similar effects are sought through the use of medical needling, though objective clinical data on its efficacy are largely lacking. Alopecia is a problem when scars affect the scalp. Often, the healthy skin is expanded through skin expanders over several weeks so that the scar can then be excised with the expanded skin now covering the defect. However, such treatment is often difficult because of expander malfunction and infections. Other options include free-flap reconstruction after scar excision, followed by hair transplantation. Especially in hair loss of the eyebrows and lashes, hair transplantation remains the gold standard, and achieving a near natural result in the hands of an experienced surgeon is often possible. Scarring of the hands can result in the loss of self-reliance in affected patients. Oftentimes, the web spaces are contracted thus limiting abduction of the thumb or spreading of the fingers. This can be addressed through deepening of the web spaces, for example, through double opposing Z-plasty. Afterward, compression gloves with silicone spreaders are fitted to ensure permanence of the achieved results and to inhibit renewed contractures. If contractures on the dorsum of the hand inhibit closure of the fist, complex reconstructions can become necessary if larger areas of scarred tissues need to be replaced. Laser treatment can assist in improving scar quality. Overall, a combination of treatment options should be considered. Physiotherapy and occupational therapy as well as compression garment therapy should be included into the treatment algorithm to improve functional results and to inhibit renewed pathological scarring. On the feet, scars often lead to toe deformities which impair walking and make wearing regular shoes uncomfortable or impossible. Here, surgical intervention is indicated. Since the feet are exposed to a lot of strain throughout the day, scars are often unstable and repeatedly crack and tear, leading to chronic wounds and strong patient discomfort. Here, excision and skin replacement through skin grafts, often together with dermal substitutes or even free flap reconstruction, can become necessary.

Overall, it is important to remember that scarring is a multifaceted problem. Through their firmness and contraction, they cause functional problems, their irregular appearance and color can be aesthetically displeasing, and all of these effects can put an enormous strain on the quality of life of the affected patients. Treating such scarring, especially in exposed areas or where function is greatly impaired, should therefore address the complexity of this problem. This is oftentimes only possible by combining surgical, laser-based, and conservative treatment paradigms into an individual treatment plan for the affected patients. This ensures not only immediate but also long-term improvements and inhibits renewed scarring.

Take-Home Messages

- Common functional impairments after scarring of the face include microstomia and lagophthalmos that require swift surgical attention to avoid secondary damage to the affected organs.
- While surgery remains the standard for severe functionally impairing scars of the face, fractional lasers have become a staple in improving scar firmness and surface irregularities and should be used in combination with surgery to improve overall results.
- Hair loss in scarred areas can be addressed in a variety of ways. Expanding healthy, surrounding tissue can help create enough tissue so that the scar can be excised in its entirety and the resultant defect can be covered with the expanded skin.
- If this is not possible, the scarred tissue can be replaced by fasciocutaneous free flaps, and these flaps can then be contoured afterward and receive hair transplants.
- Hair transplants are the gold standard for hair loss of the eyebrows and eyelashes.
- Improving function in scarred hands is imperative to maintain self-reliance in affected patients. Contractures of the web spaces can easily be treated through local flaps to deepen the web space, and results are commonly good when assisted by compression garment therapy afterward.
- Scarring of the feet can be severely impairing for affected patients. Contractures that result in toe malposition or deformities should be addressed to ensure that the patients can walk and wear shoes comfortably.

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Management of Scars in Skin of Color

Huidi Tchero

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43.1 Background

Scars are a normal process of dermal healing following laceration, skin incision, or tissue loss. Frequently, they are associated with burns, penetrating wounds, or surgical cuts. Morphologically, they appear erythematous and firm with elevated fibrous masses that are evolving within the margins of the wound and might revert later. They can cause cosmetic disfigurement, functional impairment, and psychological negative outcomes, affecting the patients' quality of life. These patients often seek medical advice to recover the color, texture, pliability, and relief of the associated pain [1]. In this chapter, we discussed how scars evolve differently in the skin of color, explored the available treatment modalities, and recommended planned treatment modalities in keloid management based on the published evidence.

43.2 How Scars Evolve Differently in Skin of Color?

Injury to the tissue could significantly produce inflammation, which is in turn associated with infiltration of neutrophils, monocytes, and macrophages, and release of pro-inflammatory cytokines, which induce fibroblast migration and proliferation, resulting in disproportionate extracellular matrix (ECM) deposition besides collagen accumulation [2]. This process is exaggerated when it affects the deep dermis, which would be complicated by the formation of a permanent scar. The scope of scar types varies from atrophic, flat, to raised dermal scars [3].

The pathogenesis of hypertrophic scars might be returned to atypical ECM metabolism following an odd and exaggerated fibroblastic stimulation. Histologically, it exhibits organized overexpression of types I and III collagen, deposition of fibronectin, and overexpression of pro-inflammatory interleukins (IL), such as IL-4, IL-6, IL-13, and IL-21, as well as downregulation of IL-12 and interferon (IFN)-γ expression [2]. The incidence of hypertrophic scars associated with a burn is up to 78%. The risk factor for hypertrophic scar includes dark skin, neck or upper limb age (younger), site, female gender, healing time, the severity of the injury, and the increase in a number of operations.

Keloids are different from hypertrophic scars in a variety of ways: they propagate outside the margins of the wound zone and invade the adjacent skin with no regression, conversely to hypertrophic scars that develop within the edges of the original wound and frequently regress in months. Keloids are a common fibroproliferative disorder that could happen due to abnormal healing process succeeding cutaneous injury. Keloids could evolve in any race; however, persons with more pigmented color (Fitzpatrick IV, V, and VI) are more vulnerable. In Hispanics, African-Americans, and Asians, keloids develop in up to 6–16% of those populations. The tendency for keloid expansion was also observed in patients suffering from dermatological diseases which lead to a protracted inflammatory reaction [1].

The presentation of keloid and hypertrophic scars can vary in patients with skin of color. Scars can be hyperpigmented or very large in patients with darker skin. Although keloid and hypertrophic scars appear usually within 1 year after trauma or surgery, few cases of people with skin of color who developed spontaneous keloid scars were reported within the literature as well.

Under the microscope, keloids appear as a twirling nodular arrangement of collagen fibers, characteristically with hyalinized, coarsened collagen bundles. Moreover, they have an acellular collagen center with adjoining hyper-proliferative fibroblasts. Their center covers dense fibers of immature collagen that are feebly supplied by blood vessels without lymphatic or elastin.

Several mechanisms have been hypothesized for the development of keloids, for example, deviant collagen production, abnormal growth factor regulation, and genetic vulnerability. Elevated levels of *transforming growth factor* beta (TGF-β) are suggested to be involved in keloid development; nonetheless, several other mediators are tending to be elaborated. Still, there is a lack of confirmed hypothesis that could elucidate keloid pathogenesis. Immune cells were also suggested to be involved in keloid scar formation.

Inherited genes increase predisposition for keloid tissue development; however, still, exact genes involved have not been acknowledged. Remarkably, keloid is exclusive to humans, and the animal model of keloid scars is absent. A large Japanese genome-wide association study (GWAS) discovered four single-nucleotide polymorphisms (SNPs) in three chromosomal segments in patients with keloid scars. These SNPs include rs8032158, situated in intron 5 of chromosome 15 that downregulates NEDD4 gene, which chiefly affects keloid severity. A study of admixture mapping recognized potentially mutual genetic regions between a group of Black, Chinese, and Japanese patients on chromosome 15q21.2–22.3, within which NEDD4 inhabits.

In analogous studies among relatives, one on *chromosome 2q23* and the other on *chromosome 7p11* were recognized in Japanese patients and African-American patients, respectively. Notwithstanding evidence of familial keloid formation, there was a changeability in phenotypic presentations and scar severity between families; hence, polygenic inheritance pattern is mostly included in keloid inheritance [4].

Although there are no clear evidence regarding the influence of inherited genes on the higher frequency or severity of scar among patients with skin of color, it was

previously observed that the ethnicity of families with multiple affected members is mainly African-American and Indian. Variations in the age of onset, severity of the scars, and response to treatment in the same ethnic group may highlight the role of multiple gene mutations in the pathogenesis of the scar. Nevertheless, the pattern of gene involvements in scar pathogenesis is an area of further research.

43.3 Management of Scars in the Skin of Color

The prevention of scars can be achieved by proper cleaning and debridement of wounds, avoidance of unnecessary invasive procedures in high-risk population, and prophylactic measure. Modalities that prevent wound stretch – such as silicone gel sheets or tapes – and intralesional corticosteroids exhibited promising results inn scars prevention; however, the evidence is still weak.

To identify the most suitable management strategy, a thorough clinical examination should be done. This assessment must contain a full medical history, a detailed keloid scar history, any family history of keloids, and a psychosocial assessment. Moreover, a detailed examination should be conducted, including location, color, contour, size, pliability, and symptoms, i.e., pain and itching. Keloid is an untreatable disease, but nonetheless, physicians might be able to manage the manifestations of keloid, counting reducing scar size and redness and mitigating inflammation; this might reduce the recurrence rate of such lesions and may even yield complete extinction of lesions. Deterrence of signs and symptoms' exacerbation and impediment of recurrence after therapy are the main treatment goals of keloids.

Clinically, it is challenging to forecast if a scar will progress into either a hypertrophic scar or keloid. Increasing skin tension in specific locations and orientations while closing the wound and the existence of infections and foreign bodies may amplify the chance of keloid development. The more susceptible sites on the body for keloids include the earlobes, mandibular angle, posterior neck, shoulders, upper arms, upper back, and anterior chest. Bleeding, ulcerative, or firmly attached scars should undergo histopathologic investigation as a differential diagnosis of keloids. The possible differential lesions might be keloidal scleroderma, scar sarcoidosis, dermatofibroma, dermatofibrosarcoma protuberans, morphoeic basal cell carcinoma, and metastatic skin nodules.

Several therapeutic modalities are used in the management of keloid; though, due to unknown resolution rates and high recurrence rates, it is challenging to support any specific therapy. While several strategies exist, owing to the absence of level I evidence, none of them is universally demarcated as the standard. Presently, the treatments used have at best inadequate or indefinite effectiveness, with possible adverse drug reactions. Furthermore, many of these treatments require long treatment durations, might worsen the lesions, or could not prevent recurrence [3]. Multiple treatments for keloid, with varying efficacies, have been stated to date. Traditionally, a number of treatment regimens, for example, cryotherapy, interferon, and verapamil, have been applied for treating keloid, with unreliable success levels. Though, more novel treatments such as intralesional steroid injections, imiquimod, silicone gel, radiotherapy, lasers, electrical stimulation (ES), bleomycin, 5-fluorouracil (FU), surgery, and photodynamic therapy (PDT) have also been tested, not all have revealed efficacy in ethnic pigmented skin. These treatment modalities were reviewed in detail (◘ Fig. 43.1). However, due to the lack of studies on ethnic skin, some included studies presented data on pigmented, as well as nonpigmented keloid skin.

43.3.1 Nonsurgical

43.3.1.1 Intralesional Steroid Injections

Intralesional injection of corticosteroid (alone or with other agents) is one of the commonest treatment methods for hypertrophic scars and keloids. They are injected each 4–6 weeks as insoluble triamcinolone acetonide (0–40 mg/mL) until pain, scar, and pruritis subside. The response of patients to the treatment ranges from 50% to 100%, while the recurrence rate ranges from 9% to 50%. However, 63% presents with complications like localized ulceration, dermal atrophy, and telangiectasia or hypopigmentation. Noteworthy, pain might be managed through applying a local anesthetic. Corticosteroids alone represent the most efficient for young keloids, while older keloids are further resistant [2].

43.3.1.2 Silicone Gel/Sheet

Using silicone gel/sheets is assumed to diminish mobility and decrease the scar tension. How silicone gel works is uncertain; however, it may serve as an impermeable membrane to preserve hydration of the skin. A former RCT with 21 patients compared silicone gel with no therapy. Gold et al. found a reduction in hypertrophic scarring and keloid incidence following silicone gel use. However, the limitations of this trial were short follow-up period (only 12 weeks), and the blinding and techniques of randomization were not stated.

In another RCT by De Oliveira and colleagues, 26 patients suffering from keloids or hypertrophic scars had a mixture of silicone gel sheeting and non-silicone gel sheeting, while the control group received no treatment. They found no statistically significant difference

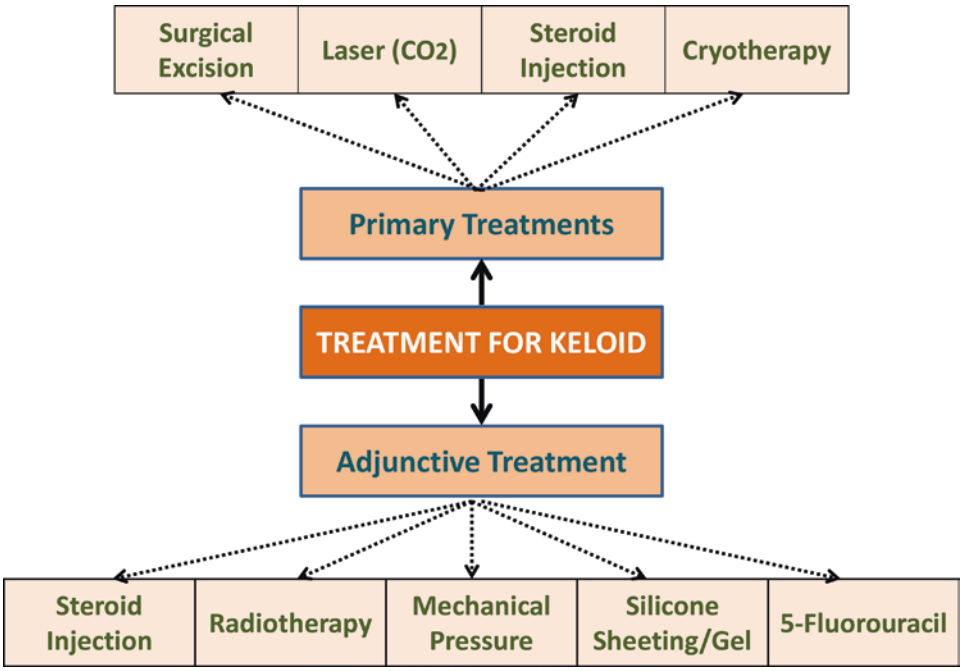

Fig. 43.1 Treatment modalities for a scar in colored skin

in the symptoms or size of scar by taking any of the treatments; however, both scar types were combined in their analysis, and the follow-up period was <6 months. These findings were in parallel with the results of O'Brien and Pandit study that was carried out among 13 trials including 559 subjects, observing the efficacy of silicone gel in the management of abnormal scarring in vulnerable groups. These studies collectively highlighted the demand for further controlled trials to approve the safety and efficacy of silicone gel sheeting.

43.3.1.3 Radiotherapy

Radiotherapy is preferred in elder adults who failed to respond to other treatments. It is used only in elderly patients because of the theoretical risk, however, there is a low risk of carcinogenesis. In resistant keloids, we could use ionizing radiation with intralesional excision. It acts via inhibiting collagen synthesis and inducing apoptosis of proliferating cells, which might rebuild a balance between keloid degeneration and collagen synthesis. It is given in doses of 15–30 Gy, ranging from 3 to 40 Gy among the studies, along six periods with accurate dosimetry and proper protection in the postoperative duration [2].

Doornbos et al. retrospectively analyzed 203 patients with keloid lesions using radiotherapy postsurgical excision. They elucidated the correlation between dose and response, with bigger doses decreasing the recurrence rate more efficiently. Conversely, Klumpar et al. found no significant dose–response correlation. Moreover, some investigators as Ragoowansi et al. and Maarouf et al. have supported the use of immediate postoperative radiotherapy [3]. Large-scale clinical trials are required to investigate a dose–response correlation among different races. Using radiotherapy as an adjuvant has revealed good scar resolution rates from 67% up to 98%. Yet, the retrospective study design, different follow-up intervals, and lacking universal clinical evaluation have weakened this success rate.

43.3.1.4 Photodynamic Therapy (PDT)

The cytotoxic effects of PDT (with methyl-amino levulinate and amino levulinic acid) were investigated in different keloid lesional sites. One study concluded that the success of PDT depends on the photosensitizer precursor, the location, and the number of fibroblasts at the lesion site. A beneficial effect of topical application of methyl-amino levulinate PDT was initially observed in a patient with resistant keloid. There is a case series with 20 keloid patients who were examined for the effect of PDT. The results showed that PDT reduced pain and pruritus scores, reduced flow of blood, improved pliability and reduced levels of collagen in keloid, and resulted in a decrease of volume of keloid without recurrence over the follow-up period (9 months) [5]. These findings direct potential utility of PDT in the management of keloid and necessitate a further high-quality clinical trial to confirm the safety and efficacy of photodynamic therapy.

43.3.1.5 Electrical Stimulation

Electrical stimulation (ES) was investigated in relieving the keloid symptoms, such as pruritis and pain. Lately, a new in vitro system examined the efficacy of various ES types on collagen expression in keloid fibroblasts and revealed that ES could inhibit formation of collagen I in keloid. Two case series confirmed the efficacy of degraded wave ES in few patients with painful keloids, and the regimen exhibited significant amelio-

ration of the symptoms [6]. Moreover, Sebastian and colleagues investigated the efficacy of PDT with and without ES and reported that the excitation improved the cytotoxic effects of PDT. Large-scale studies are needed to confirm the effectiveness of PDT-ES combination therapy.

43.3.2 Surgical

Surgery is needed in patients with hypertrophic scars with contractures, particularly when affecting joints that result in function loss. Hypertrophic scars may impede movement when they do abnormal forces on adjacent tissues or cross the joints. The elbow, knee, and shoulder are most commonly affected joints by contractures following burn injury. Surgery must be approached with caution as surgical scars may themselves increase the risk of keloid in pigmented skin. Recent studies showed no difference between surgical cutting modalities in terms of scar characteristics [7].

Surgical excision of keloids must be executed with substantial precaution, owing to the high recurrence risk. Excision could result in a bigger lesion and increased possibility of recurrence. The link between scarring and mechanical stress scarring is due to keloid scars occurring primarily in sites of excessive stress and mobility, for example, the shoulder, scapular region, and sternum. Therefore, it has been encouraged that cases subjected to surgery in these specific locations must have a long time of local skin support and splintage.

43.3.2.1 Surgical Excision and Adjuvant Therapy

The essential method in keloid treatment is surgical removal and primary closure, then injection of local steroid. Initial surgical excision followed by postoperative injection of steroid and silicone sheeting showed a 15% recurrence rate. Other modalities, for example, wearing a body corset or supportive bra, can furthermore decrease the risk of keloid in the mid-sternal region or upper trunk. Precautions to be considered while performing the first keloid surgery include not putting tension on the adjacent skin while closing the lesion. All possible causes of residual inflammation, i.e., entrapped hair follicles or dermal sinus tracts, should be excised to avoid recurrence. In case of large-sized keloid, serial excision would be well thought out to diminish skin tension. The injection of corticosteroid may be performed with surgery, then once every month for about 4–6 months. Surgeons should avoid local Z-plasties, W-plasties, and skin flaps beyond the defect to avert recurrence of bigger keloid. Of note, the use of silicone as a prophylactic method has so far been recommended in many studies except for Niessen et al.'s study. Topical steroid tape has also exhibited effectiveness in preventing recurrence, although it has the potential for unfortunate compliance because it is dependent on its continuous application by the patient [1].

43.3.2.2 Cryosurgery

Smaller keloid lesions have been treated by cryosurgery; however, substantial pain and occasionally prolonged healing times posttreatment limit its usage. The hypothesized mechanism of action is through ischemic damage that results in cellular anoxia producing necrosis of tissue. Furthermore, it modifies collagen synthesis and stimulates differentiation of keloid fibroblast near normal phenotype, thereby reducing keloid scar size [8].

Intralesional cryosurgery is a technique advanced from simple cryosurgery, which was first announced, by Shepard and Dawber. A simple cryosurgery, including pray technique or liquid nitrogen contact, etc., might produce vascular injury causing necrosis of tissue, anoxia, sloughing, and consequently scar flattening. This procedure could take two to ten treatment sessions with an interval of 20–30 days between each session. The success rate was reported ranging from 32% to 74% following two or more therapies, with superior response rates among hypertrophic scars over keloids. There are complications such as pain and immediate blistering with long-term risk of dermal atrophy that could be hyper- or hypopigmented. Conversely, intralesional cryosurgery includes introducing a recent intralesional cryoneedle (Cryoshape™) inside the scar over the long axis. This probe is formed of an elongated uninsulated needle having double lumen with a safety vent and a sealed, cutting, distal tip prepared to augment the penetration of firm, dense scar. The probe proximal end is linked with liquid nitrogen that is pressurized to circulate within the needle that results in an ice ball forming around the cryoneedle leaving the adjoining scar tissue totally frozen, thus resulting in an apparently normal collagen regarding its structure and organization with a decrease in myofibroblasts and mast cells in the scar. This technique was first described in 1993 by Weshahy and later popularized by Har-Shai et al. and has revealed superior efficacy over simple cryosurgery, with a reported clinical effect ranging from 20% to 75% reduction in the scar volume. The main complications are peritreatment edema and epidermolysis, temporary hypopigmentation, and pain (while this pain is lower than simple cryotherapy). The main advantage of intralesional over simple cryotherapy was melanocyte sparing feature that accounts for a lower incidence of dyschromia as the temperature of skin surface is less influenced in intralesional cryotherapy [2].

A hospital-based clinical trial was performed on 30 patients with keloid using cryotherapy. The findings demonstrated that cryosurgery was an essential treatment regimen for recent keloid, chiefly in smaller lesions. Also, they found that both thicknesses and duration of

keloid were the main agents in defining treatment outcome by cryosurgery. These findings were supported by Tziotzios and colleagues who recommended cryosurgery for reduction of scar size. Recently, a case study investigated the efficacy of cryosurgery plus surgical excision combination in 12 participants with keloid after 12 months. They demonstrated that shaving linked to cryosurgery was beneficial in the management of bulky keloid lesions because all cases showed improvement signs. Yet, it is arduous to follow this treatment modality owing to the small sample size [3].

43.3.3 Response Rates and Side Effects in Skin of Color

It is well-recognized that skin type significantly affects scar response to various modalities of treatment. Previous reports have shown that African-American patients had lower vascular response to topical corticosteroid than Caucasian patients. Relatively low response to bleomycin was reported among patients with skin of color. Patients with skin types IV–VI showed low response rates to different types of laser as well.

In terms of safety concerns, patients with skin of color are more reliable to higher incidence of adverse events than patients with lighter skin types. The risk of hypopigmentation after cryotherapy is more prominent in patients with darker skin due to cold sensitivity of melanocytes. While excessive melanin in patients with skin of color can absorb more laser and lead to hyperpigmentation, the high prevalence of melasma among patients with darker skin may contribute to post-laser hyperpigmentation as well. Hereditary hemolytic diseases are more prevalent among African-American, and they may impair healing after laser excision of the scars.

43.3.4 Recurrence Rate

Keloid scars are associated with high rate of recurrence, especially when treated with surgical excision alone. However, there are no current published data that address the effect of skin type on the rate of recurrence after scars treatment.

43.4 Management of Scars in Asian Skin

Recent guidelines on the management of scars in Asian patients recommended that scar prevention should be initiated in the immediate postoperative period owing to the high risk of developing poor scars. The recommended first-line therapy was silicone-based products (silicone gel and silicone gel sheets) based on their easy administration and strong supporting evidence. Several second-line therapies were recommended in case of failure of the first-line treatment, including intralesional steroid or 5-flourouracil injections, as well as radiotherapy. Despite lack of strong evidence, laser treatments have been increasingly accepted in these patients; however, further studies are needed to confirm its efficacy and determine the optimal wavelength and amount of energy required. Surgery is generally considered a last resort in resistant keloids. It can be combined with radiotherapy "sandwich technique," which has shown relatively low recurrence rates in Japanese patients [9].

43.5 Conclusions

Keloids are considered a challenging medical condition for both patients and medical health professionals owing to its high recurrence rate. The existing body of evidence has tried to investigate the pathophysiology and molecular basis involved in scar development using a reliable and reproducible model of a keloid. These endeavors would optimize the treatment and improve the outcomes of the disease. Currently, it is crucial to robust the published evidence, merged with clinical outcome, to deliver patients with the best therapeutic regimens for scars. Moreover, additional large-scale, long-term, and high-quality RCTs are indispensable to conclude the safety and efficacy of these treatment options further, and also comparative studies are compulsory to identify the best treatment modality for scars in the pigmented skin. Finally, standard guidelines and protocols are mandatory to standardize the progress of such promising treatment modalities on a global scale.

The current body of evidence has emphasized the requirement for additional long-term clinical trials with larger sample size to assess the efficacy of the aforementioned treatments strongly. Several studies were short-term clinical trials with small numbers of patients included, and the others were case series. Besides, lacking stratification of patients into categories according to the type of lesion, i.e., keloid or hypertrophic scars, location, a degree of severity, or ethnicity of the patients, was present in some of these studies. The different types of scars are diverse at the molecular level and morphologically. Furthermore, the difference in skin color, site, number, and size of the scar could respond differently to the same modality of treatment. Therefore, this variability ought to be taken into consideration when designing those studies. Likewise, the measures used to assess scar characteristic and response to treatment were variable among the studies. Therefore, it is a compulsory requirement to use universal tool for

assessment and implantation of measures to monitor cellular and metabolic activities in the tissue of keloid which, in turn, would support tailoring specific modality of treatment with each category of patients to ensure the best response of disease to treatment.

Keloid is unique for human tissue. This esoteric nature made keloids' preclinical studies scramble owing to the absence of animal models. Nonetheless, the advent of an in vitro organ culture model of keloid was fundamental in facilitating the study of disease molecular biology, pathophysiology, and the response among variable therapeutic modalities. This model was found to be a valuable tool for investigating new treatments and optimizing the treatment that would exhibit the optimum safety and efficacy in a diminution of the keloid scar mass size. Hence, it is considered as a prospective approach for new therapies assessment.

Take-Home Messages

- Pigmented skin has a higher chance of developing hypertrophic and keloid scars following wounds.
- Thorough history taking and clinical examination are essential for accurate assessment and management of abnormal scars in pigmented skin.
- Several therapeutic modalities for keloid management are available; however, there is lack of evidence to identify one strategy as the gold standard.
- Nonsurgical modalities for keloid management include intralesional steroid injections, radiotherapy, photodynamic therapy, and electrical stimulation.
- Surgery is needed in patients with hypertrophic scars with contractures, particularly when affecting joints that result in function loss.
- Combination therapies of surgical and nonsurgical modalities have shown some promising results; however, further research is needed.
- Large-scale clinical trials and clinical practice guidelines are needed to direct the development of effective treatments for keloid management.

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Scar and Scarring in the Elderly

Hester Colboc and Sylvie Meaume

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_44

Aims of the Chapter

- To provide demographic data on the elderly and the definition of elderly in medicine
- To bring elements of skin aging and dermatoporosis
- To describe the consequences of age on healing and major comorbidities in elderly that impair healing
- To address the main problems raised by scars in the elderly – these scars are not the hypertrophic scar, the keloids, or the scars due to cosmetic aspects but the recurrence of a wound on a scar, the Marjolin's ulcer, the hyperkeratosis, the unstable scars, and the adhesion to the deep plane of old scars

44.1 Introduction

The population is getting older all over the world. This means that more people are living with chronic illnesses, which reduce their independence and force them to take various medications. Healthcare professionals should take this into account when managing scar and scarring problems in older patients. Until now, research works primarily focus on the treatment and prevention of wounds in the elderly – acute (dissecting hematoma, skin tears, etc.) or chronic (pressure ulcers, leg ulcers, diabetic wounds of the foot, etc.) – but too little was done concerning the problem of scarring itself and even less on scars associated with the loss of skin function along the time.

44.2 Epidemiology of the Elderly: A Factor to Consider

According to the United Nations' report on the aging of the world population, adults over 60 years will outnumber younger people by 2050 [1], and in Europe alone, more than 20% of the population will be over 65 years in 2025 [2]. As this population ages, many older people will live with chronic conditions, reduced independence, polypathology, and polypharmacy, a situation healthcare professionals should take into consideration when dealing with dermatological, scarring, and scar conditions. While governments encourage the growing trend in Europe to promote an adapted elderly management, the specific wound healing and scarring care provided by surgeons, physicians, and caregivers is increasingly important but scarcely discussed [3].

44.3 Definition of Elderly in Medicine: Should We Make Distinctions?

If the WHO defines elderly as over 65 years of age, the increase in life expectancy in good health means that when we talk about elderly people in the medical environment, these are subjects of more than 75–80 years, and the distinction between the healthy elderly and the polypathological elderly becomes important. The state of health of the elderly is multifactorial. It depends on genetic, environmental, social, psychic factors, and the existence of multiple pathologies. It is not necessarily linked to age. For 30 years the concept of fragile old man/woman has been developed [4]. It obeys to several definitions and criteria which vary accordingly to the numerous publications of which it is the subject and makes it a dynamic medical concept. Only 10–20% of the nonagenarians or centenarians are considered fragile. These are the so-called geriatric patients who require specific management. Most people over the age of 75 are not frail and considered "fit" with good functional autonomy and good social integration and few pathologies. Conversely, the frail elderly present functional limitations and a decline in their ability to adapt and anticipate. To distinguish these two types of elderly population, standardized geriatric assessments have been developed using validated scales of autonomy, nutrition, cognition, etc. [5]. This evaluation is not only performed by geriatrician if one wishes exhaustive but can also be realized by nonspecialists and paramedics: nurses, physiotherapists, social workers, dieticians, occupational therapists, and speech therapists. The objective of such assessments is to provide a supportive plan adapted to each patient, a compromise between what is desirable and feasible or reasonable and what is not (Table 44.1).

Table 44.1 Main factors of frailty in the elderly

Age over 85 years
Loss of autonomy for an activity of daily life or more
Impairment of cognitive functions
Reduced nutritional reserves
Inadequate social support (loneliness, poverty)
Sedentary lifestyle, confinement, postural instability
Poorly compensated sensory disturbances
Kidney and liver failure
Depressive symptoms
Polymedication

44.4 From Skin Aging to Dermatoporosis

Skin aging leads to alteration of the skin and consequently to the loss of its physiological barrier role. Skin aging leads to alteration of the skin and consequently to the loss of its physiological barrier role. It is the consequence of intrinsic (genetically programmed) and

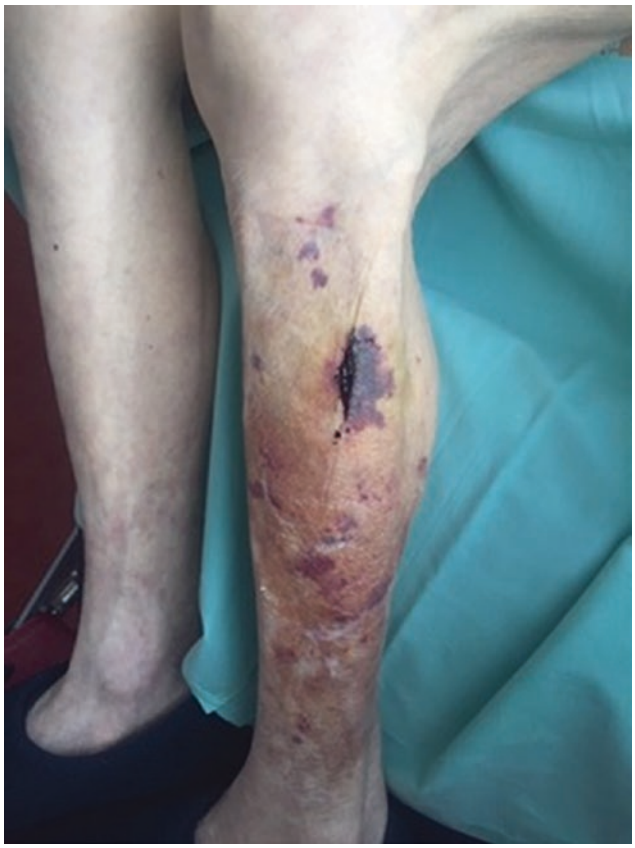

Fig. 44.1 Dermatoporosis: Bateman purpura, skin tears, hyperpigmentation, and spontaneous stellar pseudo-scars

extrinsic factors. These extrinsic factors are numerous, and include more specifically drugs aggravating the physiological xerosis (hypolipidemic oral, allopurinol, hydroxyurea and cimetidine) [6], deficits in essential fatty acids, in vitamins (B group vitamins, E, PP, C, A), zinc, magnesium as well as malnutrition frequent in the elderly patient and environmental factors such as smoking and exposure to ultraviolet (UV). For some patients, skin aging can become can constitute a real functional organ failure, far from cosmetics considerations. The term "dermatoporosis" was recently proposed by Saurat [7, 8] to cover all the manifestations and implications of this chronic skin syndrome linked to skin fragility and insufficiency.

The clinical manifestations of dermatoporosis (Fig. 44.1) include morphological markers of fragility (skin atrophy, Bateman's purpura, spontaneous stellar pseudo-scars, hyperpigmentation), as well as the functional expression of skin fragility (skin tears, poor healing, dissecting hematoma). The first signs appear around the age of 60, while the disease itself, with its related complications, is observed between the ages of 70 and 90.

On a microscopic scale, skin aging is manifested by a thinning of the dermo-epidermal junction and an extension of the keratinocyte renewal time. In the dermis, there is observed a decrease in the number of fibroblasts and thus the density of fiber collagen and glycosaminoglycans, with thinning of the dermal thickness. Associated with this quantitative drop is a qualitative drop in residual fibers. During aging, a decrease of hydrophilic character of the glycosaminoglycans, responsible for the hydration of the dermis, is observed. This chemical modification can explain the dermal thinning and xerosis seen in the elderly. These changes also affect the microvascularization, with thinning of the vessel wall, which may explain the tendency to hematoma and purpura (Batman's purpura) typically observed in the elderly.

44.5 Consequences of Age on Wound Healing

Physiological healing has three main stages, directly impacted by aging: the first stage is hemostasis and inflammation, second stage is cell proliferation, and third stage is tissue remodeling. With age, platelet adhesion to the damaged endothelium is increased, decreasing the healing time. The local inflammatory answer to injury is reduced, following a decrease in the expression of molecules of adhesion. The proliferation phase is also impaired by slowing the renewal keratinocyte evokes above and also a decrease in response to growth factors. Finally, tissue remodeling, the final stage of wound healing, is also impaired in the aging subject due to an imbalance between metalloproteinases and their physiological inhibitors, in favor of metalloproteinases and therefore the destruction of collagen [9]. The different healing phases are therefore altered by these phenomena in the elderly: reduction of the wound contraction, cell proliferation, neovascularization, delay of the inflammatory phase, and slower epithelialization [10].

Apart from these deleterious aspects, elderly healing presents some advantages. Thanks to a decrease in inflammation, pathological scarring such as hypertrophic scars and/or keloids is rarely observed in elderly. After skin excision for tumor, sometimes needing a consistent loss of substance, the aged patient skin laxity generally allows an easy reapproximation of the edges and the suture may be realized without tension, issuing to good scarring. However, suturing itself can be impacted by the increased skin tears risks due to the dermatoporosis.

44.6 Frequent Comorbidities Altering Wound Healing in the Elderly

Many comorbidities frequent in the elderly can decrease wound healing. Undernutrition and diabetes can delay all type of wound, while arterial or venous diseases and edema (linked to heart, kidney or liver failure) can delay healing of lower limbs wounds. Elderly patients are also more

exposed to treatments that can delay healing, especially systemic corticosteroid therapy and cancer chemotherapy.

44.7 What Scarring Problems Are Usually Observed in the Elderly?

Traumatic and surgical acute wound healing is rather good even in very old patients, and *hypertrophic or keloid scars are rare*, at least in the Caucasian population [11].

The poor quality of the scar is usually not a major problem (appearance, color, shape) [12] except in exposed regions (face) or when impacting the function (heel, eyelid, and periorificial areas).

Pruritus and/or pain may appear very lately after the trauma/surgery and occur after 20 or 30 years. They are linked to dermatological problem (dry skin) or neurogenic disorders. These situations may be treated symptomatically with appropriate cosmetics [13]. A few of them need surgery, but war, posttraumatic, and post-surgery scars are not usually reasons to go to see a doctor.

Atrophic and adherent scars can be improved by injecting fat under the scar, a recent technique presenting the advantage of being scarcely invasive when anticoagulation is not needed or should be stopped (Fig. 44.2).

The reappearance of a wound on a scar should be considered differently. The recurrence of a tumor may be at the origin of the scar. A biopsy or the recurrence of a chronic ulcer (arterial or venous, pressure, or diabetic foot ulcers) is needed to diagnose a malignant transformation.

It can also lead to the reassessment of the patient and indication of preventive treatment of compression or discharge (cushion, shoe, soles).

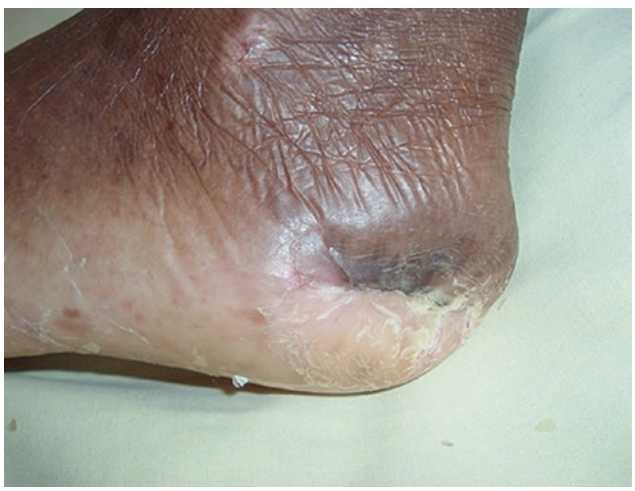

Fig. 44.2 Atrophic scar/defect: In this stage 4 pressure ulcer, the healing process led to a neoskin adherent to the underlying structures like aponeurosis, muscle, tendon, and bone. The possibility to inject adipose tissue under the skin should be discussed

Post-irradiation scars in cancer treatments (breasts for example) pose the problem of radiodermatitis and radionecrosis which evolves and worsens over time, in particular in the elderly who were irradiated at a time when the administered doses were high.

Some scars from childhood linked to operated orthopedic malformations are associated with joint deformations of osteoarthritis because of mechanical forces pressure or friction exerted on those scars or because of underlying medical problems in the region: arterial disease or neuropathy.

Marjolin's ulcer [14], a rare and aggressive skin cancer, develops late on scars from burns (Fig. 44.3) or from delayed wound-healing problems: chronic osteitis, burns, pressure ulcers, lupus scar, skin graft, and radiodermatitis. Squamous cell carcinoma are more frequently observed than basal cell carcinoma, melanoma, or sarcoma. The occurrence of a wound on a scar aged of more than 20 years always requires a biopsy [15].

Hyperkeratosis is common especially on scars on plantar aspect of the foot, the heel, next to the Achilles tendon, or on the toes and the lateral aspects of the foot, due to a thickening of the stratum corneum reaction to friction or to mechanical conflict, especially in case of loss of sensibility (diabetes, nerve damage). Cracks can appear and constitute entry doors exposing to the risk of deep infection (Fig. 44.4).

Unstable scars may appear because of their location, sometimes due to a poor quality of the dermal component (absent or fibrotic) or insufficient preventive measures taken against external agents (shoes, stockings, bandages, prosthesis, etc.).

These wounds finally closed after a succession of closure and multiple reopenings, source of discomfort, and risk of cancer transformation (Fig. 44.5). The treatment of these unstable scars becomes more and more complex due to the underlying diseases and comorbidi-

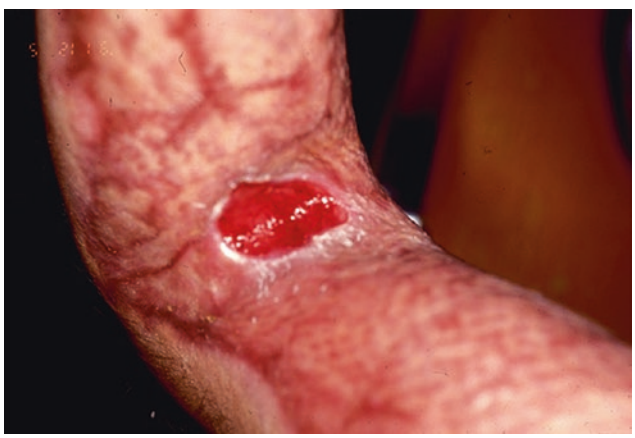

Fig. 44.3 Marjolin's ulcer on an old burn scar

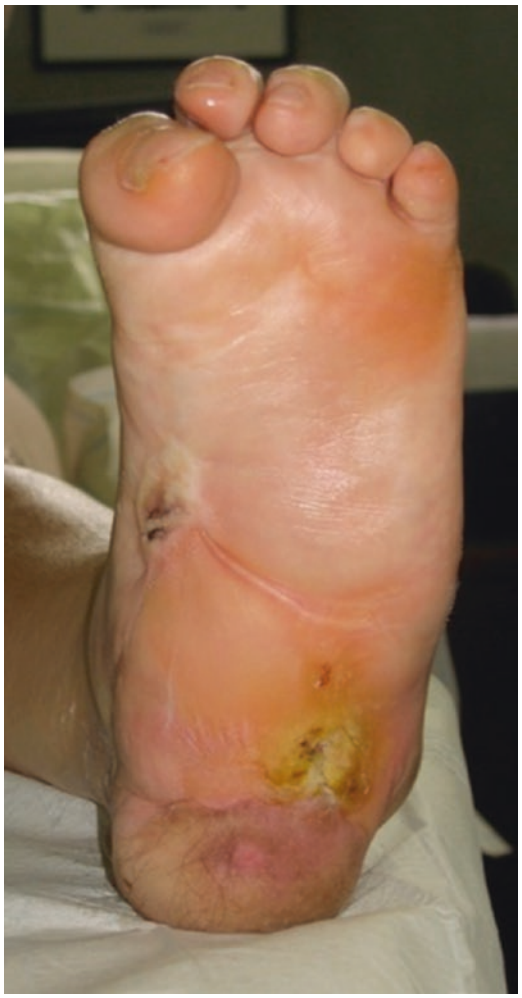

Fig. 44.4 Scar becoming problematic with the age due to mechanical forces, trauma, pressure over the scar, underlying pathology (osteitis, diabetes, vascular diseases venous or arterial) issuing to hyperkeratosis, and potential neoplasic transformation

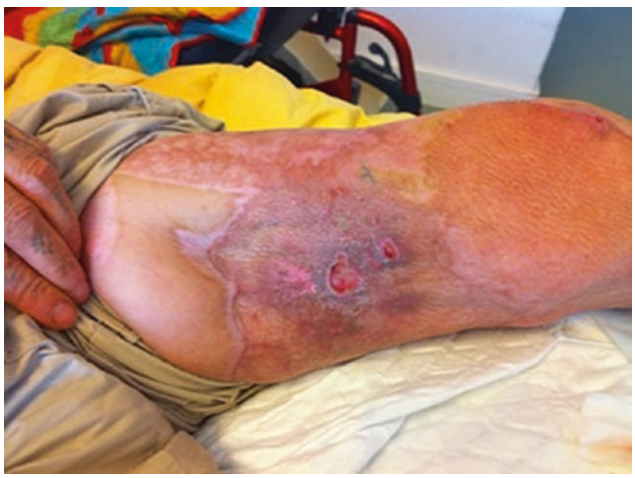

Fig. 44.5 Scar instability: consequence of poor quality of dermal component (absent or fibrotic) and poor preventive measures taken against external mechanical agent (shoes, stocking, bandage, prosthesis, etc.). Succession of closure and reopening phases

ties. Biopsies often need to be done to rule out a malignant degenerescence.

Adherence to the depth is a problem that worsens with age. Healing occurring on a wound with loss of deep substance (dermis, fat, gliding capacities) and not correctly repaired (for exemple using negative pressure therapy, skin substitute or flap) may lead to an atrophic scar adherent to the deep plans. These adherent scars can disrupt normal skin movements and mobilisation of the patient, specially when located near an articulation. These adherences are exposed to skin reopening due to the loss of elasticity of age-related skin.

44.8 Conclusion

Epidemiological studies are lacking and the literature is poor on the subject. Hypertrophic and keloids do not seem to be a frequent problem in the elderly. The absence of inflammation and tension on the scar is undoubtedly an explanatory factor that perhaps merits more basic research. However, persistent functional problems lead aged patients to consult. Chronic wounds or sites of a long-lasting healing process are associated to an increased risk of malignant transformation, that must be take into consideration by the clinician. Regarding scars, elderly patients are usually less concern by the cosmetic aspects and its impact on the quality of life. The existence of underlying diseases can reopen certain scars or pressure ulcers and therefore the treatment must be adapted according to the comorbidities. The geriatrician sometimes has a role to play in establishing the therapeutic plan.

Take-Home Messages

- The number of elderly people is increasing.
- The tension on the scars is often less because the skin of the elderly is less elastic (modification of the extra cellular matrix).
- Keloid and hypertrophic scars are rare in the elderly.
- Scars problems are more often malignant degenerescence, hyperkeratosis, atrophy, instability, or adherence to the depth.
- A biopsy must be performed if the scar reopens or persists in an elderly patient.

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Management of Scarring Following Aesthetic Surgery

Alexandra Chambers

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45.1 Introduction

Aesthetic (Cosmetic) Surgery
Aesthetic surgery's principal purpose is to improve physical appearance and self-esteem.

Demand for cosmetic surgery procedures continues to grow at a rapid pace around the world, with a 9% increase in treatments performed in 2017 compared to the previous year. This translated into 20 million more cosmetic surgery procedures [1]. According to the International Society of Aesthetic Plastic Surgery (ISAPS), the USA, Brazil, Japan, Italy, and Mexico account for 41.4% of the world's cosmetic interventions. Breast augmentation, liposuction, eyelid surgery, rhinoplasty, and abdominoplasty were the most popular treatments.

All surgical procedures have inherent risks, and aesthetic surgery is not an exception. One of the risks is poor scarring, and this can occur from postoperative infection, wound dehiscence, tissue necrosis, or simply from abnormal healing tendencies. Unfavorable scarring is not uncommon following cosmetic surgery; the incidence can vary from 5% after breast augmentation to as high as 8% after abdominoplasty [2, 3]. The impact of excessive scarring can be disturbing to a patient and can incite significant morbidity and psychological distress. The experience can also be disheartening for the surgeon, as the patient will likely blame them for scars. For example, in the UK, approximately a quarter of medical malpractice claims after cosmetic surgery are related to poor scarring and, on average, generate roughly £300,000 in awards [4]. The cost of remedial scar treatment can be quite expensive, taking time and resources of both the patient and the surgeon.

Given the risks of poor scarring, it makes sense for cosmetic surgeons to take as many precautions as possible to avoid inferior outcomes. This chapter explores preventative measures to preclude the occurrence of unacceptable scars, as well as treatment strategies for when they nevertheless develop.

45.2 Patient Selection for Cosmetic Surgery

All cosmetic procedures are elective, and identifying patients at risk for poor scarring is a key starting step. It is important to develop a selective approach in offering aesthetic treatments to reduce unfavorable outcomes and to mitigate potential problems. Patients must be included in the decision-making process, beginning with providing a clear explanation of the risks for their specific case. The surgeon must take the time to explain and to provide realistic management of patient expectations. Only after clearly describing the risks and answering questions can patients make a valid informed decision.

The scar risk and acceptance matrix (Table 45.1) is an example of a simple clinical tool that can be used to quantify the risks of cicatrix formation. This is a communication tool that can help a patient's understanding and, when used in a clinical practice, only requires a few minutes of consultation time. The parameters taken into account for this calculator are the preexisting medical conditions that might affect healing, life style risks, the patient's constitutional tendencies to poor scarring, and the patient's expectations about scar appearance.

Each row of the matrix can contribute an integer value from 1 to 5 according to the descriptions in each column. Adding the results from each row gives a total score, with low values corresponding to low risk. Patients with medium and high risk should be well counseled before their procedure, and the preventative measures (to be described later in this chapter) should be taken before surgery. A very high-risk score might justify declining treatment. The following subsections describe each row of the calculator in more detail.

45.2.1 Evaluating Medical Risks

Reviewing a patient's medical history is key for identifying patients who might be at risk for the types of complications that can lead to poor scarring. The following examples illustrate some of the issues to consider.

- Individuals with cardiovascular disease and hypertension might be at higher risk of bleeding or inadequate tissue perfusion.
- Chronic lung disease and poor peripheral circulation can cause inadequate oxygenation of skin. This in turn could lead to a potential necrosis at the surgical site.
- Autoimmune and connective tissue diseases can give rise to excessive fibrosis and scar thickening. They can also lead to suboptimal collagen deposition, resulting in atrophic or widened scars.
- Immunosuppressed or diabetic patients will have a greater chance of postoperative infection and a problem healing.
- Allergies to certain medications or substances, like latex or adhesive dressings, might compromise an otherwise successful surgery.
- Some medications and supplements can promote postoperative bleeding or predispose to hyperpigmentation.
- Patients, who have previously developed unsightly scars, might be prone to keloid and hypertrophic or atrophic healing.

Table 45.1 Scar risk and acceptance matrix

Score	1	2	3	4	5
Medical risks	None	Hypoxic chronic state CVD Hypertension	Suppressed immunity, including steroid use Diabetes	Autoimmune connective tissue diseases Post-bariatric surgery malabsorption	Peripheral Vascular disease Hyper-viscosity states
Fitzpatrick skin type and constitutional tendencies	Skin 1–3 No history of poor scarring Dry skin with low sebaceous activity	Any skin type Red, pigmented or slightly uneven and lumpy scars BMI > 30	Any skin type Multiple stretch marks, very loose skin Atrophic scars present	Skin 4–5 Previous hypertrophic scar Post-inflammatory hyperpigmentation BMI < 18 Thick skin, higher sebaceous activity	Skin 6 Previous keloid scars
Lifestyle	Healthy life style	Sedentary, hectic lifestyle Binge dieting	No sun protection and overuse of sun beds	Alcohol abuse Recreational drugs use	Smoking (any type) Nicotine replacement
Psychological assessment and patient expectations	Expects scarring Accepts possibility of a poor scarring, including keloid	Expects scarring Hopes for no poor scarring	Expects scarring, which can be easily disguised	Expects scarring but only a minimal	Expects no scar at all

A cumulative score of 5 or below is indicative of low risk for unfavorable scarring and low probability of patient distress with a scar. Scores 6–10 indicate medium risk, scores 11–15 predict high risk, and scores 16–20 very high risk

In summary, a good understanding of the patient's medical history and how this could affect the scar formation process is important for the surgeon's treatment plan, which also helps the patient understand their specific risks. A discussion of these issues is an important part of helping the patient to make an informed decision.

45.2.2 Assessment of Constitutional and Genetic Risks

Being either under- or overweight increases surgical risks, and this also has an effect on postoperative recovery [5]. Patients with one of these characteristics may suffer from nutritional or metabolic abnormalities (or both). Accounting for this before proceeding with a cosmetic surgery is strongly advisable.

Also of note is the specific case for patients who have undergone bariatric surgery to control their weight. These patients often develop a condition of malabsorption and a significant metabolic shift.

For some individuals, there will be inherent familial or racial risks that can contribute to excessive scarring. Although, no specific genetic mechanisms have yet been identified, individuals with the skin type 4–6 on the Fitzpatrick scale are at higher risk for more noticeable scars [6]. Both the *MYH9* gene (coding for a non-muscle myosin) and apolipoprotein1 (APOL1) have been implicated in non-diabetic kidney disease and keloid scarring in people of African descent (see Fig. 45.1). There is a hypothesis that a haplotype *MYH9-APOL1* is likely responsible for keloid formation [7]. Brown et al. [8] found a genetic association between *HLA-DRB1∗15* status and the risk of developing keloid scarring in individuals with a pale complexion.

In a practical clinical consultation, the surgeon can simply enquire about ethnicity and make an examination of the patient's skin. Pigmentation tendencies and any previous scars or marks (for example from vaccinations or injections) will help estimate risks. Figure 45.2 illustrates a tendency to form a keloid scar following mesotherapy injections for improving fine décolletage lines.

Note that age plays a role in constitutional scarring tendencies. Older patients with thinner and dryer skin have almost no chance of developing keloid scarring, whereas teenagers with higher sebaceous and cellular activity have a higher chance of developing pronounced scars.

As already stated, poor scarring can negate the benefits of the cosmetic surgery. A careful explanation of the risks is essential before embarking on a procedure.

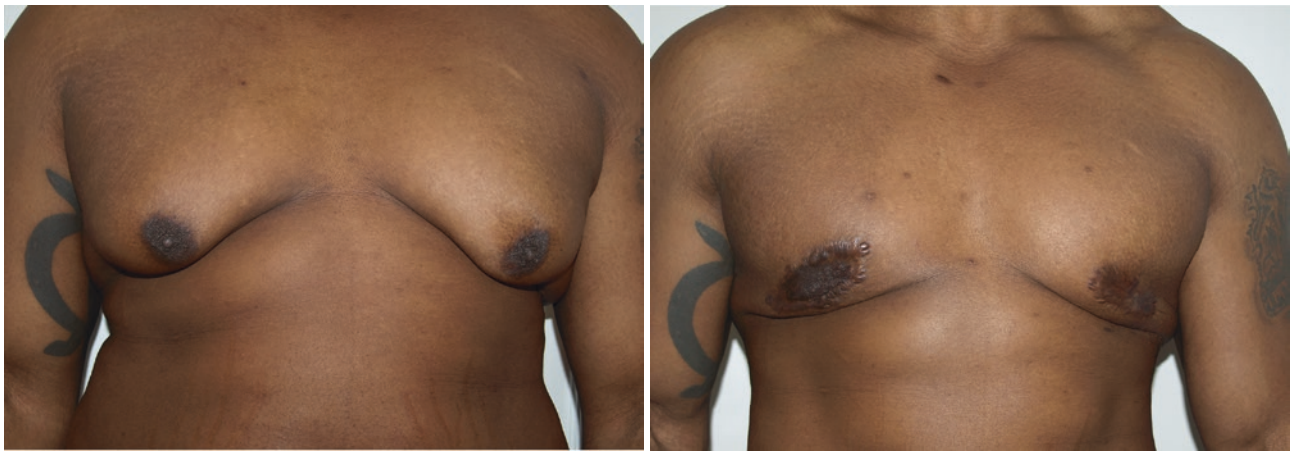


Fig. 45.1 Unilateral keloid scar formation after gynecomastia and mastopexy surgery in a patient of African origin with skin type 6

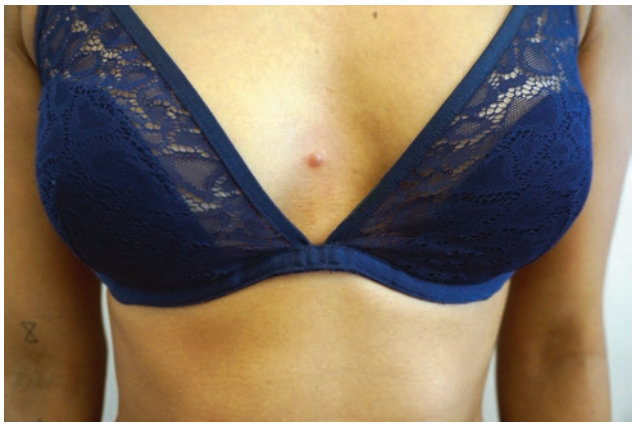


Fig. 45.2 Nodular keloid scarring after a needle prickle of presternum skin

The patient needs to be fully informed and should have the time to weigh the risks versus the benefits of a procedure. Procedural planning and early preventative interventions can change the balance toward a more acceptable final outcome.

45.2.3 Modification of Lifestyle

A patient's lifestyle choices can have important effects on their postoperative recovery, including scarring. It is important to assess these types of risks and to advise the patient on the steps to be taken before and after surgery. Furthermore, as some patients may not fully follow proposed lifestyle modifications, it is wise for the surgeon to plan on compliance tests and to enter these into the patient's medical record prior to surgery.

It is well known that smoking tobacco products has a detrimental effect in the perioperative period by exposing tissue to the effects of nicotine, carbon monoxide, hydrogen cyanide, and nitric oxide. These all impair wound healing. There are numerous retrospective and prospective cohort studies of levels 2 and 3 evidence demonstrating the relationship between smoking and delayed postoperative healing.

That said, there are studies with level 1 evidence showing ameliorating effects on surgical outcomes when preoperative smoking is discontinued for 4 weeks or longer prior to surgery [9]. When embarking on a smoking cessation protocol, patient compliance should be checked with a carbon monoxide breath or urinary cotinine test just prior to surgery.

Heavy use of alcohol can cause vasodilatation and increase perioperative bleeding. Patients should be advised to refrain from drinking alcoholic beverages for 2 weeks before and after their surgery. A blood test for gamma-glutamyl transferase (GTT) can establish whether a patient is abstaining and compliant with the recommendation.

A balanced diet and supplements of vitamin D, zinc, and iron have a positive impact on postoperative healing.

Substance abuse can have complex effects that potentially include reducing a patient's compliance to preoperative protocols, and this can also decrease their immunity. These types of issues are serious enough; however, it should be noted that in some regulatory contexts, individuals suffering from addictions might not be considered capable of giving a valid consent to cosmetic surgery.

Physically fit, active, and psychologically stable individuals tolerate surgery better and recover faster [10].

In summary, it is important that the patient be informed that their surgical outcome will depend on lifestyle. This should be particularly emphasized for those who need to make changes prior to surgery.

45.2.4 Psychological Assessment and Expectations Management

Evaluating a patient's psychological state of mind can be challenging for cosmetic surgeons; however, it is an essential component of every presurgical consultation. It is important to evaluate a patient's motivations for surgery for several reasons. First, it can give an indication of whether they will be apt to follow the key pre- and postsurgical advice they have been given to optimize their surgical outcomes. Second, it can help identify those patients who may have unreasonable expectations and give an indication of the likelihood of them becoming combative or litigious (regardless of the outcome). Finally, it is a required step in determining whether a patient suffers from body dysmorphic disorder (BDD), which, depending on the regulatory context, could potentially legally disqualify them from surgery.

Psychological assessment and expectations management is a difficult process, especially since most surgeons are not trained in how to do this. There are some common sense steps that can be used without too much difficulty. The first is to look for indicators of psychological imbalance during the consultation process. For example, note whether the patient is overly concerned with minor cosmetic defects. If this is the case, then even the most nominal scarring will likely be unacceptable to the patient.

Show the patient before- and after-photos for a broad spectrum of surgical outcomes, and ask them for feedback on which ones correspond to their hopes and expectations. If the patient indicates a strong preference for an unrealistic outcome for their body type and age, the surgeon should factor this observation into the score.

The consultation process should be used to determine the history of psychological treatments, as well as the patient's history of past cosmetic procedures. Although a patient may hide their psychological care, a physical examination will turn up scars that may be easily associated with past cosmetic surgeries. This can be used to begin a conversation about the patient's satisfaction with past procedures, and what revisions they have undergone.

Finally, the surgeon should always ask the patient for permission to contact their general practitioner (GP) for a confirmation of their medical history. If the patient refuses, this might be a warning flag, although it may simply be due to negative social perceptions of aesthetic surgery. However, if the patient's medical condition or medical history might possibly contraindicate a surgical procedure, it is essential that the patient obtain a letter from their GP indicating that undergoing surgery would be safe.

Realize that no psychological evaluation will be 100% effective. Some patients with psychological issues such as BDD will have learned how to game doctors with credible answers. Nevertheless, the surgeon must make a good effort at trying to provide the patient with an honest assessment while also avoiding harming patients who are at risk. There are some practical tools that can be considered for this.

First, consider making a video recording of all consultations with every patient. This will be the primary record of what was discussed, including facts presented about surgical risks, and indications of the patient's expectations.

Make liberal use of before- and after-photos. It can be quite difficult to understand a patient's perspective, and it is equally difficult for a patient to understand the likely outcomes without concrete examples. Particularly important is the patient's appreciation of scarring patterns and their acceptance of their inevitability. The before- and after-photos present an excellent opportunity for gauging the patient's sentiments on scarring.

Asking the patient for permission to contact their GP is an important step of the consultation process. The GP can often provide relevant information about the patient's medical history that is relevant to the safety of a surgical procedure.

Finally, it is worthwhile to be abreast of psychological risk factors for various segments of the population and to fold such statistics into the patient's overall evaluation. For example, some patients might not be open about their true motives for cosmetic interventions, and in some contexts, their aims might be controversial [11]. Recognized factors associated with a poor psychosocial outcome of aesthetic surgery include [12] the following:

- Being of a young age and of male gender
- Having unrealistic expectations of the procedure
- Having had previous unsatisfactory cosmetic treatments
- Exhibiting minimal deformity
- Motivations based on relationship issues
- A history of depression, anxiety, or personality disorder

For cases where the surgeon has a serious doubt about a patient, it makes sense to defer surgery while collecting more data. The surgeon can insist on a letter from the GP stating their opinion that it would be safe for the patient to undergo surgery. In highly borderline cases, it might make sense to ask the patient to undergo a psychological assessment before proceeding with treatment.

45.3 Prophylactic Measures in Cosmetic Surgery to Reduce Excessive Scarring

Scarring is an inevitable result of all surgeries; however, as already discussed, patients will be more critical and less accepting of scars from cosmetic procedures than for those obtained after surgeries for illness or injury. Even after extensive preoperative counseling, patients

typically do not fully appreciate the realities of scarring. This means that cosmetic surgeons should make every effort to minimize scarring by utilizing all available tools and methods to optimize healing. This section reviews a range of current options.

45.3.1 Choice of Surgical Techniques

Careful planning is the best approach to achieving success for any surgery, and this is especially true for elective cosmetic procedures. The following discussion provides a list of points that should be planned for prior to surgery.

Meticulous surgical field preparation and antibacterial prophylaxis are crucial in mitigating risk of infection. Infiltration with local anesthetic and adrenaline, combined with a careful hemostasis, will help reduce bleeding during and after the operation. Both infection and hemorrhage can be detrimental to wound healing and should be avoided at all cost.

The surgeon must take care not to damage vascular dermal plexus when undermining skin and take into account blood supply via a vascular pedicle when lifting flaps and cutting through tissues. Inadvertently damaging local circulatory pathways will lead to skin necrosis and devastating consequences.

Incisions should be made bearing in mind the natural skin tension vectors. Avoiding crossing these will diminish the likelihood of wound dehiscence, scar widening, or hypertrophy. Similarly, avoid areas with tight skin such as the presternal, upper shoulders, and over the extensor surfaces of joints [13].

Try to strategically hide scars by placing incisions as much as possible in the natural creases of the skin or where imperfections can be disguised by clothing.

Finally, a cosmetic surgeon must handle tissues gently, approximate edges of the wound carefully, and make use of fine instruments and suturing materials. While closing tissue incisions, a surgeon should bear in mind how the tensile strength of the wound will evolve during the healing process. The tension strength of the wound, related to cross-linking of collagen, will only be 3% of that of a normal skin after roughly 1 week, 30% after 3 weeks, and 80% after about 12 weeks [14]. This should be reflected in the choice of suturing techniques and materials. Nonabsorbable sutures can be removed after 7–10 days, but appropriate additional scar holdup is required during the first 3 months with adhesive tapes, dressings, and garments.

45.3.2 Methods to Control Better Healing

Postsurgical techniques to influence and optimize scar formation are varied. Some methods are well established, while others are still experimental. A brief review of modalities currently in use is summarized here.

- Compression garments to reinforce tensile strength across a wound and to reduce stretching and friction
- Adhesive tapes and plasters
- Topical flavonoids
- Botulinum neurotoxin type A (BoNTA)
- Platelet-rich plasma (PRP)
- Microneedling + topical applications
- Imiquimod
- Bioengineering and recombinant DNA

The first step in postsurgical scar optimization is the use of compression therapy. Although the effects are poorly understood, compression keeps wounds reinforced and prevents both stretching and friction. A wide range of compression and support garments are available. Pressure levels should be sustained at 15–40 mmHg for at least 23 h/day over a period of 6 months. This presents, however, a problem of patient compliance due to restrictiveness of such a regime.

This can be managed with the use of various adhesive tapes and plasters to cover the already closed wounds. These keep the scar undisturbed and protected and can be more comfortably used over a longer period of time. A randomized controlled study of 70 patients using a paper tape on their wounds showed this to be an effective strategy [15].

More specialized dressings and skin substitutes can be utilized to promote epithelization by creating matrix for a cellular migration, providing a protective barrier, and sustaining a moist environment. Silicone gel and sheets have been shown to reduce unfavorable scarring in randomized controlled studies [16, 17], but a meta-analysis of 13 trials involving 559 patients demonstrated only weak evidence that silicone can reduce the incidence of abnormal scarring in high-risk individuals [18]. That said, silicone softens the scar and makes it more comfortable for patients, and because of this, it may be worthwhile. It is recommended to use silicone dressing for at least 12 h a day for 2 months from 2 weeks after the surgery.

Topical flavonoids such as Contractubex (Merz Pharma, Frankfurt, Germany) or Mederma skin care gel (Merz Pharmaceutical, Greensboro, CA, USA) are used to keep scars soft and supple from the second week after surgery for up to 6 months. Their efficacy has been found to be controversial, but the dietary bioflavonoid quercetin can also improve scarring by suppressing fibroblasts proliferation via inhibition of SMAD intercellular transduction protein [19]. This reduces the actions of the transforming growth factor β (TGF-β) and reduces fibroblasts activity.

In clinical practice, cosmetic surgeons can use botulinum neurotoxin type A (BoNTA) immediately after wound closure. Injections of 15U of the preparation have been shown to improve scarring following 6 weeks after a facelift [20].

Platelet-rich plasma (PRP) has gained some popularity for skin anti-aging, chronic wound management, and scar therapy. Treating a wound bed with PRP has shown substantial benefits for better wound healing, an increased survival of fat grafts, and the acceleration of cartilage and bone grafts uptake in a systematic review of 15 randomized controlled trials and 25 case-controlled studies [21]. Platelet-rich fibrin also proved to be useful in aesthetic and reconstructive applications.

Also note that the repeated microneedling at a controlled depth and topical application of retinol and marine collagen reversed both atrophic and hypertrophic scars to a more even appearance after a year of treatment [22].

Attempts have been made to use Imiquimod 5% cream to prevent keloid recurrence after surgical excision. This topical immune-response modulator stimulates a proinflammatory cytokine interferon, which increases collagen breakdown. Imiquimod also alters the effects of apoptosis-associated genes. The preparation was used daily for a fortnight after a surgery. Later it was applied three times a week under a dressing for 1 month. The efficacy for this prophylaxis is still questionable, as the result of this double-blinded, placebo-controlled pilot study showed no significant difference in keloid deposition rates in the two groups [23].

Interesting research in tissue bioengineering is attempting to bring new methods to improved wound healing, with an objective of even achieving scarless regeneration. Promising results have been obtained using therapies based on TGF-β. A preparation of a recombinant version of this cytokine marketed as Juvista by Renovo Laboratory (Manchester, UK) has shown a 70% improvement in wound healing and scar appearance in a phase 2 trial. Other therapies developed by the same company include formulations of mannose-6-phosphate (M6P; marketed as Juvidex) and another preparation based on estradiol (marketed as Zesteem) [24].

In another study, a preparation of recombinant human TGF-β3, called avotermin, was injected before the skin was cut and again 24 h after wounding in healthy participants. A dose of 50 ng/100 μl of the drug per linear centimeter achieved 10% scar improvement in three double-blinded, placebo-controlled studies. However, the investigators had commercial interests in TGF-β3, which may weaken their claim. Nevertheless, they demonstrated a strict adherence to established protocols and research standards and conducted a rigorous statistical analysis [25].

Whatever methods be used to prevent unfavorable scarring, they must be initiated early enough to influence the processes of tissue healing. Failure to do so might lead to florid scarring that might subsequently be more difficult to treat.

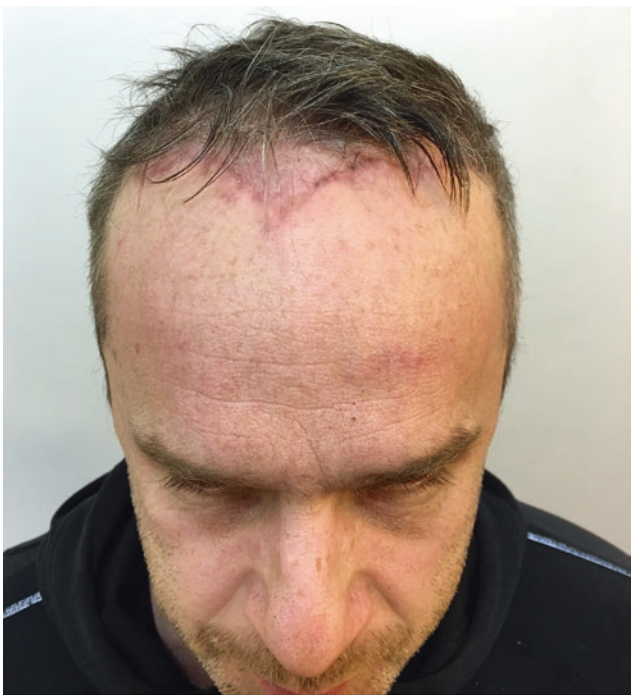
45.4 Treatment of Scars Following Aesthetic Surgery

Pronounced scarring following surgery is common. Up to 40% might display hypertrophic scar features, and 6–16% of these will evolve into a keloid scar (especially for patients of African descent). Scar atrophy can result from wound infection and inflammation, but it is less common.

If, after all other precautions, a scar begins to display features of pathological healing, or is simply too noticeable, treatment plans are still available and can do much to remediate the situation. Management of scars after aesthetic surgery does not differ from any other scar treatment. The therapeutic approach can be divided into surgical and non-surgical methods.

45.4.1 Surgical Treatments

Traditionally, keloid and hypertrophic scars are excised, and tissue is manipulated to allow for more favorable healing afterward. Excision with a linear, tension-free closure should be used. If the defect is a large one, or the wound is in a high skin-tension area, a split- or full-thickness skin grafting with Z-plasty or W-plasty skin closure flaps is recommended (◘ Fig. 45.3). That said, hypertrophic scars tend to spontaneously regress for up to 12 months. This suggests that surgical revisions should probably not be made until after a 1-year time window.



◘ **Fig. 45.3** Skin flap closure with W-plasty following a forehead lift with hair line advancement surgery

Hypertrophic scars rarely recur after excision, and as such, they require no adjuvant treatments following the removal. Keloid scars on the other hand can redevelop after excision. This will occur in more than half of all cases, and so will likely require additional therapeutic interventions. This should be undertaken immediately after their excision.

The most commonly used methods for controlling keloid scar recurrence include corticosteroid injections or radiotherapy. In recent years, a mixture of 5 fluorouracil (5FU) with triamcinolone has become popular. The cocktail is made of 3 ml of 5FU 50 mg/ml and 1 ml of the steroid containing 40 mg/ml triamcinolone. An amount of 1–2 ml of this mixture is used for postoperative tissue infiltration at the level of excision plane and below it. The treatment can be repeated after full epithelization of the wound. Postoperative pressure should be applied for 6 months afterward, and silicone gel should be used for 2 months.

45.4.2 Non-surgical Treatments

A broad range of treatments with no cutting of scars is available for cosmetic surgeons. Therapeutic choices vary from injectable preparations to interventions based on a variety of technologies. Whatever method is being employed, it should be done in a timely fashion with stepwise escalation to the next option if the current one is ineffective.

The first choice of non-surgical treatment for early keloid formation scars is intra-lesional corticosteroid injections. In most cases, steroid injections act as a second-line modality for hypertrophic scars if less-invasive options, such as silicone dressings and support tapes, fail.

Corticosteroids suppress inflammation in the wound; they reduce collagen and glycosaminoglycans synthesis, while increasing collagen degradation. Glucocorticoids inhibit fibroblasts proliferation and enhance their degradation. The most commonly used preparation is triamcinolone 40 mg/ml. A dose of 10 mg or 40 mg is injected into a scar, every 1–2 months. Usually two to three sessions are all that is required. Scars become flatter and softer with alleviation of symptoms, but a recurrence rate is common and can be as high as 50%. Side effects of corticosteroid injections are telangiectasia and dermal atrophy. Topical corticosteroid preparations in the form of creams can be massaged into post-blepharoplasty scars. Corticosteroid tapes are sometimes applied after aesthetic surgery for breast reduction. However, efficacy of topical corticosteroids for scar reduction has never been proven.

Laser treatment modality is next in line after corticosteroids. Pulsed-dye laser (PDL) with a wavelength of 585 nm is most commonly used for treating scars as a stand-alone intervention or in addition to other treatments. Pulse-shots at a fluency of 3.5–5.5 J/cm^2 are fired to cover the entire scar, making sure the shots do not overlap. Treatments are repeated four to six times every 3 weeks. Hyper- and hypopigmentation, blistering, and small bruises are possible after the treatment but tend to be transient.

It is sometimes possible to destroy scar tissue by subjecting it to subzero temperatures. For example, cryotherapy with liquid nitrogen is an option. Rarely used to improve scars caused by cosmetic surgery, it can be nevertheless be useful for pretreatment before repeating injections of corticosteroids in smaller scars. This is especially the case if laser is unavailable or has proven to be ineffective.

Recalcitrant scars can be subjected to radiotherapy. This method is mostly combined with the surgical excisions but is rarely used in aesthetic practice. The methods of radiotherapy choice include superficial X-rays, electron beam therapy, and low or high-dose-rate brachytherapy. They all can be utilized, but not for breast or tummy tuck scars due to their potential for carcinogenic side effects.

Atrophic tissue healing is another type of pathological scarring, leading to a volume loss and an indented surface formation. The treatment objective is to restore the tissue deficit and to reinforce thinning and hollowing of the scar surface. For the former, corrections are made with fillers and fat grafts. The latter can be achieved with stimulating therapies such as microneedling, Sculptra injections, free-floating PDO, or gold threads. An example study using a controlled depth microneedling approach proved to be effective for both atrophic and hypertrophic scars [22]. Early keloid scars can also respond to this type of intervention (◘ Fig. 45.4). This suggests that all pathological scars may have similar pathways for regression.

Another promising modality for treatment of scarring is botulinum neurotoxin type A (BoNTA). Keloid can be treated successfully with diluted BoNTA and the technique for that is described in ► Chap. 8.

45.4.3 Long-Term Management of Patients with Scars After Cosmetic Surgery

Even with a conscientious effort made by both the patient and the surgeon to control and optimize scarring, some patients will find it difficult to accept their outcomes. These patients may be especially psychologically vulnerable if their scars are located in areas easily seen. Examples include the eyelids after a blepharoplasty or in front of the ears after pretragal incision used during rhytidectomies.

The surgeon has some responsibility to help these types of patients come to terms with their scars. The

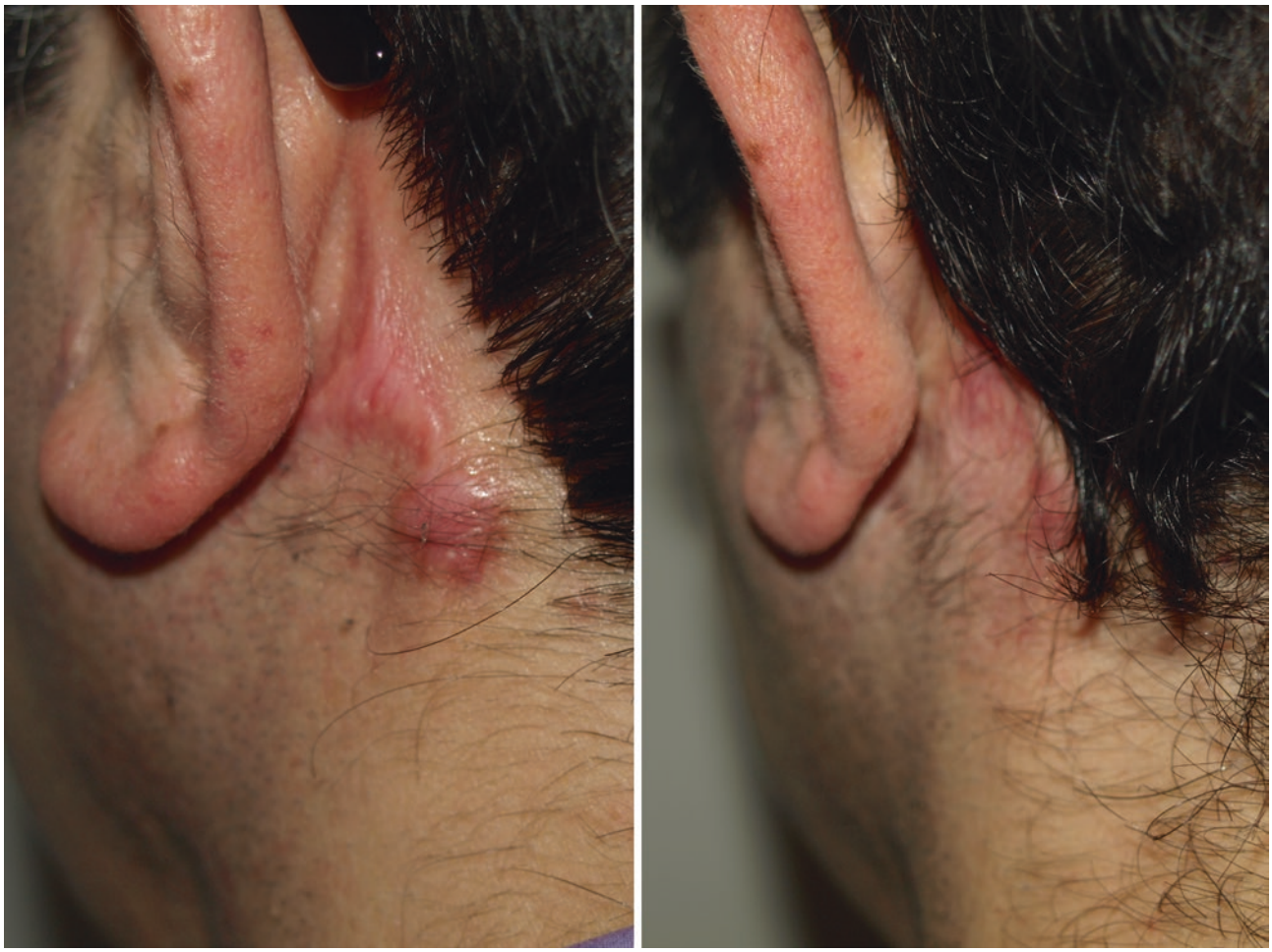


Fig. 45.4 Keloid scar following rhytidectomy was improved by using microneedling and topical retinol

process will likely involve a combination of approaches, including counseling, cognitive behavioral therapy, camouflage makeup, and medical tattooing. A multidisciplinary approach to the psychological rehabilitation of the patient will likely be needed to succeed. The surgeon should be empathetic to the patient's perspective and be prepared to help with what can often be a lengthy and arduous process.

45.5 Conclusion

Scarring after cosmetic surgery is the same as that from accidents, disease, or other types of surgical procedures. The context, however, is completely different. Patients primarily choose aesthetic surgery for non-essential health reasons. Because of this, when poor scarring occurs, cosmetic surgeons are at much higher risk for patient dissatisfaction and potential legal action.

A wide variety of therapeutic and prophylactic methods are available for the management of posttraumatic and postsurgical cicatrix. Thus, the main point of this chapter is that surgeons should put into place pre-, intra-, and postsurgical processes to mitigate scarring risks.

Finally, regardless of the objective severity of cosmetic surgical scars, this is an important component of a patient's perception of the success of the procedure. Surgeons should take an active role in providing patients with information and compassionate support.

Take-Home Messages

- Always bear in mind that a scar following aesthetic surgery impacts a patient far more than its objective evaluation and it negatively contributes to the overall perception of otherwise successful treatment.
- Carefully evaluate the potential risk of scarring and take appropriate measures to reduce it prior to surgery.
- Manage patient expectations by providing sufficient explanation of the range of potential outcomes.
- Avoid offering elective cosmetic surgery to people at high risk of very poor scarring or to those with highly unreasonable expectations.
- Plan and execute an appropriate surgical technique.
- Employ prophylactic measures and treatments in a timely fashion.
- Take active measures to minimize the formation of keloid and hypertrophic or atrophic scarring should they occur.
- Keep careful records (written and video) of the consultation process, surgical techniques, and postsurgical treatments, making specific mention of the management of scarring.
- Provide emotional and medical support to a patient, who is troubled by a scar after her or his aesthetic surgery.

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Scars in Pediatric Patients

Anne Le Touze

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_46

46.1 Introduction/Background

A child is not a miniature adult. Although physiological healing process is not different in children, their growth potential gives them some specificities in terms of healing and scaring. Disturbance of healing process or inappropriate wound treatment will lead to pathologic scar. Pathologic scars can disrupt growth in children.

46.2 Healing Specificities in Children

46.2.1 Fetal Healing

Experimental and clinical studies point that fetal healing is scarless [1]. Fetal healing mechanisms are still poorly known, although many endogenous and exogenous factors seem to differ from those of adult healing mechanisms. The main difference probably lies at the level of the immune system and the inflammatory response. All these studies concern different animal species and any extrapolation towards human species should be cautious.

Macrophages are known to be the major agents of the inflammatory response and tissue regeneration process in adults. In early gestation, healing process is accomplished with poor influx of macrophages, while the influx of macrophages in the wound is more important at the end of gestation [2]. The embryo seems to be able to heal without macrophages, and therefore without undergoing inflammatory response. Nevertheless, the embryo is able to respond to inflammatory stimuli [3]. Explanation for this paradox could be the immaturity of the inflammatory system, but we need further exploration to understand this ambiguity.

Collagen is scarce in the healing wound due to the lack of response of the fibroblasts to transforming growth factor beta 1 (TGFβ1). TGFβ1 induces glycosaminoglycan synthesis all along gestation: glycosaminoglycan is much more important than collagen in the scar matrix in fetus [4].

Amniotic fluid provides the fetus with an environment rich in growth factors necessary for its development. High concentration of hyaluronic acid in the amniotic fluid has been supposed to be the extrinsic and intrinsic factor of non-inflammatory fetal healing [5]. Further experimental studies need to prove that the quality of fetal wound healing is due to intrinsic factors [6]. Even if scarless fetal healing mechanisms are uncertain, absence of inflammatory response seems to be the key point.

Nevertheless, at the end of gestation, inflammatory response appears and scar becomes visible. Further exploration of fetal healing and better knowledge should allow for promising clinical applications.

46.2.2 Pediatric Peculiarities in Healing

Very few data on this subject is available in the literature. Nevertheless, "healing behavior" is peculiar and varies all along childhood [7].

- 0–6 months

  Infants before the age of 6 months heal very fast and with very discreet scar. It happens as if the inflammatory response was immature, therefore attenuated. Perhaps some phenomena of prenatal period are perpetuated after birth.

- 2 years – teenage

  On the contrary, the inflammatory expression of the scar dominates this period, and the phenomena of remodeling seem amplified, major, and disabling. The few comorbidities of healthy organisms and the physiological mechanisms linked to growth are an undeniable asset for the good evolution of the child's wounds. Scarring is often very fast but can be explosive. Hypertrophic scaring could be considered as physiological at this age, as it is constant.

- 6 months – 2 years

  The evolutive pattern of scar is unpredictable at this age, sometimes still discreet, sometimes already very inflammatory.

46.2.3 How to Manage Wound Healing in Children

As the inflammatory response is constant and "explosive," the healing process must be carried out over a short period of time to prevent excessive production of collagen.

Except for children under palliative care, most of the wounds can undergo surgery: mechanical cleansing, suturing, grafting, flaps. Before, instead of or after surgery, we use dressings or negative pressure wound therapy (NPWT).

Management of pain is essential and difficult: pain and fear are often entangled; level 2 painkillers are not recommended before 12 years old. Therefore, level 3 painkillers are often necessary but to be administrated in health institutions. Inhalation of 50–50% N_2O–O_2 mixture and any adjuvant technique of analgesia may be useful (hypnoanalgesia, video distraction, virtual reality, etc.) [8, 9].

Surgical techniques have to be adapted according to age, psychomotor development, thickness of teguments, and potential of growth. Thinner sutures are used with young children. Rapid absorbable sutures that generate an inflammatory response are to be avoided on exposed areas. On the contrary, intradermal slow absorbable sutures are a good option to avoid marks. Cyanoacrylate

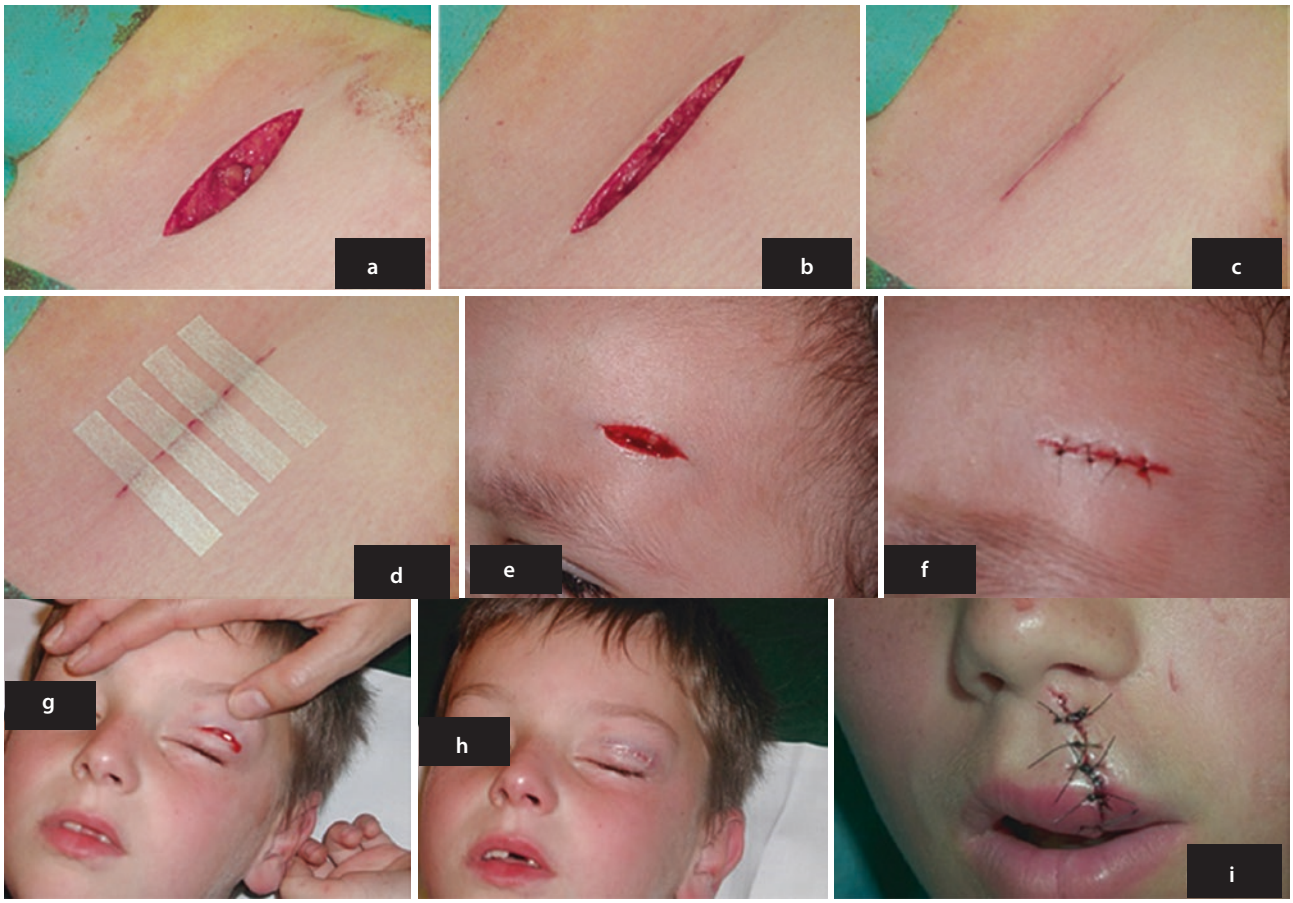

Fig. 46.1 **a**–**d**: Good-quality intradermal suture; **e** and **f**: good-quality epidermal suture; **g** and **h**: cyanoacrylate tissue adhesive; **i**: poor-quality epidermal suture, too thick sutures and under wedging

tissue adhesive may be used but is appropriated for very superficial wounds (Fig. 46.1).

Dressings have to be painless at removal, easy to apply. It is better to realize dressing with hand rather than with forceps because it is quicker and less frightening. Topics should be elementary; healing is rarely a problem in pediatric practice as child's body continuously synthesizes tissue for growth. Therefore, NPWT is most often rapidly effective, preparing wound to be grafted. Flap indications are therefore less frequent in pediatric practice than in adult practice.

46.3 Pathological Scars

Scar is the result of the healing process. Ideal scar is thin, flat, white, supple, elastic, and painless, but it exists and is perfectly identifiable under microscope (Fig. 46.2).

Pathological scars are due to dysregulation of healing phenomena, especially due to the dysregulation that occurs during the modeling phase. This results in prolonged or definitive inflammation and are called hypertrophic or keloid scars [10].

46.3.1 Clinical and Histological Aspects

At the beginning of their evolution, it is not possible to distinguish hypertrophic scars from keloid scars: both remain very inflammatory beyond the normal period, red, hot, tense, and itchy. Only the evolution can distinguish them (Fig. 46.3).

- Hypertrophic scar: despite a marked and prolonged inflammation period, the inflammatory signs will eventually be amended, leading to scar enlargement and fibrosis resulting in a thick scar. Histologically, collagen is abundant, is immature (collagen III in excess), is organized in more flat bundles than in a normal dermis, and contains nodules. Secretion of transforming growth factor β (TGFβ) and platelet derived growth factor (PDGF) is abundant. Fibroblasts are numerous, responsible for the secretion of collagen in excess. Mast cells are numerous, secreting histamine which is probably responsible for pruritus.
- Keloid scar: evolution goes on forever, leading to extension of lesions beyond the initial limits of the scar, with persistence of inflammatory signs. Sometimes, telangiectasia appears at the surface of the scar. Histologically,

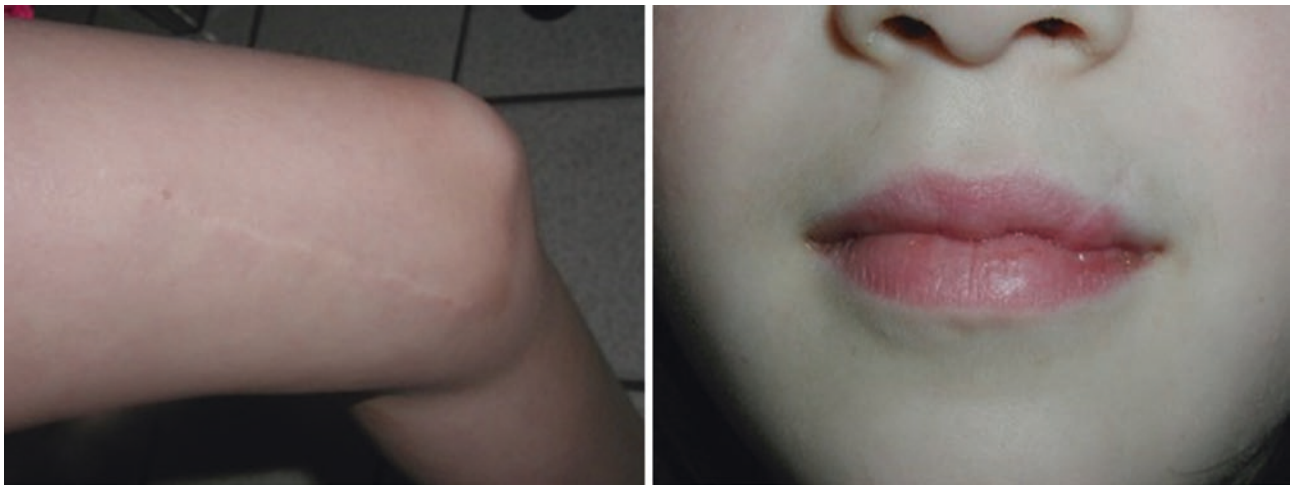

Fig. 46.2 "Ideal" scars

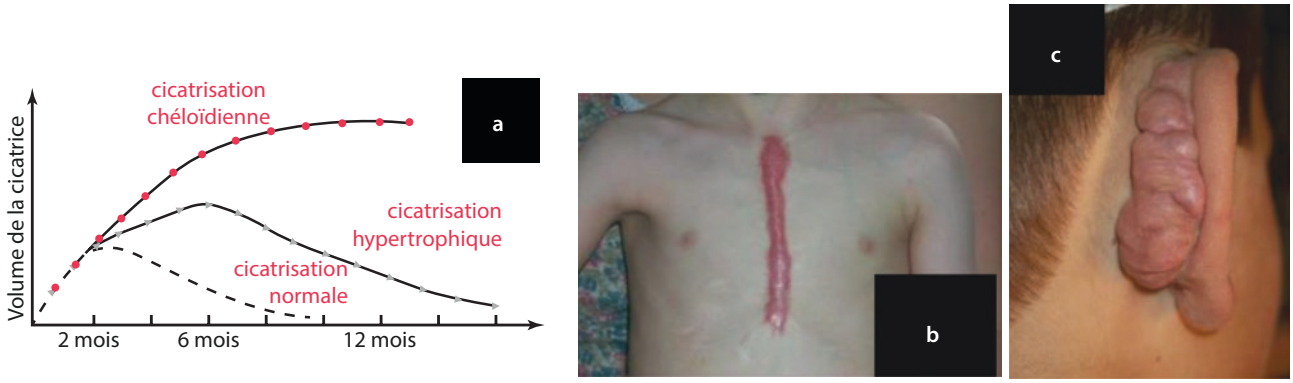

Fig. 46.3 Pathological scars: **a**: evolution diagram; **b**: hypertrophic scar; and **c**: keloid scar

we found the same characteristics as for hypertrophic scar but with a complete disorganization of the collagen arrangement: there are no more beams but collagen fibers randomly connected and poorly oriented.

46.3.2 Easing Factors

Most often, pathological scars occur on a particular field. Although the causal link is not always obvious, there are several factors that contribute to the same scar.

- There is no male or female predominance. The sex ratio for pathological scars is equal to 1.
- There is no evidence of hereditary factor. However, some authors have questioned about the hereditary characters of keloid scars [11].
- Nevertheless, the ethnic origin seems to be decisive. A preponderance of keloid scars is observed in subjects with pigmented skin (Black, Asian, Métis, etc.). Some studies submit biological hypotheses related to the characteristics of pigmented skins, but there is no evidence at the moment.
- The age of the patient is a determining factor. Hypertrophic and keloid scars are exceptional in the elderly and are very common in young people and around puberty. It is therefore essential for pediatric surgeons to be familiar with this scar pathology.
- The location of the wound plays a clear role: the scapular region, the ear area, and the midline of the trunk (presternal and medio-abdominal) are particularly concerned by the development of pathological scars.
- The types of wounds, such as deep burn, soiled wounds, and presence of foreign bodies in the wound, will prolong the cleansing phase and therefore the inflammatory phenomena.
- Hormonal factors: the preponderance of pathological scars at the time of puberty, the impact of pregnancy on scars, and the regression of hypertrophic scars at the time of menopause seem to evoke the role of estrogen. Some studies have looked at the use of antiestrogens in the treatment of hypertrophic scars [12].

Although all these factors may have been suggested as favoring pathological scars, only the age, the ethnic factors, and the location of the wound are really the determining factors. Mechanism of occurrence of these pathological scars is not yet totally understood.

46.3.3 Prevention and Treatment [13]

Treatment is often disappointing. Many treatments have been proposed, but they are quickly abandoned as they are ineffective. The physio-pathological approach of mechanisms has helped rationalize treatments, particularly by acting on inflammation. Nevertheless, the results often remain below the expectations of the patient and the physician.

Prevention, especially in high-risk population such as pediatric patients, is often effective.

- Prevention of pathological scars
- To be really preventive, treatment must be applied as soon the wound is healed: a few days after primary closure or as soon as epimerization is achieved in secondary closure.
  - Reduce inflammation
    - Decrease healing time by activating mechanical cleansing.
    - Decrease healing time by using surgical means of cover (grafts, flaps).
    - Use non-absorbable or slow absorbable intradermal sutures for which inflammatory response is less intense.
    - Massage of recent scars reduce edema and mechanically dissociate molecular aggregates. Therefore, massages have a real mechanical action. Massages are most often made with an emollient cream because they are better tolerated. However, massages would be just as effective as without cream.
    - Pressure therapy will also reduce edema, inducing a relative tissue hypoxia, thereby minimizing local inflammation. Silicone sheets act in a same way on inflammation [14] (Fig. 46.4).
  - Reduce tension on the scar
    - Use Langer's or Borges's lines in surgery.
    - Reduce tension on scar by using strips and splinting adjacent joints.
- Treatment of pathological scars

Some treatments are well established, even if their efficacy is disappointing. Other treatments are rather perspectives and subject to current studies. However, the evolution of these scars is sometimes so hopeless for the patient that minimally invasive techniques deserve to be tempted, even if their efficacy is very inconsistent.

Several techniques can be associated either simultaneously or successively.

When a scar becomes inflammatory, the earlier the treatment will be initiated, the more effective it will be.

Preventive techniques can be used as treatment techniques, but they will not be so effective.

- Massages
- Pressure therapy (Fig. 46.5)
- Silicone sheets
- Steroids have been used for a long time to treat pathologic scars.

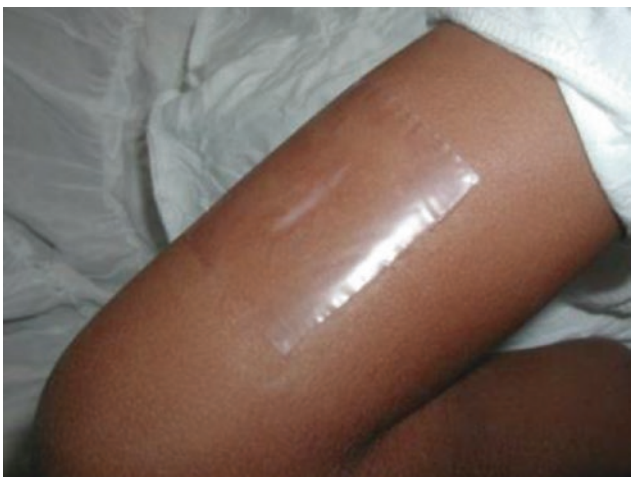

Fig. 46.4 Silicone sheet on hypertrophic scar

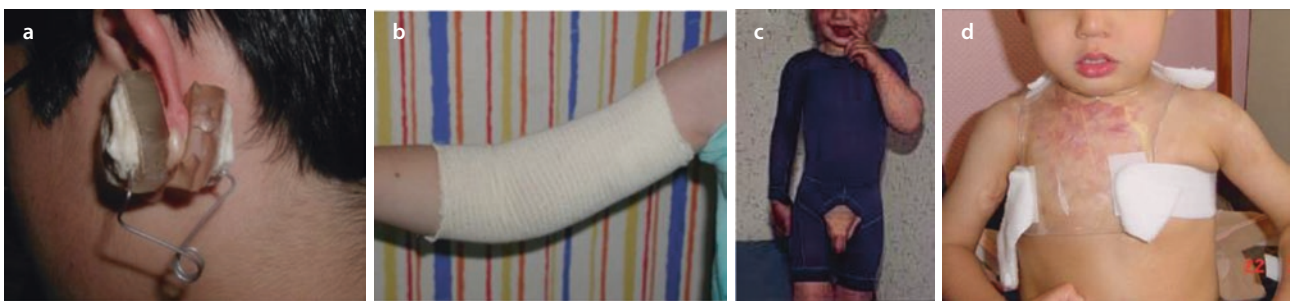

Fig. 46.5 Different devices for pressure therapy

They can be used as topic (cream or ointment) or in situ injections.

Local application may be dangerous in children, as the dose of absorbed steroids is difficult to evaluate. An overdose in steroids can lead to a partial or complete Cushing syndrome, which may occur due to abusive local application of corticoids.

For this reason, we prefer local injections of steroids in pediatric practice, using steroids of delayed action with minimal general effects. Injection is proceeded with dermo-jet or syringe and needle after local anesthesia (Fig. 46.6). Nevertheless, it is often more comfortable to do so under general anesthesia in day surgery unit. Injections can be repeated until at least 2 months between two injections so as not to overload the scar with steroids. The only contraindication is the local infection. Most of the time, flattening of the scar and disappearance of functional signs (pain, pruritus) are observed.

However, it is necessary to be cautious because steroid overload results in epidermal thinning and appearance of telangiectasia.

- Cryotherapy [15] may be used with inconsistent results: it may be used by contact or with freezing needles (Fig. 46.7).
- Surgery will induce more inflammatory reactions. Therefore, surgery on its own will not solve the problem: it must be a step in a therapeutic scheme, associating several techniques, and must be proceeded only at the end of the scar maturation, when the inflammatory phenomena have calmed down.

  Intralesional excision is the only way to prevent recurrence, but it does not mean that it consistently gives the expected result. The volume of the scar will decrease, which will improve comfort and release functional effects, and perhaps the residual scar will be more receptive to the complementary treatments that are necessary to avoid recurrence.

  An injection of delay-steroids can be performed in the dermis of the banks of the excision wound before closing by non-absorbable sutures. Pressure therapy will be prescribed systematically as soon as healing is achieved (10 days).
- Radiations (X-rays, radium, iridium) may be proposed, but they are not to be used in pediatric practice because of carcinogenic risk.
- Anti-neoplastic substances [16] have been the subject of research in recent years: Interferons, mitomycin C, bleomycin, 5-fluorouracil [17] are all molecules that are used as injections in situ, either alone or in combination with corticosteroids. These treatments have to be used very carefully and when there is no other therapeutic possibility in pediatric practice because of their interaction with growth.
- Laser therapy has been tried on pathological scars [18] and is easy to use in pediatric practice under contact local anesthesia.
- Finally, it may be wise, in some situations, to allow time for inflammatory phenomena to decrease spontaneously before initiating aggressive therapies. This implies to support the patient because the evolution often seems hopeless.

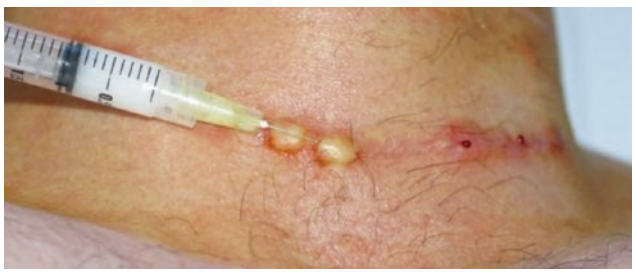

Fig. 46.6 Intralesional injection of steroids

Multiple treatments are proposed for these pathological scars due to their uncertain efficacy and the difficulty in achieving results that satisfy the patient (and the physician).

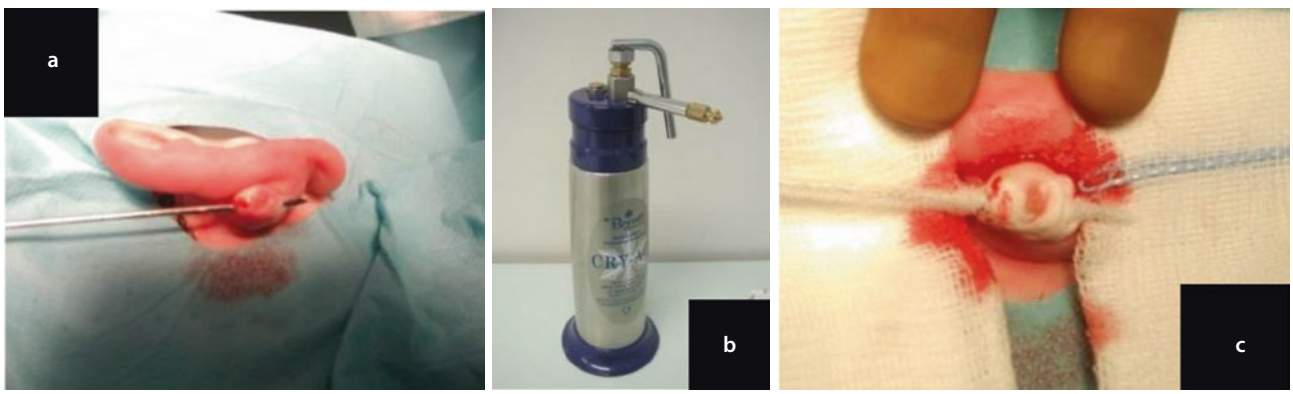

Fig. 46.7 **a**–**c**: Cryotherapy

46.4 Defective or Disgracious Scars

Some scars are defective or disgracious and do not disturb the healing process: hypotrophic or enlarged scars, adherent scars, dyschromic scars, tattooed scars, granuloma, technical defects, etc.

All scars that present defects but no pathology of the healing process can be corrected by surgery, irrespective of the technique used: surgical recovery, adipocytes transplantation (Coleman technique), dermabrasion with or without vaporization of autologous keratinocytes, etc. However, it will be necessary to wait at least until the end of the maturation phase to consider secondary surgery.

Deciding what is the best time to practice this surgery is sometimes difficult in pediatric practice. Apart from functional indications for which the question hardly arises, the indications are most often aesthetic. It is then necessary to ensure the child's actual motivations and that this is not a parental request.

If the child is voluntary, a "contract" must then be passed with the child or teenager emphasizing three key points:

- The disgracious scar will be replaced by a scar that hopefully will be of better quality. There is no magic rubber for scar.
- Postoperative scar management (e.g., strips, silicone, possible splint, and refraining from sportive activities) is constraining but necessary for a good result.
- If the patient is not able to undergo scar management, surgery is useless.

All these scar anomalies can be corrected, but it is of course essential to prevent and avoid them.

46.5 Scars and Growth

During the first 2 years after healing, the scar matures. Contraction of the scar is current and normal due to the action of myofibroblasts. After this period of time, the scar is quiet and more or less definitive.

In pediatric practice, the patient will grow with the scar. This may induce tractions because the scar is fibrous and does not grow as much as the patient. If this is not corrected, it may induce bending because of asymmetric growth.

Psychomotor development may be disturbed by scars. Physicians should be aware that psychological impact of scars evolves over time all along childhood and teenage. Therefore, pediatric patients with scars have to be followed all along their growth period to detect the need for scar surgery, whether it is for functional purpose or for aesthetic and psychological purpose.

46.6 Conclusion

Healing physiology is not different in children but the importance of inflammatory mechanisms makes the resulting scar different. Hypertrophic scar is physiological in pediatric practice and has to be prevented.

Take-Home Messages

- Obtain rapid closure of wound in children.
- Always prevent hypertrophic scaring in pediatric practice.
- Follow-up children with wide scars until end of growth.

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Genital Scars

Ursula Mirastschijski

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_47

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Background

Excessive scarring of the genitalia is uncommon despite the fact that approximately 30% of men are circumcised worldwide with minor complication rates and no mention of scarring. After burn injury, severe scarring is commonly seen in the perineal or suprapubic area but rarely occurs to the outer genital organs. Skin anatomy, inflammatory response, and hormonal metabolism differ between the genitals and the extragenital skin and might therefore account for differences in wound healing and scarring. Owing to the high regenerative potential of genital skin, the management of genital wounds aims at the stabilization of the local tissue with infection control and demarcation of necrotic tissue. Reconstruction of tissue defects and scars comprises plastic surgical skin tissue transfer, including flap surgery and the restoration of the urinary and sexual function in an interdisciplinary context.

- **The objectives of this chapters are as follows**
  - To give an overview on the epidemiology and cause of genital scarring
  - To point out specific features of genital skin anatomy
  - To inform on the pathophysiology on skin wound healing, lymphology, and scarring of the outer genitals in women and men
  - To describe management of genital wounds and tissue defects
  - To give an overview on conservative and surgical treatment of genital wounds and scars

47.1 Epidemiology and Etiology of Genital Wounds

Since the ancient times, male circumcisions have been practiced by many communities mainly as a purity or religious ritual (◘ Fig. 47.1). Female genital mutilation (FGM)/cutting is still a common practice in many African countries, no matter the religious background of the people. Little is known on the incidence and severity of scarring in the genital area despite the fact that 30% of all men on the earth are circumcised [37].

Aside from circumcisions and ritual cuttings, other types of injuries, infections, tumors, skin diseases, and malformations can lead to abnormal wound healing and scarring of the genital skin. Due to the multitude of causes for genital trauma with subsequent scarring, a general incidence for genital scars is difficult to provide. As a consequence, I will first describe different origins for genital tissue defects with special focus on cutaneous wound healing and scarring of the outer genitalia, that is, the vulva, the scrotum, and the penis. For wound repair of the urinary system or the vagina and uterus, I would like to refer to the corresponding urological or gynecological literature and textbooks.

- **Causes for genital scarring and fibrosis**
  - Trauma, for example, burns, injuries to the pelvic area, autoerotic injuries, genital self-mutilation
  - Sequelae of any type of infections, for example, Hidradenitis suppurativa/acne inversa, Fournier gangrene, viral infections, and sexually transmitted diseases

◘ **Fig. 47.1** Ritual act of *circumcision*: relief in the tomb of *Ankhmahor* at *Saqqara (sixth dynasty, 2345 BC; © CC BY-SA 3.0)*. This work is licensed under a Creative Commons Attribution-ShareAlike 3.0 Unported License

- Dermatological diseases, for example, various inflammatory autoimmune diseases (e.g., Behçet's syndrome or Crohn's disease with ulcerations, pyoderma gangraenosum), bullous skin diseases, lichen sclerosus et atrophicus (LSC), lichen planus
- Religiously/culturally motivated, for example, circumcisions, FGM/-cutting, or self-inflicted procedures, for example, piercings, tattoos, foreign body insertion
- Iatrogenic/surgical interventions, for example, aesthetic surgery, cosmetic procedures, including foreign body application; circumcision for phimosis; treatment of malformations; genital reassignment surgery
- Tumors followed by oncological surgery with/without radiation therapy
- Lymphatic disorders: congenital (Milroy's or Meigs' disease) or acquired (e.g., after tumor surgery, lymph node excision, irradiation; infectious: filariasis)

The literature search for causes of genital wounds that result in scarring yields some information on burns or combat injuries with concomitant affection of the genital organs. The incidence of burn injury to the genitalia is rare with around 1.5% [15] but associated with a higher mortality rate with 17% in comparison to non-genital burns (4.7%) [12]. In contrast to perineal and inguinal scar contractures that are a common sequela after burns to the lower abdomen and groin area, excessive scarring is rarely attributed to the outer genital organs (Fig. 47.2).

The shift from high velocity to more explosive weapons during the end of the twentieth century and the use of improvised explosive devices resulted in more genital injuries in military conflicts than noticed before [1]. Genitourinary trauma accounted for only 5.3% of all combat-related injuries being mostly associated with severe polytraumatic incidents (62.1%). There are no reports on scarring after this type of injury.

Infections are quite common in the genital area. With several body orifices being anatomically located in close relation, a multitude of commensal microbia is constantly present. In case of small lesions, lacerations, or immune incompetence of the host, germs can penetrate into deeper tissue layers and cause severe infections, for example, abscesses or gangrenes with high mortality rates. Predisposed patients develop chronic infections of the sweat glands and hair follicles in the groin and genital area, also called hidradenitis suppurativa or acne inversa. Without appropriate treatment, they develop fistulas with recurrent infections and subsequent scarring to the perineal crease. The annual prevalence of hidradenitis suppurativa is around 1% with an estimate of 70 million patients worldwide [14].

Fournier gangrene is a life-threatening necrotizing fasciitis of the genitalia with an incidence of 1.6/100,000 patients that affects mostly men (10:1) [18]. The only sufficient cure is the radical surgical debridement of the entire infected and necrotic tissue with accompanying antibiotic treatment. Massive tissue losses can be the consequence with plastic surgical reconstruction after successful elimination of the infection. Because the tissue defects have a tendency to spread over the groin area as well, scar contractures are found as remnants of this type of genital infection (Fig. 47.3).

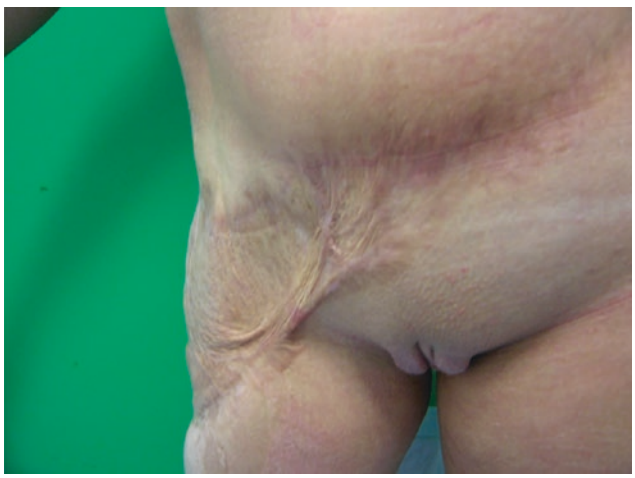

Fig. 47.2 Inguinal scar contracture with impairment of the abduction of the right leg but without involvement of the big labia after severe burn injury

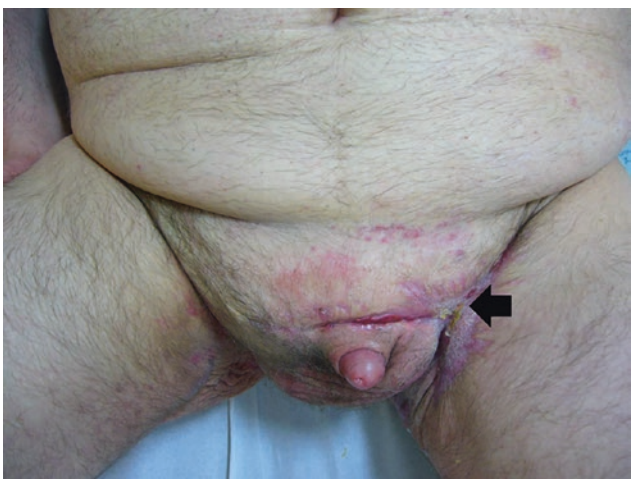

Fig. 47.3 Inguinal hypertrophic scarring with scar contractures after hidradenitis suppurativa and recurrent inguinal infections that culminated into a Fournier gangrene with vast tissue excision and postoperative scarring. The resulting scar contractures impaired the abduction of the left leg. Please note the instable scar with recurrent ulceration between the prepubic area and the left inguinal crease adjacent to the contracture (arrow). Aside from severe scarring, a buried penis grade III is present. No scarring of the penile skin or glans but of the pubic skin and groin is present

The incidence of autoerotic or self-inflicted genital injuries has not been determined but is extremely low and patients present sporadically. Genital lesions can derive from blunt, strangulating, or penetrating trauma and go as far as to incomplete or total amputations. Self-inflicted genital injuries can derive from neurotic, psychotic, and various other types of mental disorders or associated diseases and are seen in gender dysphoric conditions.

It appears that the genital skin tends more to chronic ulcers or fistulas seen in various dermatological diseases or infections than to healing with excessive scar formation. Despite reports on scarring after Behçet's syndrome, it seems that the genital skin heals with atrophic rather than hypertrophic scarring. Of note, excessive swelling of the outer genitalia is another feature that occurs typically after trauma or surgery and that differs to skin wound repair of other body areas. Genital lymphedema can be idiopathic and associated with congenital malformations but is also present after cancer therapy and infections, for example, filariasis. Chronic genital lymphedema can ultimately lead to severe fibrotic conditions and elephantiasis.

The genitalia differ in several regards from other body sites. Urogenital and anal orifices and the surrounding skin are colonized by resident microbia in a moist environment, there is abundant highly elastic skin around the external genital organs that is loosely fixed to the pelvic bone, and the cutaneous microstructure, inflammatory reaction, and hormonal responsiveness are different compared to other tissues. In the following sections, all these features and their influence on genital wound repair and scarring will be elucidated in detail.

47.2 Genital Skin Anatomy and Microstructure

For a better understanding why genitalia behave differently to skin from other body sites, the macro- and microstructure of the genital skin and organs, including lymphatics, are important and will be described in the following paragraphs. The knowledge of the anatomy is the prerequisite for the appropriate conservative and surgical treatment.

47.2.1 Development of Genital Organs and Homology Between Sexes

Female and male outer genitals derive from the same embryological origins with different development depending on the sex of the infant. The development of the external genitalia is presented in detail in Fig. 47.4, which depicts the common origin of respective anatomical entity at the embryonic stage and further differentiation into male and female genitalia during the fetal period. Table 47.1 summarizes the homologous anatomical and microscopic structures.

47.2.2 Anatomy of Male and Female Genitalia

The main anatomical differences between genital and skin of other body areas are the lack of fat tissue to the scrotum, penis and labia minora, the absence of hair to the penile and small labia skin, and the reduced or missing cornified epidermal layer of the epithelium of the prepuce and the small labia. With regard to biomechanics, the genital skin is highly elastic and flexible because it lacks a firm attachment to underlying structures, for example, bones or cartilage. A subcutaneous smooth muscle layer, also called Dartos muscle or Tunica dartos that is found in the scrotum and big labia, is reminiscent of the subcutaneous carnosus muscle in fur bearing animals and enables a gliding between the skin and the underlying connective tissue. Of note, the anatomic relict of the carnosus muscle in humans is the Scarpa fascia that is found in most other parts of the body underneath the subcutaneous fat layer. The genitalia are devoid of fat and the Scarpa fascia. Instead, the Dartos fascia is found here. An illustration of the genital anatomy for both sexes is shown in Figs. 47.5 and 47.6.

Summary: Differences Between Genital and Nongenital Skin

Genital skin differs from other regions:

- No subcutaneous fat tissue, no Scarpa fascia; instead tunica dartos with smooth muscle cells (scrotum and big labia) or dartos fascia with loose attachment of the skin (penis)
- No tight attachment of the skin to underlying bone or cartilage
- Little or no keratinizing epithelia—mucous surfaces of small labia, glans, and prepuce
- Reduced hair growth—skin of scrotum and big labia
- Moist environment due to mucous surfaces and a multitude of mucous secreting glands
- Constant microbial contamination—cutaneous, genitourinary, and intestinal flora

47.2.3 Microstructure of the Genital Skin

The skin is the largest organ of the human body that protects us against biological (e.g., microbial), chemical (e.g., acids, bases), physical (e.g., irradiation, pressure), thermal (heat, cold), and other threats, including exsic-

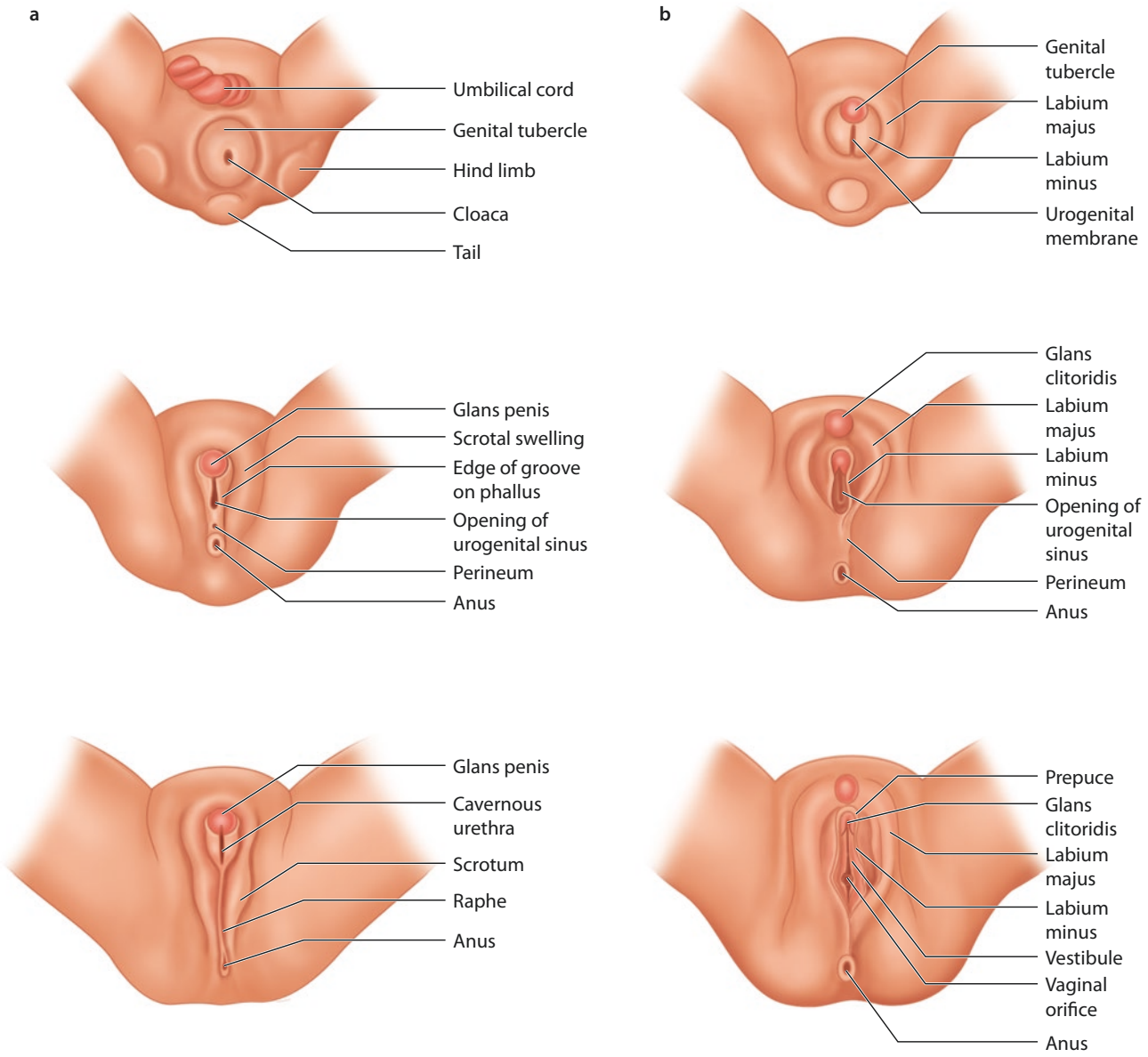

Fig. 47.4 Development of the external genitalia in **a** men and **b** women

cation. We sense our environment by touching things and we are simultaneously protected by pain receptors in the skin. We regulate our body temperature via the cutaneous vasculature, and we communicate with other people via mimics or smell—all provided by our intact skin. To ensure its protective function, the skin possesses an intricate architecture that can vary depending on the body site, for example, eyelid, back, palms, oral cavity, or genitals. The general micro-structure of the skin comprises three different entities, that is, the epidermis, the dermis (cutis) consisting of the upper/papillary and the lower/reticular dermis, and the subcutaneous fat layer. Epidermis and dermis are separated from each other by a basement membrane that is also the limit for vasculature. The epidermis is free of vessels and nourished by means of oxygen diffusion. The subcutaneous fat is separated from the deeper fat by a superficial fascia, called Scarpa fascia. In the genitalia, this superficial fascia is called Colles (women) or Dartos fascia (men). This anatomical structure is of importance because it serves as a fixation point between fat layers whereas it provides elasticity and sliding properties to the genital skin.

The cutaneous surface of moist environments is characterized by the absence of the cornified layer and

Table 47.1 Homology of male and female genitalia

Male	Female	Microscopic structure of the skin
Glans penis	Glans clitoridis	Multilayered, nonkeratinizing epidermis, dermal tissue with abundant innervation
Penile foreskin	Clitoral prepuce	Outer face of foreskin: epidermis with cornified layer; Inner face: nonkeratinizing epidermis; mucous epithelium; no subcutaneous fat tissue
Frenulum penis	Frenula clitoridis (pair)	Nonkeratinizing, mucous epithelium, no fat tissue
Penile shaft skin	Small labia	Penis: epidermis with cornified layer Labia: outer surface with thin cornified layer; inner surface: no cornified layer Both sexes: no hair; no subcutaneous fat tissue; many elastic fibers; Penis: highly flexible attachment to underlying tissue via Dartos fascia (fascia penis superficialis)
Scrotal skin	Big labia	Hair bearing epidermis (labia: only outer surface), epidermal cornified layer Labia: subcutaneous fat layer and smooth muscle cells Scrotum: no fat, but contractile tunica dartos with smooth muscle cells and myofibroblasts

hair follicles. Instead, different types of glands, for example, apocrine and eccrine, secrete fluids that moisturize the surface and protect the mucous epithelium (Figs. 47.7, 47.8, and 47.9).

47.3 Pathophysiology of Genital Wound Healing, Lymphedema and Scarring

Cutaneous scarring with tissue fibrosis is the result of a postnatal wound healing process. The longer the duration and the excessive the inflammatory response in the healing course, the more likely is the development of aberrant scarring and severe tissue fibrosis. However, scar formation varies depending on the body site, the skin architecture and anchorage to underlying structures.

Little is known about the pathophysiological processes of genital cutaneous wound repair except for the general clinical statement that genital wounds heal fast, with enormous swelling and almost invisible scarring. In the following, I will describe features that are different between the genitalia and the skin of other areas of the body and that influence acute wound healing or chronic scarring (Fig. 47.10). It is beyond the scope of this chapter to include urethral, vaginal, or anal epithelial repair; tissues that derive from different developmental origins and with differential healing behavior (e.g., ulcerations, adhesion or fistula formation) compared to genital skin.

47.3.1 Skin Architecture and Biomechanics

The genital skin has to master many challenges, for example, fast volume changes during sexual activity, sex steroid sensitivity with permanent hormonal changes, the presence of several body openings with constant commensal microbial presence, and infectious threats deriving from sexual contacts. In that context, it is breathtaking to understand the extraordinary adaption of the genital skin to its multiple tasks. To encounter aforementioned challenges, it is excellently equipped anatomically and physiologically to address specific features of the genital microenvironment.

Notably the male genital skin has to manage fast volume changes that occur during sexual activity and for thermal regulation of the testes. These physiological tasks are addressed by several means: (i) abundance of skin tissue on both the penile shaft and the scrotal sac, (ii) the Dartos fascia on the penile shaft and the Tunica Dartos with the Dartos muscle in the scrotum, and (iii) a high amount of elastic fibers in the dermis. In all three items, the genitalia differ from skin of other body areas that is firmly attached to the underlying structures by a rather immobile fat layer. High skin elasticity and abundance of tissue are the prerequisite for tension-free acute wound healing with unapparent scars—optimal repair conditions present in the genitalia. A drawback is the tendency of the outer genitals to enormous swelling and edema after surgery or trauma. The good side is that due to its elasticity and intricate lymphatics, the swelling of the genital tissue resolves as fast as it occurs in healthy subjects.

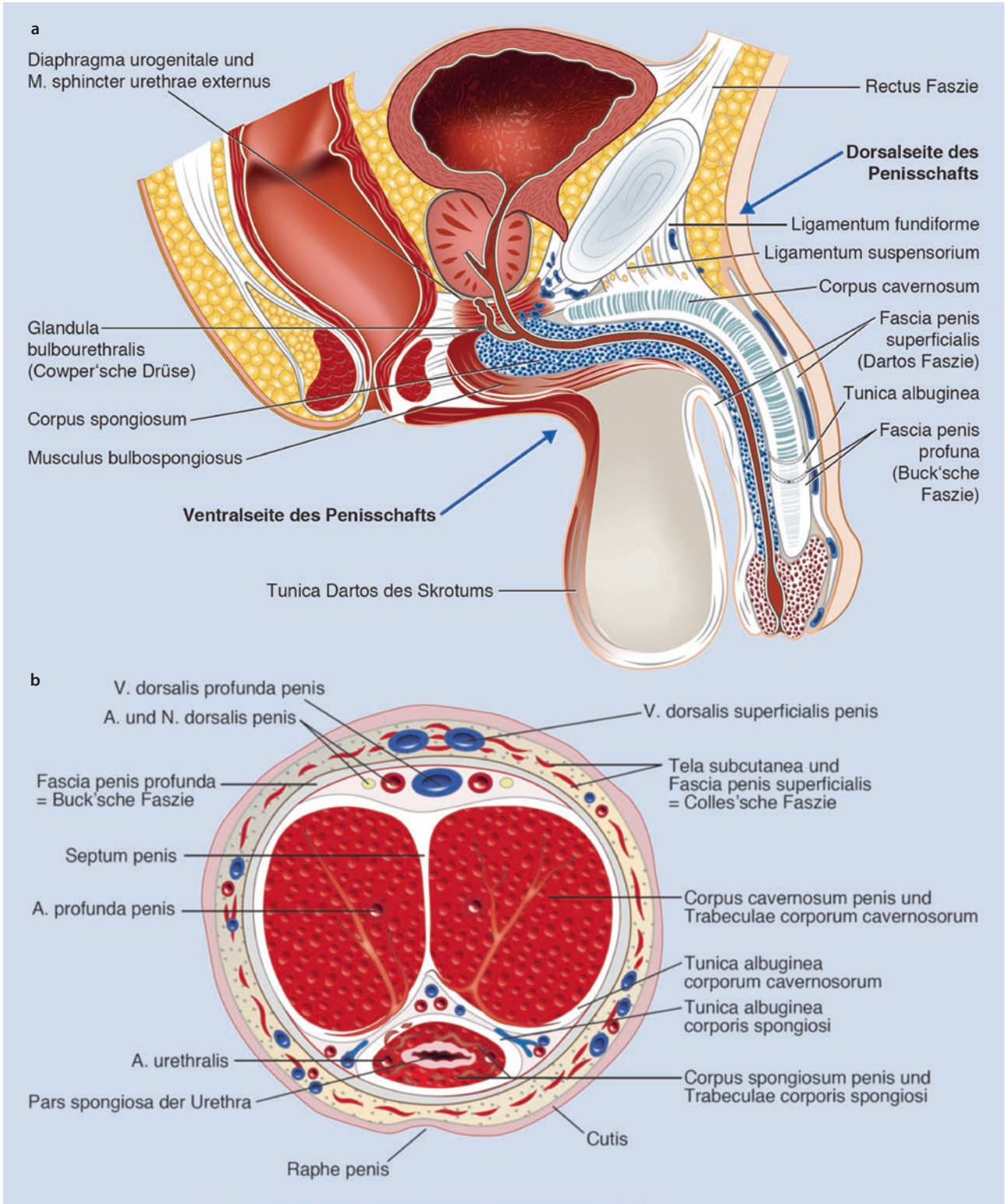

Fig. 47.5 Anatomy of the male external genitalia. Of note, no fat tissue is present in the penis or scrotal tissue underneath the skin. (Source: Mirastschijski & Remmel, Intimchirurgie, Springer Verlag, 2019)

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47.3.2 Moist Environment and Bacterial Colonialization

Urethral, vaginal, and anal orifices are transition zones between mucous membranes and keratinizing skin. As depicted previously, parts of the genitalia are covered by little or nonkeratinizing squamous epithelia. The secreted fluids of multiple glands prevent the exsiccation of mucous membranes and provide a moist microenvironment. It is an established fact that moist wound healing contributes to faster wound closure and reduced scarring.

The proximity of the genital skin to different orifices is Janus sided. Aside from the beneficial moist milieu, bacterial load and stringent body fluids such as urine bear constant threats to the fragile mucosal skin lacking the protective epidermal cornified layer. And again, the genital mucosal skin is well prepared to address both biological and chemical challenges. In contrast to other parts of the body, keratinocytes and fibroblasts of the

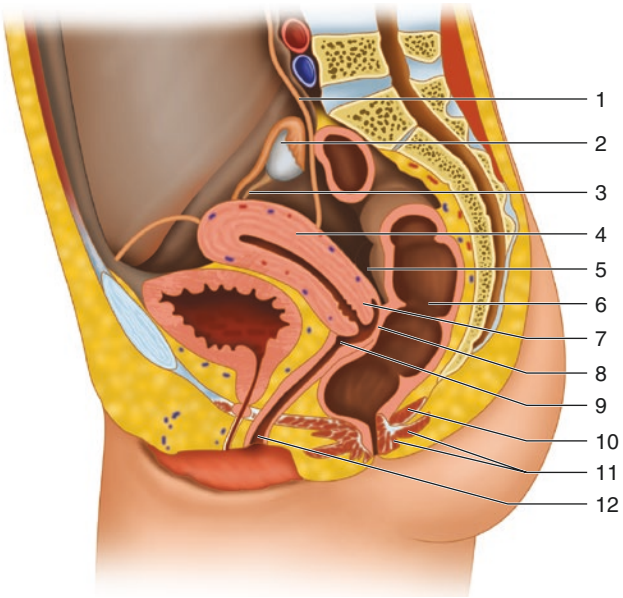

Fig. 47.6 Anatomy of the female external genitalia

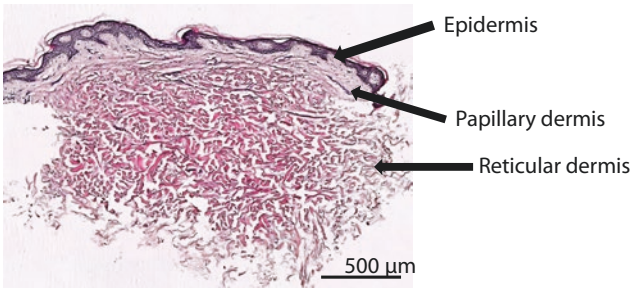

Fig. 47.8 Histological section from the abdominal skin stained with hematoxylin-eosin. (By courtesy of Dr. D. Jiang and Dr. Y. Rinkevich, Helmholtz Center Munich. © All rights reserved)

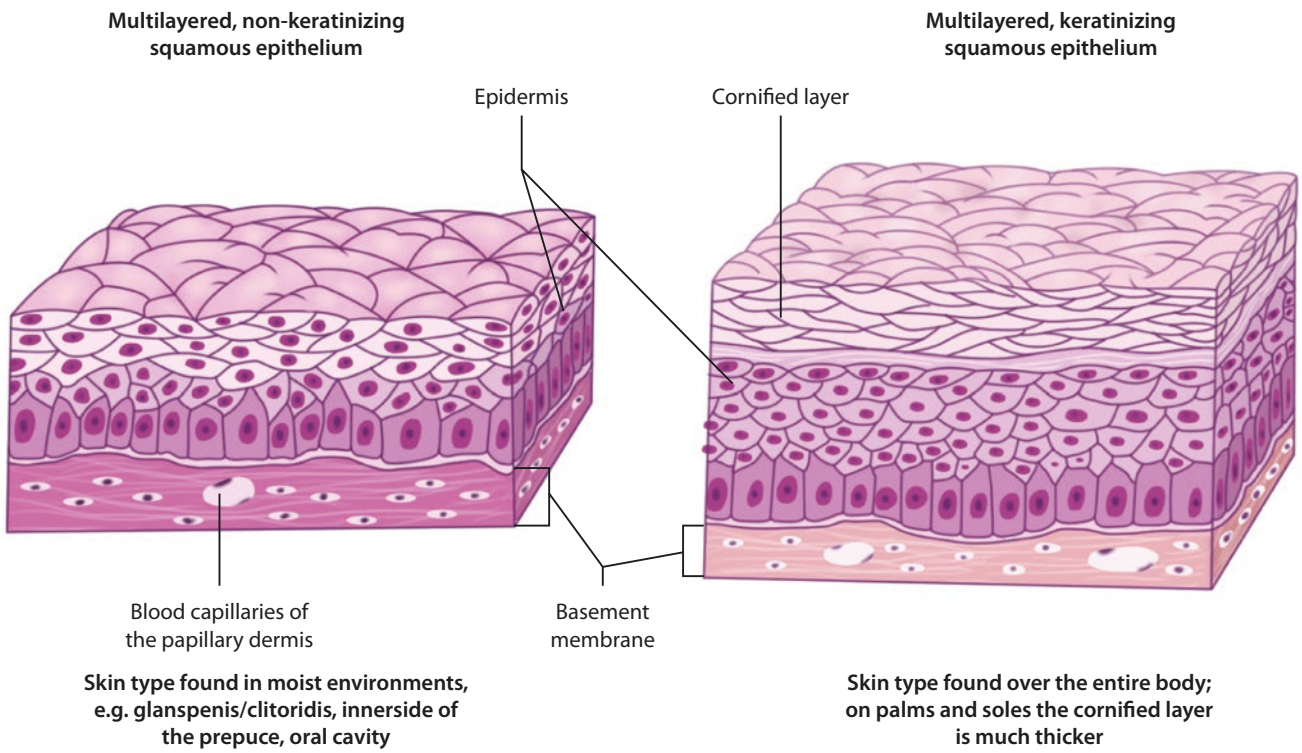

Fig. 47.7 Microstructure of nonkeratinizing and keratinizing skin

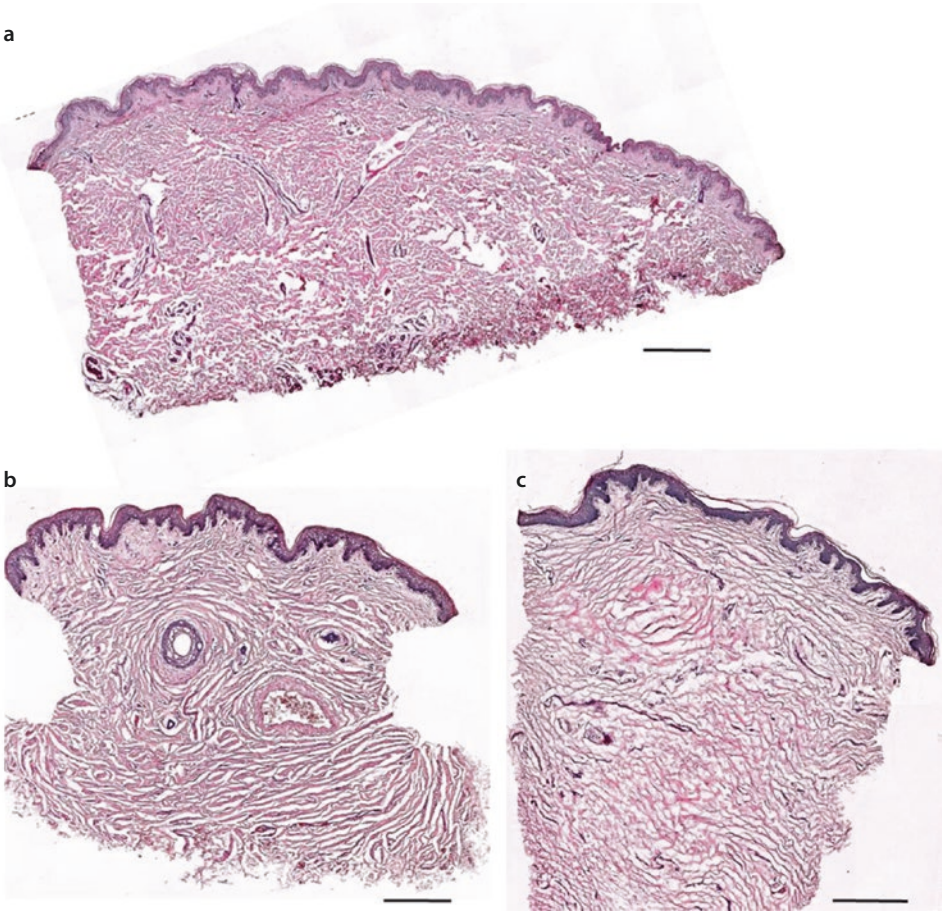

Fig. 47.9 Microstructure of the skin from different body areas: **a** arm, **b** penis, and **c** small labia. Note the dense dermal structure with multiple vessels in **a** and lose collagen bundles in **b** and **c** with high similarity of penile and labial skin. Scale bar in all sections 500 μm. (Elastica-van-Gieson stainings; by courtesy of Dr. D. Jiang and Dr. Y. Rinkevich, Helmholtz Center Munich)

genital skin are equipped with a fast immune response to bacterial presence. By secreting antimicrobial peptides (AMPs) and defensins and with glandular mucous fluids, bacteria are held at a distance. The immune response is fast and so is the resolution with quick conversion of M1 to M2 macrophages and reduced expression of proinflammatory cytokines [38]. Upon injury, skin cells increase the interleukin (IL)-1α production 15-fold in comparison to vaginal epithelial cells with only threefold increase. IL-1β and tumor necrosis factor (TNF)-α were only secreted by cutaneous epithelia in contrast to mucous epithelial cells [9]. With regard to profibrotic mediators, TGF-β is significantly elevated in normal skin keratinocytes but not in mucosal epithelia and without induction of fibrotic processes in the underlying connective tissue. In summary, the reduced inflammatory response of mucosal epithelia to injury is sufficient to ensure wound closure without inducing serious scarring.

47.3.3 Hormonal Influences

47.3.3.1 Increased Aromatase Activity and Intracrine Estrogen Production

Hormone responsivity of tissues has profound impact on wound healing. Estrogens accelerate wound closure whereas testosterone delays healing [10]. Skin is a major source of extraglandular sex steroid hormones that are produced from circulating dehydroepiandrosterone (DHEA, [24, 28]) (Fig. 47.11). The intracellular enzyme aromatase converts DHEA downstream into the weaker estrogen Estrone or via testosterone into the more potent 17β-estradiol. Both estrogens act via the estrogen receptors (ERs) α and β, and stimulate keratinocyte and fibroblast migration [11]. In genital fibroblasts, aromatase expression is androgen dependent. Interestingly, estrogens stimulate fibroblast contractility without increasing alpha-smooth muscle actin expression or myofibroblast differentiation [31]. Upon

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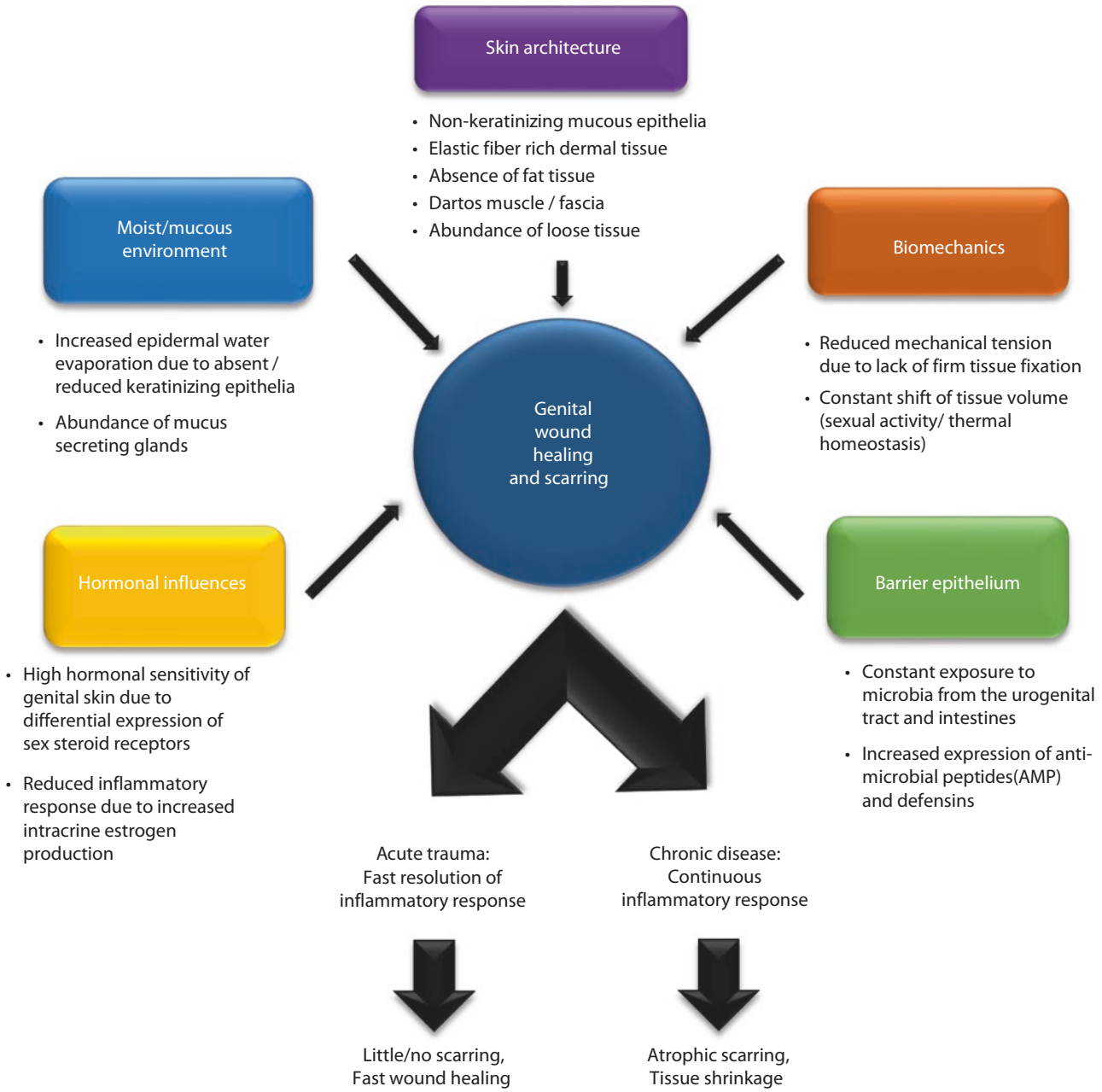


Fig. 47.10 Factors that influence genital wound repair and differ from skin from other body regions

mechanical wounding, aromatase activity increases 400-fold in keratinocytes with increased intracellular bioavailability of estrogens. Testosterone reduces aromatase activity, albeit this effect is not present in case of low oxygen levels in tissues. Estrogens reduce the cellular inflammatory response via downregulation of the proinflammatory cytokine macrophage migration inhibitory factor (MIF) [6], by reduced TLR-4 mediated MAPK activation, by the reduction of macrophage infiltration into wounds and by dampening the proinflammatory signaling of IL-6 and TNF-α [5]. Of note, estrogens are also important antioxidants that reduce cellular oxidative stress and apoptosis and increase keratinocyte migration and collagen synthesis by dermal fibroblasts [38]. In menopausal women, cutaneous estrogen insufficiency manifests by atrophic skin changes and a diminished defense against reactive oxygen species.

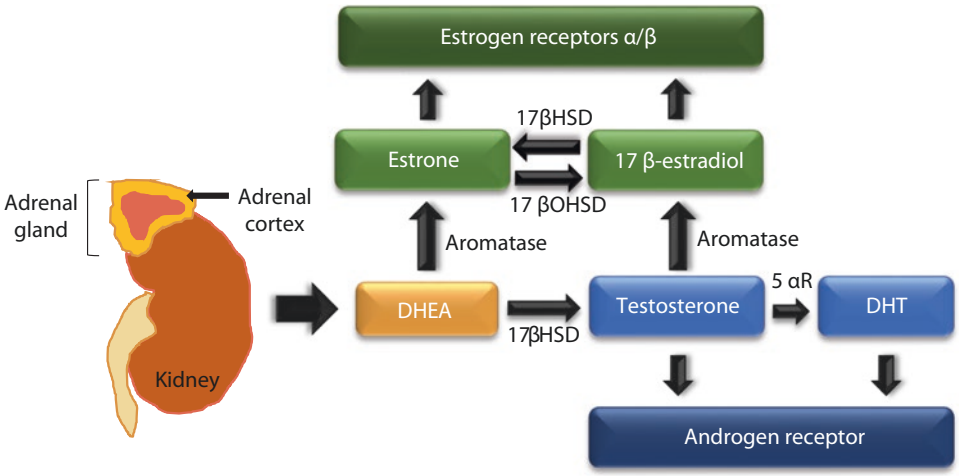


Fig. 47.11 Simplified description of intracrine sex steroid hormone production by skin cells. Dehydroepiandrosterone (DHEA) is released by the adrenal cortex and further processed directly into estrogens by aromatase or into testosterone by 17-β-hydroxysteroid dehydrogenase (17-β-HSD). Estrone is reversibly oxidized into 17β-estradiol by 17β-OHSD. Testosterone can be either directly converted into the estrogen 17β-estradiol by aromatase or irreversibly converted into dihydrotestosterone by 5-α-reductase (5αR) [39]

47.3.3.2 Androgen and Estrogen Receptor Expression in Genital Skin

Estrogens act via estrogen receptors and testosterone via androgen receptors (ARs) that are expressed by many cell types. For instance, AR expression differs between genital and nongenital skin with upregulation in genital fibroblasts. In general, it appears that sex steroid hormone expression is higher in stromal cells than in epithelial cells, implying higher responsiveness of fibroblasts to hormonal influences. Aside from receptor expression, the binding capacity and metabolism of sex steroid hormones differs between different skin regions. Testosterone binding capacity of the AR is higher in genital compared to nongenital skin cells [39] from both sexes—independently of age—and testosterone degradation is up to 30 times faster in genital skin compared with nongenital skin [30].

Sex hormone receptor expression in genital skin differs between prenatal and adult genital skin due to the terminal differentiation of the external genitalia that is dependent on hormonal influences. In fetal skin, ARs are very similarly expressed in both sexes with the absence of ARs on the preputial skin, penile shaft/labia minora, and scrotal skin/labia majora. ARs are expressed in the tissue of the glans and inner prepuce of both sexes and in the stromal tissue of the labia.

ER was present in fetal female genital skin except for labia minora and majora [16] and prominent ER staining was found in the entire developing fetal penis including skin, glans, inner prepuce, and stromal cells [4]. Interestingly, ARs and ERs were colocalized in penile tissues.

Less detailed information is available with regard to adult genital skin. In women, ARs are found in keratinocytes and fibroblasts of the labia majora and minora and in the adjacent extragenital skin. ER immunopositivity was found in the labia minora and nongenital skin. There are no differences in sex hormone receptor expression between pre- and postmenopausal women. Progesterone receptors are not present in genital skin. In men, ARs were located to basal keratinocytes and stromal fibroblasts of the penile foreskin. No AR expression was found in nongenital cutaneous keratinocytes or fibroblasts but in fibroblasts of hair follicle papillae or in cells of pilosebaceous ducts and glands, skin structures that are influenced by androgens in their function and structure. The highest intensity of AR staining was noted in genital skin. ERs were similarly expressed in postnatal penile skin with localization to basal epithelia and stromal cells adjacent to the urethra and the urethra itself with age-dependent reduction [27]. Aromatase is not colocalized with estrogen receptors, and levels of aromatase, ERα, and ERβ decrease with age [27].

In summary, ARs and ERs are highly expressed in genital skin in contrast to skin of other body areas with fast binding and degradation of testosterone or conversion into estrogen by increased aromatase activity. A summary of hormonal differences between genital skin and nongenital skin is given in Table 47.2.

47.4 Acute Wound Repair of Genital Skin After Trauma

Depending on the type and severity of the injury, two main clinical symptoms characterize traumatized genitalia, namely enormous bleeding and swelling. When the hematoma resolves and the swelling disappears, wounds heal with almost no visible scarring even after major trauma. An example for invisible genital scarring is the fact that one-third of the male world population is circumcised [37] without any report of hypertrophic

Table 47.2 Hormonal differences between genital skin and nongenital skin

	Genital skin	Nongenital skin
Androgen receptor	Higher expression in labia majora and minora Upregulated in fibroblasts and basal keratinocytes Colocalization with ER	Only present in hair follicles and pilo-sebaceous duct keratinocytes Low expression in extra-genital skin
Estrogen receptors	Highly expressed in penis and labia minora Restricted to basal keratinocytes and stromal fibroblasts Expression decreases with age	Lower expression compared to vulva or vagina Expressed by keratinocytes and fibroblasts Absence in skin appendages or blood vessels
Testosterone	Higher AR-binding capacity of testosterone 30 times faster degradation Reduced effect on aromatase activity in low-oxygen conditions	Higher rate of conversion into DHT Higher 5-α-reductase activity with irreversible formation of DHT
Estrogens	No conversion of 17β-estradiol into the weaker estrone Stimulate fibroblast contractility without alpha-smooth-muscle actin (ASMA) expression	Threefold increased metabolism of 17β-estradiol into estrone
Aromatase	Higher activity in fibroblasts with conversion of testosterone into 17β-estradiol Dose-dependent reduced activity by testosterone Aromatase expression androgen dependent	Expression in skin fibroblasts, keratinocytes of the outer root sheath and in terminal hair follicles and in cells of sebaceous glands and ducts

AR androgen receptor, *ER* estrogen receptor, *DHT* dihydrotestosterone

scarring to the preputial skin. Despite major trauma after female genital mutilation/cutting, the genital skin heals uneventfully if the girl survives postinterventional bleeding and infection. Cutaneous genital infections are disastrous and can rapidly lead to septic conditions with high lethality. Fournier gangrene is one example of necrotizing fasciitis of the genital skin with a mortality rate of 80% without surgery [18]. Obviously, the loose architecture of genital skin provides optimal means for rapid subcutaneous bacterial spreading leading ultimately to multiple organ failure and death.

The aforementioned characteristics of the outer genitalia with regard to architecture, fixation, microenvironment, hormonal influences, and reduced inflammatory response orchestrate the fast resolution of the acute wound healing process with reduced scar formation. Albeit the apparently scar-free wound healing properties of genital skin, there is one exception. The ventral part of the prepuce ends in the so-called frenulum that is fixed to stromal tissue of the ventral side of the glans bridging to the penile shaft. In case of excessive tissue removal during circumcision, the frenulum can shrink and pull the glans in direction of the penile shaft that is painful, gives discomfort during erection, and can cause reduced sensation of the glans penis (Fig. 47.12).

47.5 Chronic Inflammatory Diseases of the External Genitalia and Tissue Fibrosis

Several skin diseases with autoimmune background can affect the outer genitalia with chronic inflammation leading to tissue shrinkage and atrophy. Chronic lymphedema after tumor surgery and/or irradiation, with infectious background or due to congenital malformation of lymphatic organs, leads to tissue fibrosis and stiffening and to verruca-like epidermal changes in the long run. In the following, the most common chronic diseases and changes to the genital skin will be described in detail.

47.5.1 Lichen Sclerosus et Atrophicus/ Balanitis Xerotica Obliterans

Lichen sclerosus et atrophicus (LSC), also called balanitis xerotica obliterans in men, is the most common chronic dermatitis localized to the mucous membranes and skin of the genitalia. LSC is found in females and males with a ratio of up to 10:1 and has a double peak in females with occurrence in prepubertal and postmenopausal age. In men, LSC is the most common

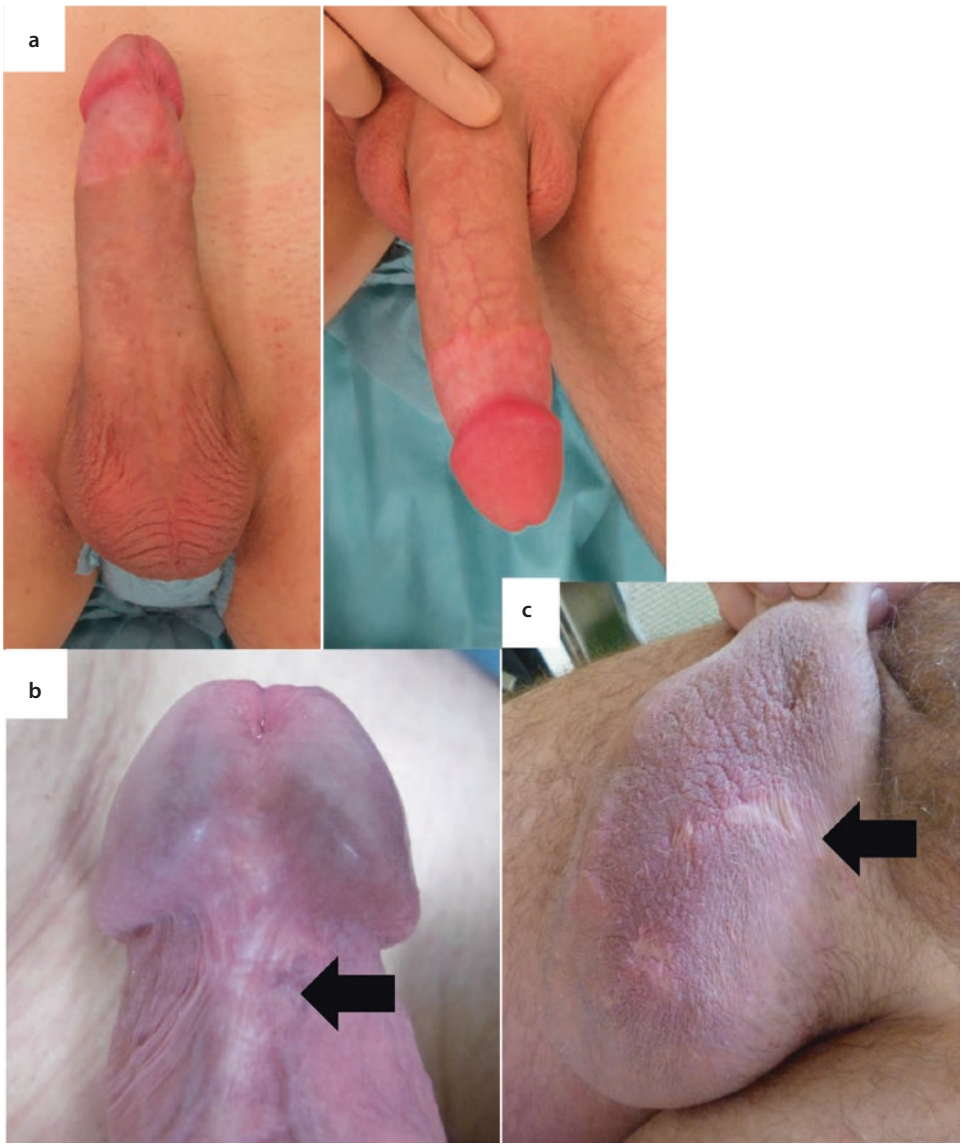


Fig. 47.12 Examples for scar formation to the male genitalia. **a** Invisible scar after circumcision. Note differential pigmentation of the outer penile skin and the remaining inner part of the prepuce. **b** Scar after excessive circumcision with shortening and scarring of the frenulum (arrow). **c** Scrotal scar (arrow) after multiple excisions of silicone granuloma and subcutaneous fibrotic tissue

cause of acquired phimosis [3] and affects the glans and the prepuce (Fig. 47.13). Typical symptoms are a thickening of the foreskin that impairs retraction. Whitish plaques can extend over the entire glans with affection of the urethral meatus followed by stenosis and voiding problems. In females, the anogenital area is frequently affected forming an 8-shaped efflorescence around the vulva and the anal orifice with opaque plaques and papules. In chronic disease, these atrophic lesions can lead to a complete destruction of the vulva with resorption of the small labia, narrowing of the vaginal introitus and burying of the clitoris. The patients' quality of life is severely reduced due to chronic pruritus, pain, and obstipation resulting from painful defecation in women and painful erection and hygienic problems in men. Of note, LSC is associated with squamous cell carcinoma formation in 5% of women [17] and up to 30% of men [3]. Other LSC-associated diseases comprise autoimmune thyroiditis, vitiligo, or pernicious anemia. The etiology of LSC is not fully understood. An autoimmune origin with T- and B-cell-driven response to a yet unknown antigen is discussed because dense T-lymphocytic infiltrates with concomitant vasculitis and extensive tissue destruction are found in LSC-tissue sections. The glycoprotein extracellular matrix protein 1 (ECM 1) has been targeted as putative autoantigen because the symptoms of the autosomal recessive disorder lipoid proteinosis resemble acquired LSC with thickening and scarring of skin and mucosa [2]. Another related dermatosis, the Lichen planus, presents with similar symptoms and etiology that makes the initial differentiation between lichen sclerosus and lichen planus difficult [35].

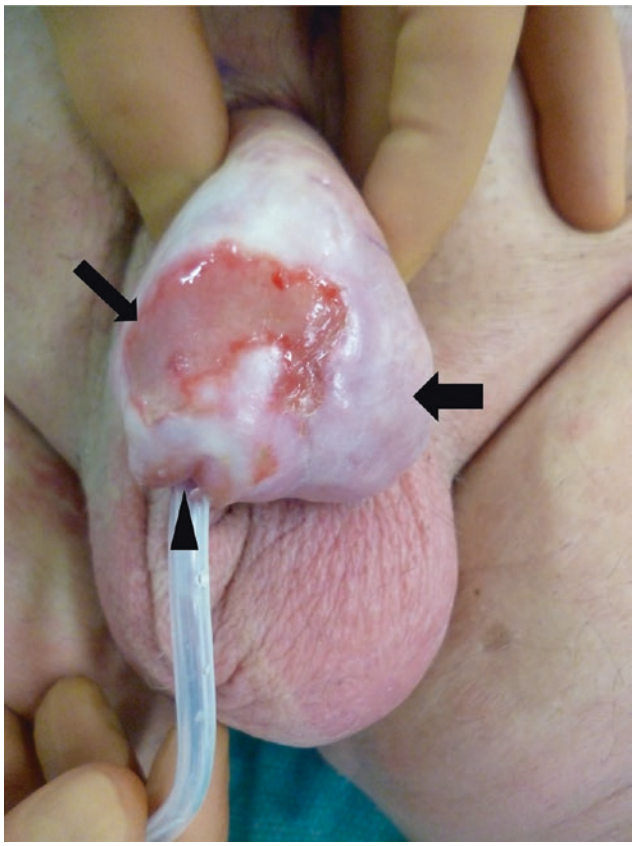


Fig. 47.13 Patient with Lichen sclerosus et atrophicus to the penile glans and after several circumcisions and reconstruction of a buried penis. Note central ulceration (thin arrow) surrounded by opaque and shiny skin changes of the glans including meatal stenosis (arrowhead) and granuloma formation (thick arrow)

47.5.2 Behçet's Disease

Aphthous stomatitis (oral ulcers) and genital ulcers are common features of Behçet's disease. The etiology of the autoimmune vasculitis is unknown. The most common site for genital ulcer formation is the scrotum in men and the big labia in women. Interestingly, scrotal and big labia ulcers heal with normal, nonhypertrophic scarring whereas skin lesions on the small labia heal without scars similar to oral ulcers [22].

47.5.3 Chronic Inflammation due to Foreign Body Reaction

The size of the penis is of central importance for many men who build their self-confidence on the penile length. In that context it is not surprising that a plethora of different substances were used for penile enlargement over centuries. Vaseline, paraffin, liquid mercury, silicone (Figs. 47.12c and 47.14), or cod liver oil were injected in to the scrotum or under the penile skin for girth enhancement with catastrophic complications such as granuloma formation, infections, swelling, and local tissue necrosis [33]. Alternatively polymethylmethacrylate (PMMA) microspheres or autologous fat are used as fillers or silicone implants for permanent enlargement [19, 20]. The placement of permanent, alloplastic foreign body material in an environment populated by a variety of commensal microbes is risky due to the inherent danger of infection. In case of granuloma, tissue necrosis, or implant infection, the foreign material must be removed with subsequent tissue loss. Foreign body materials can initiate a chronic inflammatory process with cutaneous thickening and subcutaneous tissue fibrosis leading ultimately to a shrinkage of the entire penile shaft. Details of the surgical treatment after foreign body injection are shown in Fig. 47.14.

47.5.4 Congenital and Acquired Genital Lymphedema and Tissue Fibrosis

Lymphedema is defined as low- (<1 g/100 ml) or high- (>1 g/100 ml) protein fluid retention in the interstitial space [8]. Congenital malformation of lymphatic vessels can cause chronic lymphedema. Acquired lymphedema occurs after surgery (Fig. 47.15) for various reasons (cancer, gangrene, foreign bodies, etc.), irradiation, or filariasis. The swelling is due to an imbalance of the production and absorption, including drainage of the lymph that can be caused by an obstruction, disruption, or insufficiency of the lymph vessels. Chronic lymphedema affects the surrounding tissue with fibrosis and the skin with rhagades and recurrent infections, blister formation, wart-like epidermal excrescences, and scarring.

47.6 Treatment of Genital Wounds and Scars

The manifold the causes for wounding and scarring to the genitalia are, the diverging are the treatments as well. The choice of the appropriate surgical technique is orientated on the depth, magnitude, and location of the defect and the quality of the surrounding tissue. Needless to say that the delicate genital anatomy of both sexes and the variety of tissue defects or scars that can extend over to adjacent body areas require highly skilled surgeons with expertise in reconstruction of the genitalia. Aside from defect closure, restoration of the voiding and sexual function are central to each reconstructive procedure and require often an interdisciplinary setting.

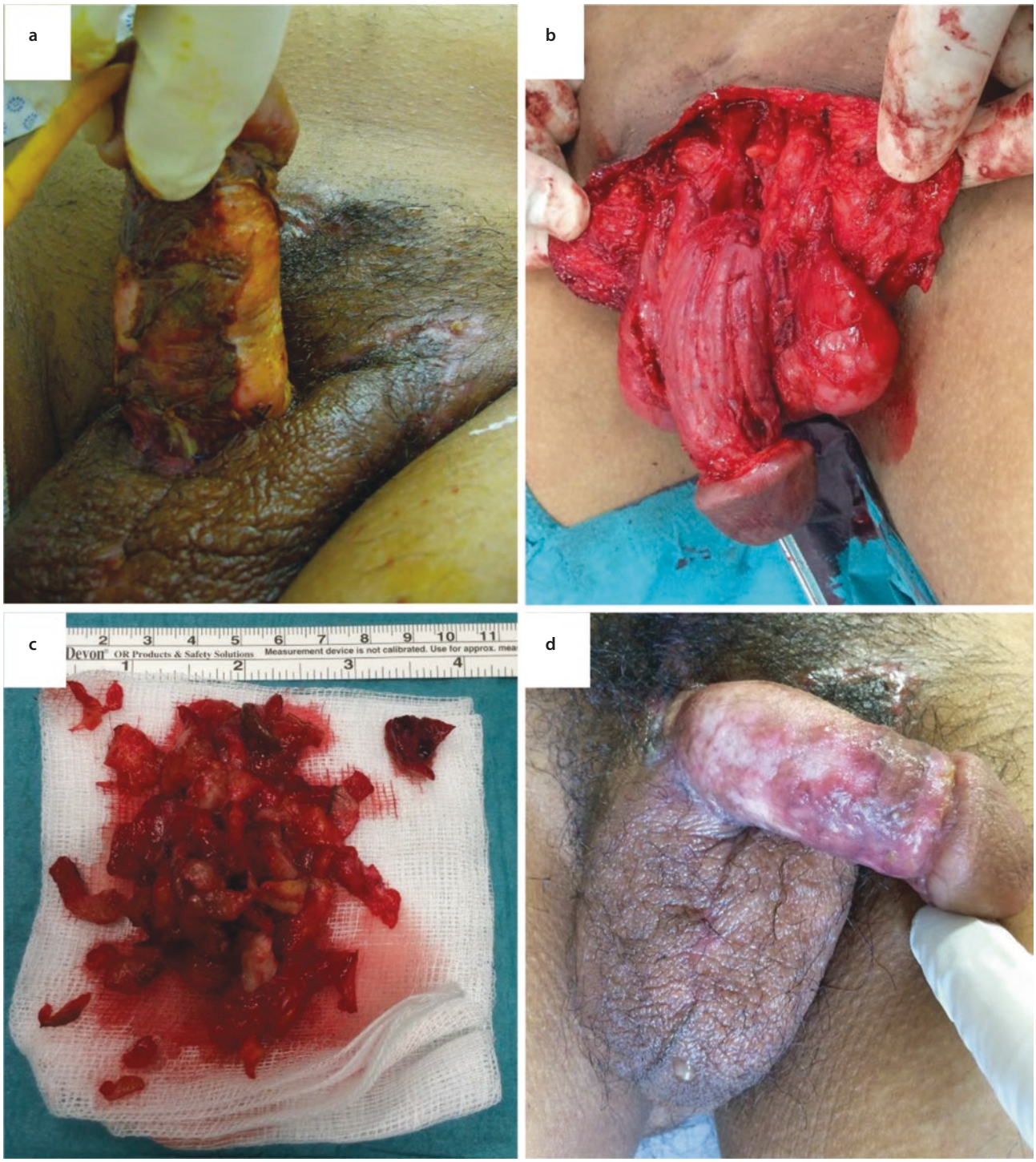


Fig. 47.14 Penile skin necrosis after silicone oil injection. **a** Tissue necrosis over the entire penile shaft preoperatively. **b**, **c** Intraoperative situs **b** after meticulous excision of all foreign body material and granuloma **c**. **d** Postoperative result after full-thickness skin grafting with epidermal thickening and hypopigmentation 6 weeks after grafting

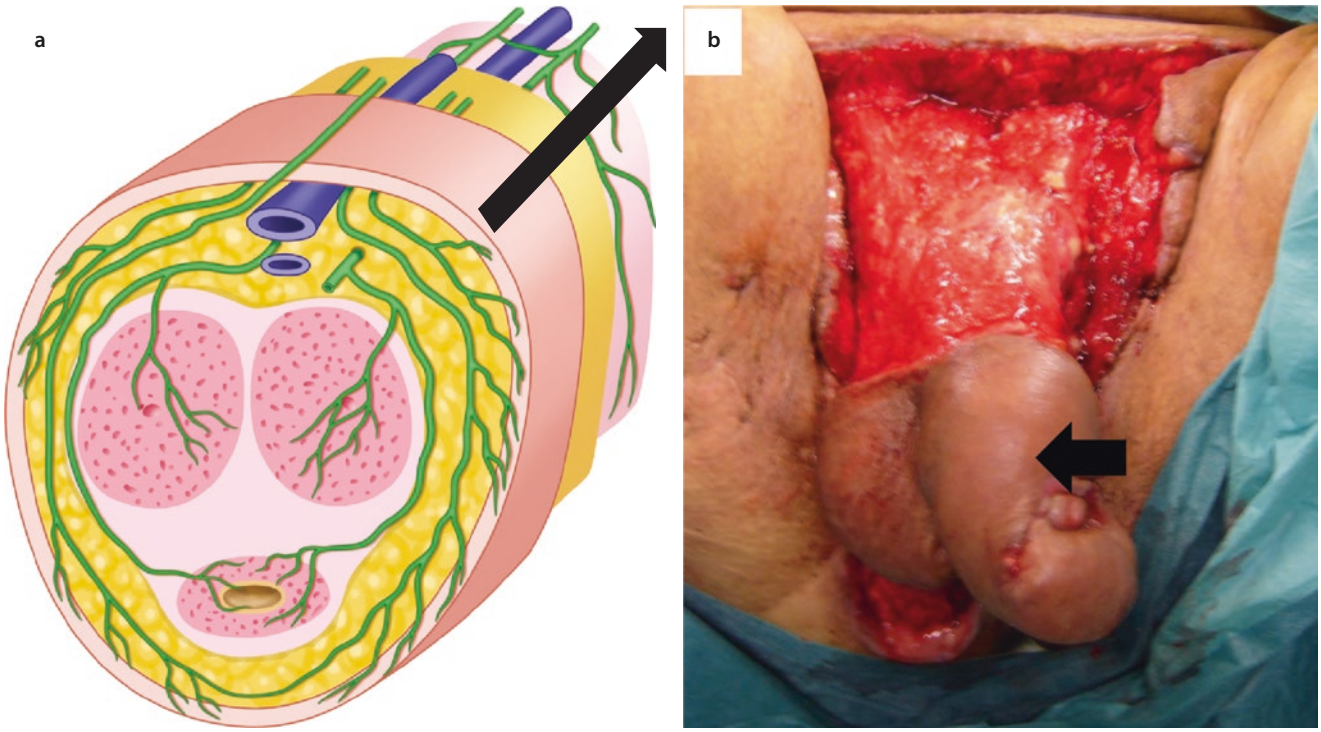


Fig. 47.15 Penile lymphedema **a** Penile lymphatic vessels and lymph drainage on the dorsal side of the penile shaft (arrow). **b** Fournier gangrene on the base of a chronic acne inversa with massive tissue resection of the prepubic and groin area after necrotizing infection with a multiresistant *Staphylococcus aureus* and different enterobacteriaceae. Note massive swelling of the penile shaft (arrow) with burying of the glans due to loss of dorsal lymphatic vessels and drainage pathways after debridement

47.6.1 Treatment of Acute Wounds and Tissue Defects

Small acute wounds and tissue defects are commonly closed primarily due to the abundance, elasticity, and loose fixation of the genital skin and tissue. For instance, primary closure of scrotal defects after up to 50% tissue loss is feasible, otherwise local or distant flaps (e.g., bilateral gracilis flaps; Fig. 47.16) or skin grafts are used to reconstruct the scrotal sac [18]. Superficial skin loss to the penile glans recovers by conservative treatment, and deeper tissue defects need skin grafting, for example, with oral mucosa or thin split-thickness skin [34]. Penile shaft defects can be elegantly closed using preputial flaps in case the patient is not circumcised. Otherwise, split-thickness or full-thickness skin grafts are the current state-of-the-art for penile shaft reconstruction. Drawback of free skin grafts is the lack of cutaneous elasticity and sensation. In case of abundant scrotal tissue, local neurovascular flaps (e.g., midline raphe scroti artery, MiRA-flap) can restore—at least in part—tissue texture and sensation [26].

The reconstruction of the female genitalia is similar as in men with primary closure of small lesions and flap surgery in case of larger tissue losses. An elegant procedure for reconstruction of the big labia is the anterior obturator artery perforator flap (aOAP) that is harvested from the groin area [29]. Interestingly, the flap tissue heals with minimal scarring once it is transferred to the vulva in contrast to its harvest site in the groin that is prone to hypertrophic scarring (personal communication with Prof. Dr. Uwe von Fritschen, Desert Flower Center, Helios Klinikum Emil von Behring, Berlin).

47.6.2 Treatment of Genital Wounds and Scars After Burn Injury

The golden standard for treatment of partial-thickness (deep second degree) and full-thickness (third degree) burns is debridement of the necrotic tissue with skin grafting. Due to its high regenerative potential, a more conservative approach is the current clinical practice for genital skin until full demarcation of the necrotic tissue. As mentioned earlier, the genitals are capable of

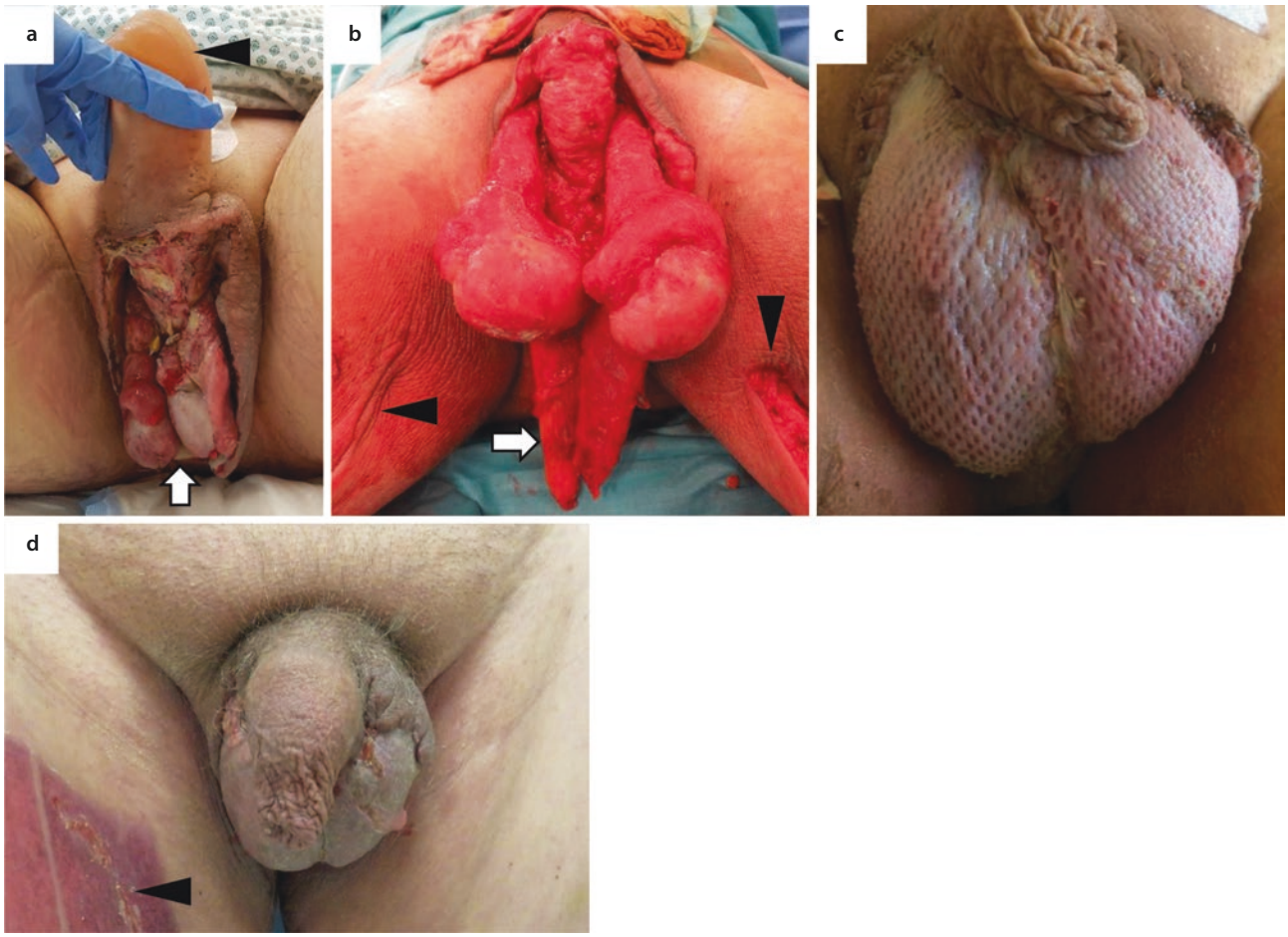


Fig. 47.16 Plastic–reconstructive surgery of the scrotum with bilateral gracilis muscle flaps covered by a split-thickness skin graft. **a** Preoperative site with almost complete loss of the scrotal tissue. Both testes are exposed (white arrow) with lymphedematous swelling of the penis (arrowhead). **b** Intraoperative situs after debridement. Both gracilis muscles (white arrow) are mobilized and rotated into the defect by tunneling underneath the perineal crease. Harvest areas are depicted with arrowheads. **c** Postoperative site after 1 week with almost complete skin graft take. **d** Situation after 3 weeks with little scarring and a skin texture resembling the natural scrotal appearance. Note split-thickness harvest site to the right thigh (arrowhead)

compensating for rather large tissue losses with only minor scar formation [15]. In contrast, severe scarring and scar contractures are common to the groin and perineal area that can impair the movement of the lower extremities (Figs. 47.2 and 47.3). After scar excision, local skin flaps, for example, Z-plasties, are usually used for wound closure and tension release. In case of insufficient local tissue, distant, pedicled, or free flaps with microvascular anastomosis are standard procedures and belong to the repertoire of a plastic–reconstructive surgeon (Fig. 47.17). For further detailed information, the recently published textbooks for genital [25] or burn [13] reconstructive surgery are recommended.

47.6.3 Gender Reassignment Surgery

Genital gender reassignment surgery comprises the formation of a female vulva, including big and small labia, a clitoris with a clitoral hood and a vagina in male-to-female transsexuals and the formation of a penoid with functional elongation of the urethra and a scrotum in female-to-male transsexuals. Highly specialized surgeons perform these extraordinary procedures in an interdisciplinary context with astonishing results. Notably scarring is minimal despite extensive surgical intervention to the genitalia with relocation of ontogenetically homologous entities. My profound fascination for absent or minimal genital scarring derives from patients after gender reassignment surgery (Fig. 47.18).

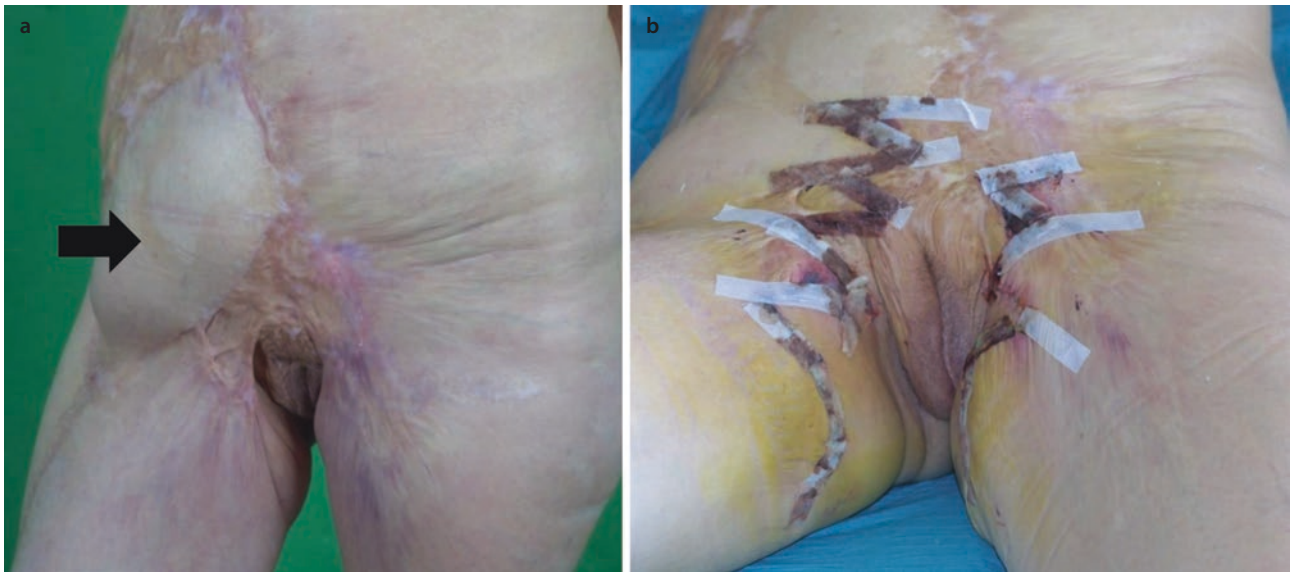


Fig. 47.17 Scar contractures to the inguinal and perineal region after burn injury. **a** Preoperative situs with scar contractures spanning over both groins that impair the range of motion of both legs. Of note, the genital area, including the big labia, is devoid of scarring. Previous reconstructive surgery included local tissue transfer for scar release to the right groin (arrow). **b** Postoperative situs after multiple Z-plasties

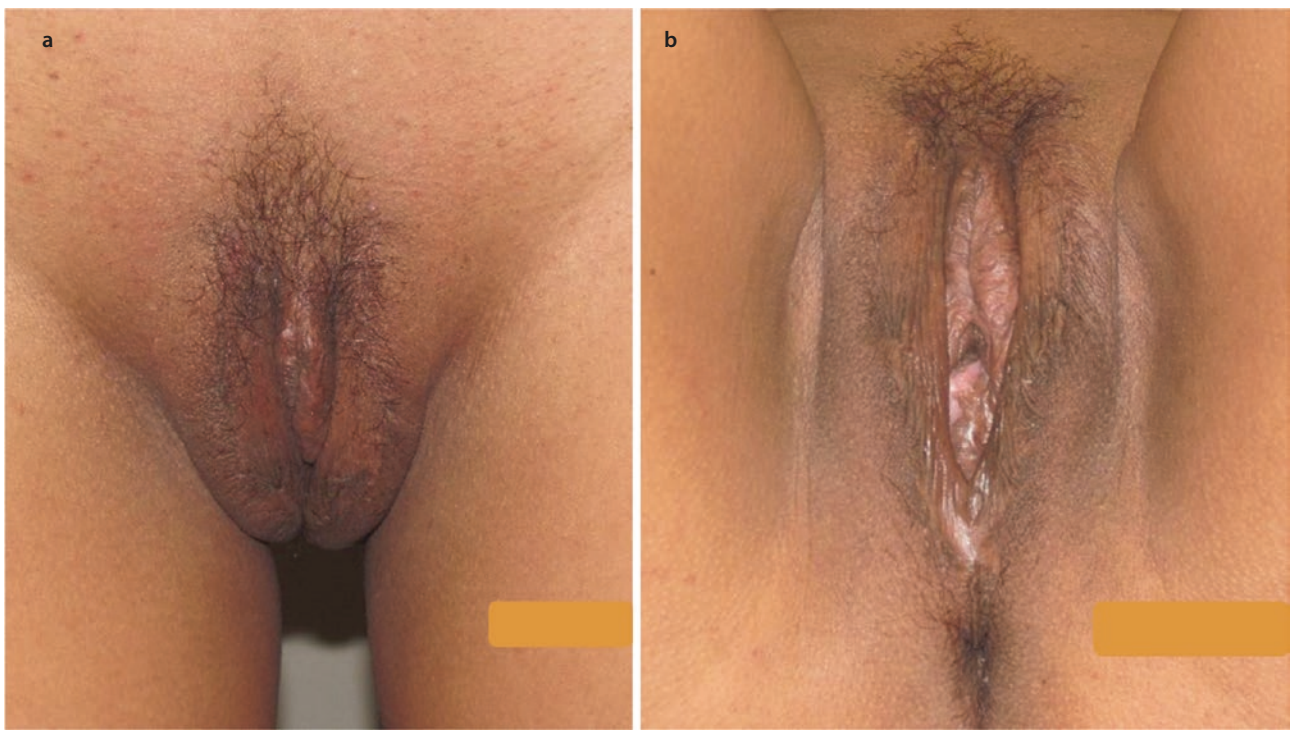


Fig. 47.18 Male-to-female transsexual patient after genital reassignment surgery. Note construction of all vulvar structures with big and small labia, a clitoris covered completely by the clitoral prepuce and the vaginal entrance. **a**. ventral aspect, **b**. caudal aspect (By courtesy of Dr. Jürgen Schaff, PSC Munich)

47.6.4 Treatment of Chronic Genital Skin Diseases

Chronic genital ulcers can originate from autoimmune diseases, infections, pressure sores, etc. Describing details on the systemic rheumatologic treatment of autoimmune disorders is beyond the scope of this chapter. More information on diagnosis and therapy of dermatologic autoimmune disorders is provided in excellent reviews [7, 32].

LSC in women responds well to topical corticosteroid ointments whereas phimoses in men require surgical intervention. Circumcision with complete removal of the penile foreskin is the gold standard that leads to relapse-free recovery from LSC [3, 7].

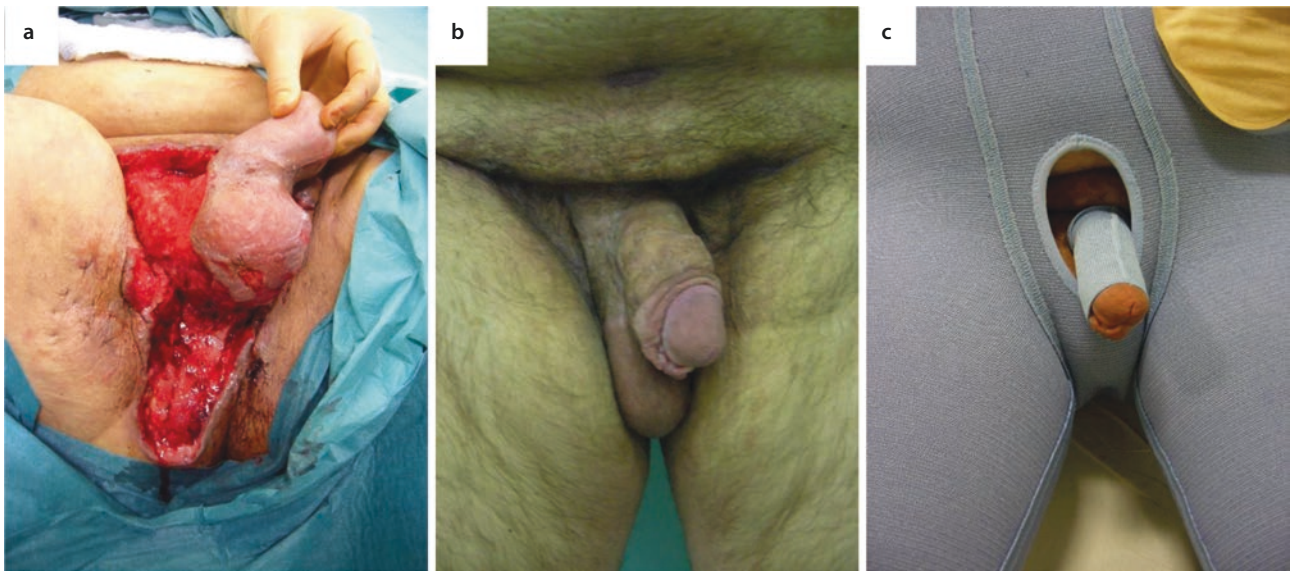
47.6.5 Lymphedema Treatment

Depending on the underlying cause of noninfectious genital lymphedema, the treatment is primarily conservative with a complex decongestive physiotherapy (CDP), according to Földi [8]. To ensure permanent lymphatic drainage, compression therapy is recommended not only in patients with lymphedema but also in patients after genital reconstruction. Surgical intervention in secondary genital lymphedema is controversially discussed and should be limited to selected patients in the hands of experienced surgeons and physiotherapists [23, 36].

The treatment of filariasis is antimicrobial; in case of genital elephantiasis, surgical removal of penile and scrotal tissue is indicated for debulking although clinical studies on the postsurgical outcome are scarce [21].

47.7 Postoperative Management for Scar Prevention

Postoperative excessive scarring of the genitalia is rare and limited to free partial-thickness skin grafts to the penile shaft. In contrast, hypertrophic scarring and scar contractures are common to the perineal and inguinal area with postoperative compression therapy and mobilizing physiotherapy being imperative. With regard to the genitals, lymphedema formation is more common and an issue for intensive postoperative care. Standard or tailor-made individual compression garments are available and recommended for 3–6 months. Compression panties for women are available in different sizes. With regard to male compression therapy, the issue is more problematic due to difficulties in handling penile compression stockings and the fixation to the penile base. Our group has developed such a penile compression stocking in cooperation with highly qualified orthopedic technicians who produce individually tailored pressure garments for men after skin grafts or flap surgery with postoperative lymphedematous swelling. After a short training period, all men were capable of handling the stocking by themselves (◘ Fig. 47.19).



◘ **Fig. 47.19** Postoperative treatment after reconstruction of a genital and perineal defect after Fournier gangrene. **a** Preoperative site after multiple debridements. **b** Postoperative situation 4 weeks after defect closure with split-thickness skin grafts. **c** Adjuvant treatment with tailor-made pressure garments to prevent excessive scarring. Note separate compression panty for the perineal area and a tailor-made stocking for the penile shaft

We recommend the prescription of at least two pairs of garments to ensure daily changes and washing for better hygiene.

47.8 Conclusion

Hypertrophic scarring to the genitalia is uncommon, possibly due to the high regenerative potential of genital skin, the abundance and elasticity of the local tissue, and the rapid and reduced immune response to traumatic events. Chronic inflammatory diseases such as lichen sclerosus et atrophicus or chronic lymphedema lead to tissue fibrosis with epidermal thickening and to a shrinkage and atrophy with complete destruction of the genitalia in the long run. In contrast to the genital skin, hypertrophic scarring and scar contractures are frequently seen in body areas adjacent to the genitalia, for example, the groin or the perineal crease. The reconstructive procedures for scar release or tissue defect coverage should aim not only at defect closure but also at the functional restoration of micturition and sexuality and should exclusively be performed by experienced specialists preferably in an interdisciplinary setting.

Take-Home Messages

- Genital skin wounds heal fast and with almost invisible scarring.
- The anatomical microstructure of genital skin differs in its architecture and elasticity to skin from other body sites.
- Extensive tissue loss can be compensated—in part—due to the abundance of genital skin.
- The inflammatory response of genital skin is adapted to the permanent microbial colonialization with fast-onset and quick resolution.
- Androgen and estrogen receptors are highly expressed in genital skin. Genital wound repair benefits from hormonal responsiveness and increased presence of sex steroid hormones due to intracrine production by skin cells.
- Chronic inflammatory conditions caused by autoimmune disorders, infections, or foreign material can lead to severe tissue fibrosis followed by shrinkage and destruction of the outer genitalia.
- Chronic lymphedema manifests in enormous swelling of the outer genitalia with long-term tissue fibrosis and wart-like epidermal changes.
- Reconstruction of tissue defects or scar contractures should include the functional restoration of micturition and sexuality.
- Reconstructive interventions to the outer genitalia are complex and delicate and should exclusively be performed by experienced surgeons specialized in genital surgery.

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Psychological Impact of Burn Injuries

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48.1 Background

There is no getting around it: a severe burn injury is a major life event that can dramatically disrupt a person's life. The traumatic nature of the event, the long hospitalization and co-occurring high pain intensity, and the suddenly changed appearance can have a profound impact on those affected. Along with medical advances, more people with severe burns survive their injury and live with scars in a society where a high premium is placed on physical appearance and attractiveness. Scars resulting from burns can have a conspicuous look and may capture attention from the environment. When scars are hypertrophic, they are typically firm, raised, red, and have a rough surface. Hypertrophic scars can be difficult to conceal when they are located at visible body parts. Also, scars in less visible areas can pose a burden on someone's life in specific situations such as the swimming pool, or when the weather is warm and more revealing clothing is indicated at that time.

Living with scars may become even more complicated in the current society. Professionals and academics are concerned about the changing notions of normality related to appearance and the increasing demands of beauty. A recent paper [1] mentioned that an increasing amount of people in the UK consult the plastic surgeon or use cosmetic products to look as good as possible. Pictures on social media are manipulated to present persons in the best possible way. Body image and the perception of bodies are changing and result in increasing engagement in beauty practices that are justified by the new concept of normality. Unsurprisingly, living in a world that values beauty can be challenging for those with a visible difference. It can be particularly challenging for the individual himself or herself when there is a high personal standard placed on beauty. Also, society may be less acceptant toward those with a visible difference. Therefore, even minor scarring may increase the call for plastic surgery and cosmetic interventions. Underlying psychological problems may therefore be a point of attention.

This chapter has the general purpose to provide information about the psychological impact of a burn injury and psychological difficulties that may be encountered when living with scars. Because survival rates have increased, more people live with the physical and psychological consequences of burns. Consequently, appropriate psychosocial support and interventions that help burn survivors deal with scars, from a personal view and the view from the outside world, become increasingly important. Also, an understanding care environment including all professionals, that is, medical doctors, nurses, and physiotherapist, can improve outcomes. Learning objectives of this chapter include to know the prevalence rates of diverse psychiatric disorders that can develop in the aftermath of burn injury, to be aware of signals that may require an in-depth examination of underlying problems, to be aware that psychological problems can affect the perceptions of scar outcomes, to have some knowledge of risk factors, and, finally, to have knowledge regarding psychological treatment options to support people living with scars.

48.2 Psychological Problems After a Burn Injury

A burn event happens suddenly and can be life threatening. This may elicit a broad range of psychological reactions. Although it is documented that a substantial group of patients has pre-burn existing psychological problems sometimes being the cause of the injury, for example, self-harm during psychosis or suicide attempts, one may also develop severe and long-term psychological problems in response to the trauma or the adjustment process to a changed appearance. In the acute phase of burn injuries, there is a large focus on physical recovery. Along with wound healing and with the stabilization of the physical condition comes the realization that scars may be permanent and that appearance has changed. Facing this change may elicit feelings of grief and diminished body and self-esteem.

Severe psychological disorders may be encountered such as posttraumatic stress disorder (PTSD), depression, and anxiety. These disorders can become chronic when persons do not receive appropriate treatment. PTSD is included in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V) as a stress disorder and can develop in response to a traumatic event. PTSD comprises four symptom clusters: *intrusions* (intrusive thoughts and memories), *avoidance* of trauma-related stimuli, alterations in *arousal* and reactivity, and *negative alterations in cognitions and mood*. Initial higher levels of acute stress symptoms may be expected and can be regarded as normal reactions to a distressing event. For a substantial proportion of the patients, the high initial stress levels largely decrease within the weeks or months following the trauma. Severe symptoms of acute traumatic stress are reported in approximately 25% of patients admitted to a burn center. In a subgroup, however, they persist and become chronic. Prevalence rates of full PTSD after 1 year postburn are around 10% and another 15% may display severe symptoms that do not meet all criteria, that is, partial PTSD.

Depression is a disorder typically characterized by a negative mood and diminished interest or pleasure dur-

ing a period of 14 days or longer. One to 4 years after the burn event, about 10% fulfilled criteria of major depression with a postburn onset. Generalized anxiety disorder (GAD) entails the presence of excessive anxiety and worry, is experienced as challenging to control, and is accompanied by physical or cognitive symptoms. GAD was also found to occur in about 10% of burn survivors after 1 year. This implicates that over time, the majority of people involved in a burn injury appear to adjust well and they will recover from initial high stress and depressive symptoms but a substantial subgroup will have long-term problems [2]. Clinical attention and screening is needed for PTSD, depression, and anxiety.

48.3 Psychological and Social Impact of Living with Scars

After a burn injury, when wounds are healing and scars start to develop, one has to adjust to this new situation in which appearance has changed. There are two perspectives that have a mutual influence: the individual perspective and the social perspective. The first refers to how people look at themselves and the latter perspective entails the social perspective.

48.3.1 Body-Esteem and Self-Esteem Concerns

People sustaining a burn injury can be faced with noticeable visible differences resulting from large wounds that lead to scarring. Besides an altered appearance caused by these scars, functional limitations can occur if they are located across joints. Both the visible and functional characteristics can diminish satisfaction with appearance and can cause negative self-perceptions and difficulties with social interactions that place people at risk to develop depression and (social) anxiety disorders. These psychological problems may be debilitating to daily functioning in key areas of living such as occupational functioning.

Important psychological concepts such as self-esteem and body-esteem can be damaged when a person is forced to live with visible differences [3, 4]. Self-esteem is a generic cognitive representation of the self. It is a multidimensional concept comprising the view of the person on the different abilities and characteristics. It influences how external information is processed, for example remarks or looks from other people. Body-esteem refers to the evaluation of one's own body and can be viewed as a part of self-esteem [5]. After acquired disfigurement, there is a change in body-esteem that a person needs to adjust to.

It is reasonable to expect that persons with more severe scarring have greater difficulty integrating the scars in daily life than a person with minor scarring. But objective characteristics such as severity of the burn injury in terms of body area affected, the number of surgeries needed, or the number of affected body parts are only modestly related to psychological well-being, indicating that psychological factors may be more important. One such factor, importance of appearance, showed to moderate the relationship between severity characteristics and body-esteem. This indicates that for those who attach little value to their appearance, scars have a lower impact on their body-esteem. For people who highly value appearance, scars negatively affect their body-esteem [6]. These aspects will be addressed in more detail below.

48.3.2 Social Self-Consciousness of Appearance

Scars can elicit negative reactions from the environment. This is well described after burns. Feelings of stigmatization is one of the documented social problems of living with scars. This feeling may result from reactions from other people such as prejudices, discrimination, being ignored, intrusive behaviors such as staring, intrusive questions and remarks, or even bullying [7]. People who have to deal with these reactions may develop a feeling of self-conscious and may perceive stigmatization which may affect self-esteem in a negative way. This in turn can induce avoidant behavior or sometimes (symptoms of) social anxiety. However, the impact of these reactions may differ across individuals. Some persons are more prone to feel stigmatized because of a stronger attentional bias toward stimuli that elicit fear. Psychological therapies can help dealing with these reactions and build self-esteem to increase quality of life.

48.4 Factors Impacting Adjustment

48.4.1 Burn Severity and Scarring

In general, the objective severity of scarring showed to be a poor predictor of psychological adjustment. Both small and large defects can elicit body image concerns and diminish satisfaction with appearance. Therefore, it has been argued that a person's subjective perception is a better starting point to assess how persons adjust [4]. However, the body of knowledge that shows (in)direct associations between injury severity and psychological problems is growing. One in-hospital study documented that there were no differences across groups with minor and severe burns, but dissatisfaction with appearance increased over

time in the group with more severe burns [6]. Another study found that persons with severe burns showed to ruminate more often—rumination is considered a cognitive strategy in which perseverative negative thinking and impaired disengagement from negative stimuli is present—which in turn predicted the level of depressive symptoms [8]. However, permanent scarring can act as a reminder to the burn event and has the potency to maintain psychological problems. Particularly when persons developed posttraumatic stress symptoms in response to the burn event, changes in appearances can trigger re-experiencing the traumatic event, which is an important symptom of posttraumatic stress disorder [9]. This indicates that more severe burns, possibly associated with more functional problems, can partly drive psychological adjustment. This does not exclude the fact that less extensive scarring can also elicit appearance-related concerns. Paying attention to the role of the scars in personal life is therefore warranted.

48.4.2 Facial Involvement

The face is a key figure in identity and it plays a key role in personal communication and expression of emotions. Sustaining a severe facial burn can be a devastating experience as it affects issues that are central to identity and social interactions. It is commonly expected that persons with facial disfigurement have more problems compared to persons with scars located at body parts that can be covered with clothes. Although there is evidence that living with facial burns may be more distressing than non-facial burns, the evidence is not that straightforward. One of the explanations put forward as to why people with facial burns may adjust relatively well is that they get used to negative reactions and are therefore better able to anticipate these unwanted reactions. Still, it is well established that persons with facial injury are presented with certain social challenges. Unwanted social reactions include staring, intrusive questions and remarks, and prejudices. A study comparing persons with facial burns to persons with the face not involved found higher problems in several domains of functioning such as: emotions, that is, they perceived more anger and sadness, and they had more social problems due to appearance issues [10]. Examples are available illustrating that facial differences is given meaning by others, for example, a woman who is pitied because she is seen as a victim of abuse [11]. Due to these responses, the risk to develop social anxiety and avoidance, low mood, and difficulties with relationship may increase and remains a concern across the lifespan. This is illustrated by a quote from a 60-year-old man who was injured during childhood: *"There is a part of me that hasn't quite made the hurdle to 100% adjustment. I'm comfortable at home and work, and among my circle of friends. Going out among strangers brings good and bad days"* [12], p. 368.

48.4.3 Concealed Scars

Scars that can be covered with clothes trigger dilemmas such as when to show the scars or how to present yourself in certain social situations, how to deal with stares in the swimming pool and at the beach. This can lead to avoidance of these situations because of the reactions of others. Hidden scars can also affect intimacy and sexuality, topics still surrounded with taboo. Scars can impact the ability to enjoy intimacy because one may not feel attractive and avoid being touched.

48.4.4 Gender

It is suggested that women are more frequently concerned about their appearance and therefore find it harder to cope with visible differences. Little research provides direct support for this assumption but, in general, there is evidence that women (with facial burns) or with more severe burns have higher depression scores and are less satisfied with appearance [13]. These findings do not exclude the fact that also (young) men can be troubled by (facial) disfigurement and can question their physical attractiveness. There is, however, evidence supporting that women were more concerned about the change in appearance. Men predominantly reported an increased awareness of their whole body and not specifically their appearance. This may indicate there is, in general, a higher risk for women to develop appearance concerns compared to men because appearance is more valued by women.

48.4.5 Importance of Appearance

How persons view themselves is closely related to how they feel. The role of scars in psychological problems after burns is therefore not straightforward. A person's appraisal of his or her appearance constitutes an important factor of self-esteem. There is evidence for the importance that persons attach to appearance in the adjustment process after burns. Importance of appearance showed to predict distress of living with burn disfigurement [6].

48.5 Interference of Psychological Problems with the Perception of the Scar

There is ample evidence that scar evaluation by health care providers does not match that of the patient and is a poor predictor of satisfaction with the treatment by patients. This may be frustrating for both the patient

and the health care provider. Understanding why these differences occur may diminish disappointment for both. Psychological problems such as depression can alter the way scars are perceived. As shown in a study [14], many patients with burns were well able to score scar characteristics within the same range as the professional. Persons scoring lower on self-esteem, however, rated their scars more troublesome, compared to the professional's view. This particularly concerned hypertrophy, possibly due to the fact that this characteristic is most conspicuous. This indicates that the psychological state influences how scars are viewed. Particularly the discrepancy between the patient's and professional's view may be a starting point to evaluate psychological factors.

Bradbury [11] underlines the importance of recognizing psychosocial issues in surgical decision-making. Having a realistic view on surgical outcomes in terms of what can be expected and psychosocial factors that may interfere with expectations and decisions is important. She proposed a three-staged approach in which individuals working with patients with visible differences all have some knowledge on influencing psychosocial factors, which forms the first stage of attention. If indicated, patients can be referred to, for example, a clinical nurse specialist trained in counseling skills. In the event therapy is needed, referral to a psychologist should be considered. It is emphasized that understanding psychological needs surrounding surgery is imperative to ensure that personal needs are met.

48.6 Management

Over the last decades, a number of interventions has been described that have the objective to help people dealing with challenges that result from living with a visible difference. Social skills training was among the first intervention programs aimed at expanding the arsenal of responses to a variety of reactions of people. Other therapies include cognitive behavioral therapy (CBT) in which dysfunctional cognitions, appraisals, beliefs, and assumptions are identified and changed in order to learn more useful ways of dealing with the visible difference [11]. CBT showed to have the strongest evidence of effectiveness and can support patients to come to terms with the visible difference, it can help in decision-making, and showed to be effective in overcoming social anxiety [3]. An online program called YPFaceIt, which includes elements of CBT and social skills training, has shown improvement in persons with a visible difference [15], although more research in larger groups is needed.

Besides psychological therapies, peer support groups have shown to be beneficial to well-being of burn survivors. Talking to a person who experienced a similar event and is faced with the same challenges increases empowerment. This was illustrated in the next quote: "*When you meet someone who really knows what you're going through, you can discuss things in a different way*" [16]. It is assumed that peer support groups can facilitate social sharing, which is a specific type of social support in which illness-related emotions are shared.

48.7 Conclusion

In sum, a burn injury can have devastating consequences in terms of psychosocial well-being. To predict who will adjust well after a burn injury comprises a complexity of factors that should be taken into account. It is an interplay of resilience and vulnerability factors; it involves a dynamic process over time. Some indications, however, may be points of attention for professionals in burn care. How persons cope with the consequences strongly depends on the significance they place on the value of their physical appearance. Objective factors such as gender, burn extent, and the extent to which the scars are visible all showed to have some relation but are poor direct predictors of dealing with the impact of scars. However, there are relationships that are worth considering. If there is a considerable deviation between the professional's and the patient's view on outcome, it is worth starting a dialogue with the aim to identify the causes. There is also a higher risk for women to struggle with visible differences as they, more frequently than men, value appearance and beauty; appearance may make up a larger part of their self-esteem and self-worth when compared to men. In men, functional problems may cause more problems.

The challenge for the health care provider is to be aware of signals that point to underlying psychological difficulties and judge to what extent another (surgical) intervention adds to the well-being of the patient. A staged approach of professionals with knowledge of psychosocial problems associated with visible differences should become more custom as it is now. It is only when the patient receives understanding, and whether it is clear for all parties what is going on in the patient, that compliance, decision-making, and outcome can be improved. Interventions focusing at psychological components may be indicated and can make a difference in the final outcome.

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Take-Home Messages

- Pay attention to the role of the scars in personal life.
- A changed appearance can have psychological and social consequences.
- Pay attention to signals that indicate underlying psychosocial problems.
- Be aware of underlying psychosocial issues in surgical decision-making.
- Consider a stepwise approach to recognize psychosocial issues.

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Makeup Therapy for Scars

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Medical makeup is a solution to hide scars and burns on the face as well as body, to both men and women. The objective is to reduce the psychological impact and to improve the patient's self-image.

Various studies have highlighted the positive effect of medical makeup on the patient's quality of life. With medical makeup, patient's self-confidence gradually comes back.

49.1 Definition

The priorities for medical makeup are different from those for cosmetic makeup, which is primarily concerned with fashion and trends. With medical makeup, first and foremost, camouflage solutions must be found that do not risk aggravating skin lesions, the objective being to reduce the psychological impact and to improve the patient's self-image. The aim is therefore not to create the "most beautiful makeup" but to find corrective products that are compatible with medical prescriptions, skin sensitivity, the expectations of the patient, and their ability to put on the makeup. Medical makeup is offered to both men and women and helps hide lesions on the face as well as the body.

49.2 Characteristics

- Makeup referred to as "medical" is formulated to guarantee complete safety even for damaged skin [1].
- Products are hypoallergenic and non-comedogenic and must contain a high sun-protection factor.
- The quality of textures is important to make it easier to apply the makeup and also to achieve a natural result.
- It is essential that the makeup be long lasting and resistant to water and sweat so that it lasts all day long. That being the case, the description of the product on the packaging should be checked to make sure they have all these qualities.
- The anhydrous forms, and stick and compact types are resistant because their outer oily phase is less miscible with water. For the other formulas, the addition of polymer increases the adhesion of the product to the skin and thus limits its migration into the water.
- By using makeup products that are resistant to water and perspiration, the makeup hold may be greater than 10 hours.
- However, one last important point should be emphasized: the makeup must be easy to remove so as not to cause a secondary irritation.

49.3 The Benefits of Medical Makeup

Various studies have highlighted the positive effects of medical makeup on the patient's quality of life, particularly in the case of treatment for scars.

49.3.1 Psychological Impact

By learning how to conceal their skin imperfections, patients:

- Find it easier to look at themselves in the mirror
- Regain a more realistic body image
- Enjoy taking care of themselves again
- Grow in self-confidence

The patient's self-esteem is boosted and they find it easier to look to the future.

49.3.2 Social Impact

After having concealed highly visible lesions, patients:

- Are less likely to notice the sometimes "intrusive" looks from other people
- Find other people look at them more approvingly again
- Maintain or return to social activities
- Are able to continue working if they wish to do so

Their relationship with others is improved, thus avoiding or putting an end to their sense of isolation.

49.4 Medical Makeup

49.4.1 Step-by-Step Process

49.4.1.1 Evaluation of Needs

The first step is to evaluate the needs and expectations of patients.

What products does the doctor recommend: emollient, sun protection, etc.?

- What does the patient want to conceal?
- Does the patient want a highly corrective or a lighter type of makeup?
- Does the patient usually apply makeup?
- Always remember to adapt the advice according to sex, age, habits, and preferences.
- And to give advice that the patient can easily replicate.

49.4.1.2 Makeup Base

Applying an emollient cream is essential for correcting a skin imperfection. Skin must be moisturized and supple to be able to spread the foundation easily. If the skin is not moisturized, the pigments contained in the makeup

will stick to raised areas of the skin, the correction will not be even, and the makeup will not last for the entire day. If sun protection is required, apply this after the emollient cream, using it as the makeup base [2].

49.4.1.3 Color Correction

Thick makeup often gives the impression of a mask effect and sometimes gives burn patients' faces a frozen look. The makeup must therefore be lighter so that the patient does not feel their personality has been stripped away after having it applied [3].

49.4.2 Using Color Correction Is the Best Solution to This Issue

By experimenting with color, we can reduce the intensity of imperfections, which means less foundation needs to be applied therefore obtaining a more natural result.

49.4.3 Complementary Colors

The principle is to superimpose two complementary colors in order to neutralize them.

As we can see from the chromatic circle (Fig. 49.1):

- Green is the opposite color to red
- Yellow is the opposite color to purplish blue
- Coral is the opposite color to dark blue

Fig. 49.1 Complementary color circle. Source: Eau Thermale Avène. © All rights reserved

Fig. 49.2 Corrector sticks. Source: Eau Thermale Avène. © All rights reserved

Therefore:

- A green corrector neutralizes imperfections that are predominantly red: inflammatory scars, rosacea, psoriasis, etc.
- A yellow corrector neutralizes imperfections that are predominantly purplish: ecchymosis, angioma, blue-toned dark circles, varicose veins, etc.
- A coral corrector neutralizes imperfections that are predominantly dark-blue: tattoos, nevus of Ota, etc. (Fig. 49.2)

After having applied a corrector, the imperfection becomes slightly grey; therefore, it is not necessary to apply as much foundation.

49.4.4 The Value of Colors

The light amplitude of a color is known as its "value," from the lightest to the darkest; adding white or black to a color is all that is required to change its intensity. For example, with orange, as we can see from the chromatic circle, its dark value is brown and its light value is beige [4] (Fig. 49.3).

In practice, if we want to correct a brown imperfection, it is necessary to apply an orange-ish shade to obtain a bright, light beige color, before applying foundation.

Therefore:

- A coral corrector neutralizes imperfections that are predominantly brown: hyperpigmented scars, melasma, brown-toned dark circles, lentigos, etc.

After having corrected the colored lesions using the complementary colors or the value of colors, we simply need to cover this with a little foundation to even out the complexion.

Fig. 49.3 Color value circle. Source: Eau Thermale Avène. © All rights reserved

49.4.4.1 Corrective Foundations

Corrective foundations offer several advantages for medical makeup.

- Their high pigment concentration allows for correction using less product.
- Their excellent resistance means that there is no need to reapply the product during the day.
- Their resistance to water and sweat means they can be used in any situation, both on the face and body.
- They have a high sun protection factor.

There are two types of corrective foundations:

- Fluid for mild imperfections
- Compact for severe imperfections

49.4.5 Compact Foundation Creams

These are the most suitable for concealing severe imperfections and particularly for a long-lasting effect and a water, sweat resistance finish.

- For post-surgery patients: it is better to use a "comfort" texture with a supple formula that is easily applied, even on the most sensitive skin.
- For remote post-surgery patients: we select a "comfort" texture for the face and a "matt-finish" texture for the body as there is no transfer and excellent resistance [5] (Figs. 49.4 and 49.5).

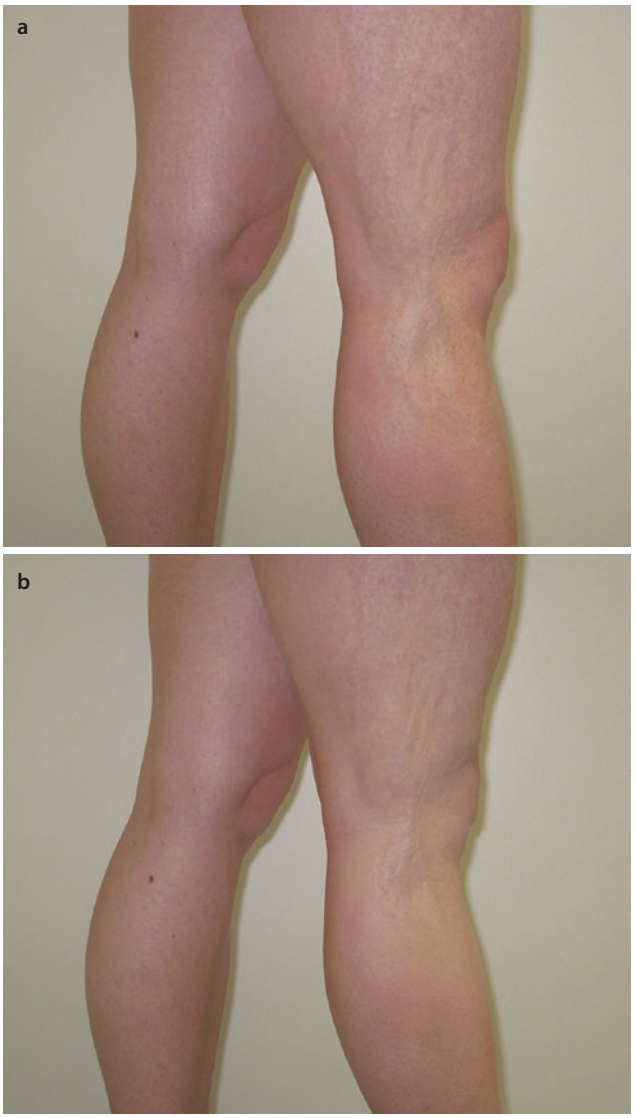

Fig. 49.4 Legs before (**a**) after (**b**) make up Source: Eau Thermale Avène. © All rights reserved

It is better to apply these products with a sponge and therefore the finish can be adapted depending on the intensity of the imperfection.

- For a high-coverage result or after using a color corrector, apply by dabbing.
- For a transparent result, apply by smoothing.

Do not forget to regularly clean the sponge with soap and water, or simply by washing it in the washing machine.

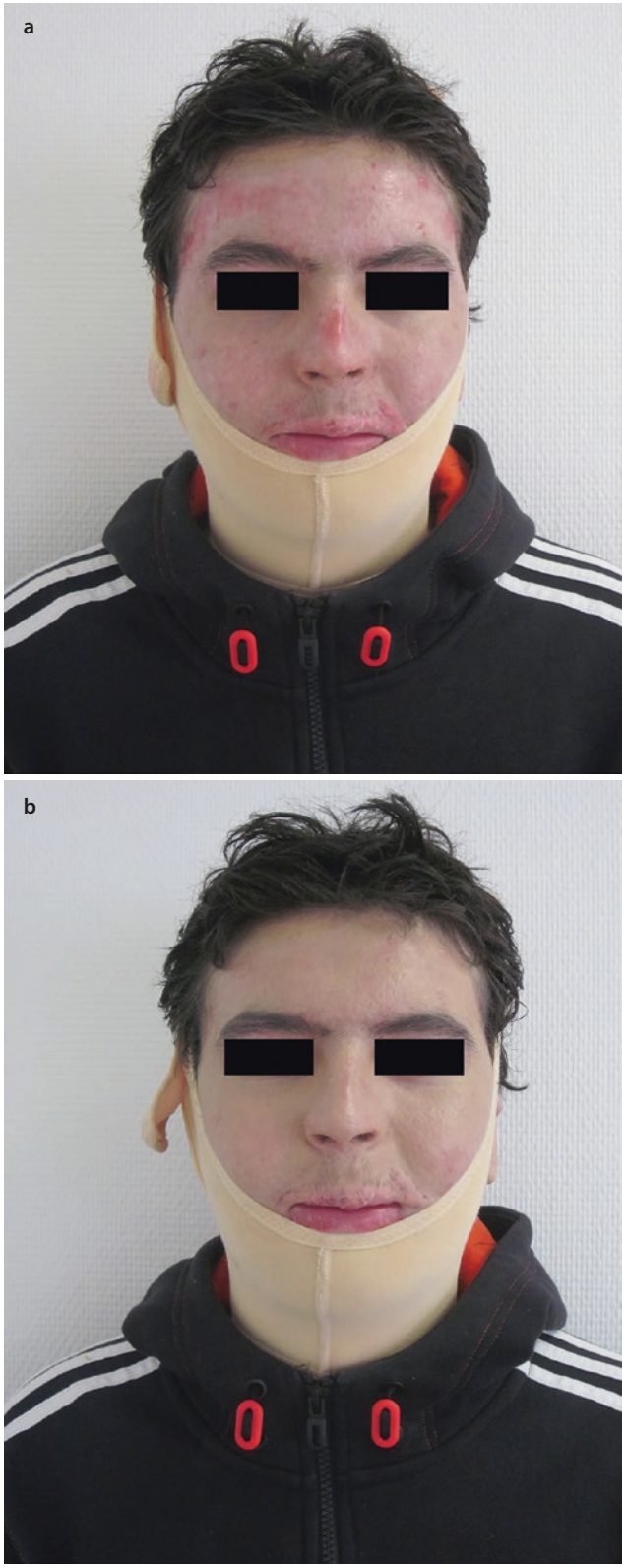

Fig. 49.5 Face make up: before (**a**) and after (**b**). Source Eau Thermale Avène. © All rights reserved

49.4.6 Fluid Foundation Correctors

These are more suitable for mild to moderate imperfections and as they have a lower pigment concentration, they are ideal for scaly skin. They can be applied using the tips of the fingers, but if the skin is very dry or scaly, a sponge is more effective to "blur" the scales. As for foundation brushes, they are chosen for a more transparent finish and for men who really like this method of application.

49.4.6.1 How to Decide on a Shade of Foundation

People often select the color of their foundation according to the color on the inside of their wrist, but this body area is quite fair and therefore this rarely achieves a natural result. The most effective method is to test the product on the jawline to check that there is no demarcation between the face and neck. For the body, test the product next to the imperfection that you are going to apply makeup to. In case of hyperpigmentation, opt for a shade that is slightly darker than the skin tone; this will help with correction.

Powder

This is essential to set the makeup and to ensure long-lasting hold. Opt for a powder suited to the skin tone and apply it with a large brush for a more natural effect. When scars are very raised, finish by applying the powder in the opposite direction to get rid of excess product so that the makeup is less visible. If skin is very scaly, it is better to avoid applying powder as it accentuates the appearance of scales.

Corrector Pencils

Eyebrows

Eyebrow corrector pencils are extremely useful for concealing localized scars around the eyebrows or to completely redefine and rebalance the eye area. The eyebrows are so important in makeup that it is said they act as a "frame for the eyes."

Lips

In case of scarring around the mouth, a lip pencil is generally applied after having concealed the scar with foundation and a little bit of powder. The lip pencil is therefore used to define the contours of the mouth [6]. In the case of cheilitis, you can suggest using a lip balm before applying lipstick, which can be used instead of lip gloss to treat dry lips at the same time.

Ensure Makeup Lasts longer

Spray a fine mist of thermal water 20 cm away from the makeup and leaving it to evaporate, this dries the makeup and makes it last longer. This is a very useful technique for body makeup, which is more subject to friction than the face.

Makeup Removal

An essential step! Most of the time, makeup remover is put on a cotton pad and rubbed against the skin with varying levels of force. If the pressure from the cotton pad is not strong enough, the makeup is not removed and if it is too strong, this could cause an irritation. The most suitable method is to remove makeup with just the tips of your fingers. The makeup remover must contain gentle surfactants, be fragrance-free, and in the form of a lotion or gel-like lotion so that it can be applied using gentle massage with the tips of the fingers. After having loosened the makeup and impurities, gently remove the rest with paper tissues before rinsing with a thermal water spray to achieve perfectly cleansed skin.

In brief:

1. Evaluation of needs: to evaluate the needs and expectations of patients
2. Makeup base: to prepare the skin before the makeup
3. Color correction: to neutralize the color imperfection
4. Corrective foundation: to unify the tone of the skin
5. Powder: to set the makeup
6. Corrector pencil: to correct scars or depigmentation on eyebrows and lips
7. Fine mist of thermal water: ensure makeup lasts longer
8. Makeup removal: to remove the makeup without creating irritation

49.5 Medical Makeup Classes

Because each patient needs personnel advice, it is important for them to learn how to hide their imperfections from medical make-up specialists or nurses similarly trained. Usually, these classes or workshops are in hydrotherapy centers specializing (in skin disorders), functional rehabilitation centers, or hospitals.

At first, patients can have individual advice, and they can also join a workshop with other patients to learn how to do it by themselves. This last solution is the best way to become autonomous and generally men should opt for this more than women, because usually men do not use makeup and they need to be more careful in applying it.

Take-Home Message

Medical makeup can be applied to all imperfections, ranging from mild to severe. It can be applied to the face and body and should be offered to men as well as women. Various studies have highlighted the positive effects of medical makeup on the patient's quality of life [7]. It improves patients' personal relationships and daily activities and reduces esthetic prejudice [8].

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Emerging Technologies in Scar Management

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Emerging Technologies in Scar Management: Laser-Assisted Delivery of Therapeutic Agents

Juhee Lee and Jihee Kim

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50

50.1 Background

Scars can cause significant impact on patients' quality life. Let alone cosmetic aspect, scars can result in functional and structural comorbidity. However, the treatment of scars is often challenging due to heterogeneity of etiologies and clinical presentations. Traditionally, surgical revision had been a mainstay for scars requiring structural remodeling to release the contracture of underlying tissue and relieve restricted range of motion. Nowadays, varieties of therapeutic options have been successfully introduced including physical therapy, silicon sheet, cryotherapy, corticosteroids, and laser modalities. Corticosteroids are often referred to as first-line treatment but its topical application is often ineffective. The major rate-limiting step for drug absorption is passage through the stratum corneum, which serves as the physiological barrier. Considering the pathogenic foci in scars are usually deep seated in the dermis, intralesional injection is considered as the best treatment option to bypass the thick stratum corneum barrier and deliver higher concentration of corticosteroids at the site. Yet the procedure inevitably accompanies excruciating pain. Corticosteroid is often associated with localized adverse events on repeated sessions causing skin atrophy, hyper or hypopigmentation, and telangiectasia. Treatment of keloid is even intriguing with varying success rates, and recurrence rates are high with conventional measures.

Target site for topically applied drug is the viable epidermis or dermis and the clinical response to a formulation is directly proportional to the concentration of the drug achieved at the target site. Transcutaneous absorption is limited by inherent skin barrier properties, minimizing the absorption to only 1–5% [1]. The innate barrier function of the skin, in particular the stratum corneum, provides the rate-limiting step in percutaneous penetration of drugs and other agents. Many different strategies have been developed to increase the permeability of the skin transiently for drug delivery. In skin with intact stratum corneum, only small (<500 Da in molecular weight) and lipophilic drugs succeed in partitioning into and diffusing through this dense lipid-rich layer. Transdermal patches have been used since 1970s but it is limited to drugs with low molecular mass. Accordingly, there is considerable interest in developing novel drug delivery methods. To enhance topical delivery of drug, currently available physical techniques include stripping, microneedling or sonophoresis, or iontophoresis to overcome the skin barrier.

The advent of lasers, particularly fractional laser systems, significantly advanced scar treatments in past decades [2]. Laser-assisted drug delivery was first described in 1987 and initially practiced with fully ablative lasers [3]. Laser-assisted delivery has been reported and evaluated in animal models for variety of skin diseases including premalignant lesions to inflammatory conditions. Ablative lasers can be effectively used to induce absorption of medications beyond the epidermal barrier. In precancerous skin lesions such as actinic keratosis, ablative fractional laser (AFL) is used to induce penetration of photosensitizer prior to photodynamic therapy. Chemotherapeutic agents and immunomodulators like 5-fluorouracil (5-FU) or imiquimod have been successfully used. Laser-assisted drug delivery has also shown to enhance absorption of topical anesthetics, nonsteroidal anti-inflammatory drugs, and corticosteroids [4].

50.2 Laser Systems Used for Laser-Assisted Delivery

Ablative lasers system has been employed to improve skin penetration of active molecules. Laser devices have traditionally been used in continuous mode, in which the entirety of the water-containing epidermis is completely ablated. Elimination of the physical barrier of stratum corneum allows transcutaneous delivery of large molecules, although it requires significant recovery time after removing large areas of stratum corneum. To overcome significant drawbacks from ablative fractional resurfacing, the concept of fractional photothermolysis (FP) was proposed in 2004 [5]. Fractional photothermolysis (FP) is a technique whereby an ablative laser is administered in a fractionated pattern instead of full ablation. Fractionated systems create discreet columns of ablated tissue, known as microthermal zones (MTZs), sparing intact portion of skin. The untreated skin surrounding MTZs serves as a reservoir of growth factors and stem cells promoting tissue regeneration and wound-healing response. Accordingly, ablative fractional lasers (AFLs) have provided an emerging option with a lower side-effect profile. AFL emerged as a promising tool in the treatment of scars with minimal pain and rapid wound healing in few days [2]. Moreover, fractional laser-assisted drug delivery is employed with high precision by controlling the area and degree of ablation through laser settings. MTZs facilitate penetration of topical molecules from the surface to the layer of interest (Fig. 50.1). Due to its predictable tissue response, it can be an effective alternative to injection or topical formulations of drugs targeting cutaneous diseases.

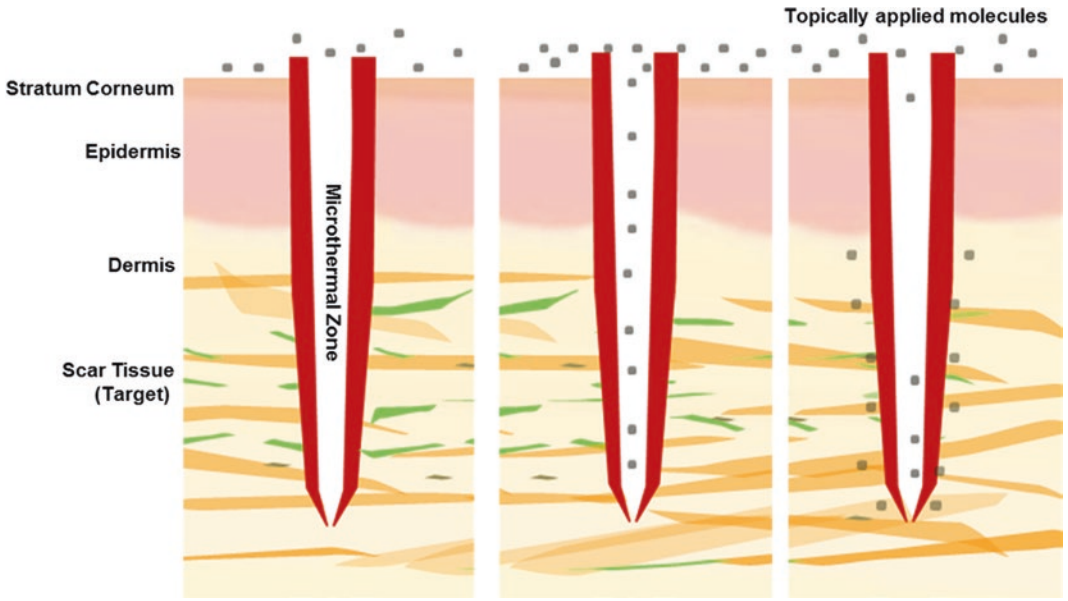


Fig. 50.1 Schematic diagram of ablative fractional laser (AFL)-assisted drug delivery. AFL irradiation creates microchannels extending from the skin surface to the dermis. Microthermal zones (MTZs) vaporize accumulated scar tissue (orange) and influence collagen remodeling (green). Microchannels transverse stratum corneum and topically applied molecules can reach target tissue in the dermis and permeate into the skin

50.3 Carbon Dioxide (CO_2) Laser and Erbium:Yttrim-Aluminum-Garnet (Er:YAG) Laser

Carbon dioxide (CO_2) laser and erbium:yttrim-aluminum-garnet (Er:YAG) laser are the two types of laser devices most commonly studied in regard to laser-assisted drug delivery. CO_2 laser (10,600 nm) heats cells instantly, resulting in vaporization and coagulation of irradiated cells. Subsequently, denaturation of extracellular proteins and heat-induced shrinkage of collagen is noted in a subjacent residual layer. Histologic studies of scar tissue after ablative fractional CO_2 laser treatment demonstrated complete re-epithelization within 48 hours. Er:YAG laser (2940 nm) system delivers energy more precisely without extensive thermal damage to the surrounding tissue, permitting quicker wound healing and recovery of dermis. CO_2 devices generate larger degrees of heat diffusion to the surrounding tissue while Er:YAG system exerts less hemostatic effect. Differences between fractional CO_2 laser and fractional Er:YAG laser are similar to their full-field counterparts in that the CO_2 systems cause more residual thermal damage. Studies have reported that fractional Er:YAG laser causes significantly less residual thermal dermal damage, with a faster healing time and less post-procedure erythema compared to fractional CO_2 laser [4]. When applicable, the combined-mode Er:YAG/CO_2 laser system can offer synergistic benefit of ablative and coagulation effect. Both lasers have been successfully applied for scar treatment with favorable clinical outcomes. Fractional CO_2 and Er:YAG provided comparable outcome, yet fractional CO_2 system was associated with a higher degree of procedural pain in few studies [6]. However, it is difficult to determine superiority between the two modalities due to clinical heterogeneity and lack of comparative study design.

50.4 Mechanism of Ablative Fractional Laser-Assisted Drug Delivery

Ablative fractional lasers irradiate high-fluence laser beam forming multiple, discrete columns of thermal damage. Ablative fractional photothermolysis (AFP) systems generate MTZs by vaporizing full thickness zones of scar tissue that may extend to deep dermis. Surrounding the denatured columns created by MTZs is a collateral area of thermal denaturation that is sufficient to coagulate collagen. Moreover, thermal irradiation stimulates neocollagenesis for collagen remodeling. Studies have demonstrated that the increased expres-

sion of heat shock proteins (HSPs) induces anti-inflammatory effect after ablative laser treatment for scars. Additionally, the altered expressions of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are noted along with increased expression of growth factors. Collectively, the differential expression of anti-inflammatory mediators and cytokines attribute to improvement in clinical appearance of scars.

MTZs facilitate penetration of topically applied drugs and other bioactive agents by acting as an alternative pathway for cutaneous drug delivery. Increased penetration of molecule can be explained by Fick's first law of diffusion. The diffusive flux of molecule goes from regions of high concentration to lower concentration, with a magnitude that is proportional to the concentration gradient. The degree of flux (J) is described as a product of partition coefficient (K), diffusion coefficient (D), and concentration difference across the barrier (ΔC) divided by the diffusion distance (L). Partition coefficient (K) indicates the equilibrium solubility of the drug molecules available for diffusion across a membrane.

$$J = \frac{K \times D \times \Delta C}{L}$$

The diffusion coefficient reflects the measure of inherent diffusivity of a molecule and determines the diffusion rate once the molecule permeates the membrane. The diffusion distance represents the length of a path for the diffusion. MTZs generated by AFL impact flux in various aspects of Fick's first-law variables. Firstly, increased permeability via MTZs enables increase in K compared to intact skin. Secondly, larger molecules with higher diffusivity can permeate directly into epidermis. Lastly, the distance of the diffusion is decreased from the skin surface and enables delivery to deeper layer. As a result, pretreatment with AFL facilitates traditionally challenging uptake of large hydrophilic molecules. The use of AFL increases the transdermal drug delivery of large molecules by 8- to 15-fold [4].

50.5 Technique and Parameters

50.5.1 Main Parameters: MTZ Density and Depth

AFL system irradiates target scar tissue with high precision by controlling the area and degree of ablation through laser settings such as power, pulse duration, percentage of skin coverage, and ablation pattern. For AFL-assisted drug delivery, the density and depth of microablative columns should be determined by operator for the given clinical characteristics of the scars. MTZs formed by AFP system can be adjusted to target specific depth and diameter by increasing the fluence and induce regulated disruption of epidermal barrier. In general, relatively modest energy fluence and density are considered applicable for laser-assisted delivery. Low energy levels are classically all that are needed to impair the physical barrier of stratum corneum. By calibrating laser settings, it is possible to influence the delivery rate and drug biodistribution, which may lead to improved clinical efficacy with shortened incubation time. Studies of the effect of laser parameters on the transdermally absorbed molecules are limited.

50.5.1.1 MTZ Density and Coverage

The MTZs consist of sharply confined tissue denaturation with a diameter of about 100 μm at intervals of about 200 μm. In animal models, increased density of MTZs achieved overall drug delivery, yet there was threshold density to achieve maximum diffusion. Fluorescent labeling demonstrated that the absorption of topically applied photosensitizers, immunomodulators, and lidocaine reached maximum biodistributions of 5%, 10%, and up to 20%, respectively, while further increase only resulted in deposition to stratum corneum [3]. More importantly, complications, such as scarring and hypopigmentation, have been observed at coverages in excess of 45%.

50.5.1.2 MTZ Depth and Energy

The depth of ablation represents how deep the MTZs extend into the skin and for a given laser beam diameter is mainly controlled by laser pulse energy. Microbeams of AFL irradiation typically induce MTZs ranging from 100 to 300 μm in diameter and it can extend down to the deep reticular dermis. The optimal depth threshold is yet undetermined as studies report drug deposition as both dependent on and independent of laser channel depth. It is expected that increase in the laser fluence and irradiation time increases the cellular uptake of large molecules across the skin in a dose-dependent manner. The usual threshold in the literature is approximately 200–250 μm in diameter. Hydrophilic or semi-lipophilic molecules (methotrexate, prednisone, and diclofenac) are generally dependent on MTZ depth while lipophilic molecules (lidocaine, ingenol mebutate, and imiquimod) do not show obvious depth-dependent uptake [6]. The variation between optimal depths for penetration can be related to the location of vascular plexus in different types of skin used for evaluation.

50.5.2 Clinical Application in Scar Treatment: Drugs and Bioactive Molecules

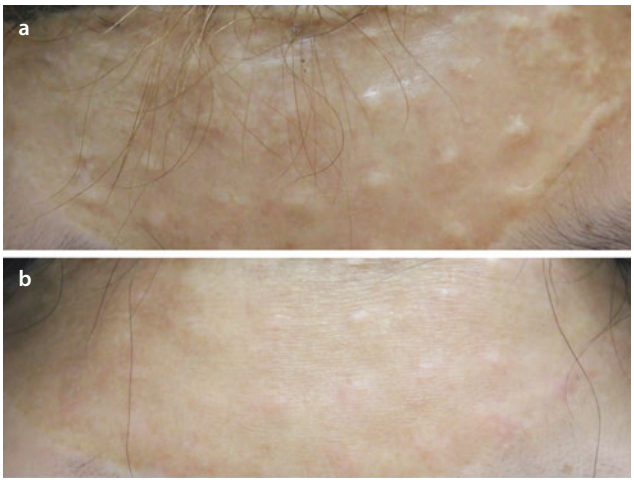
Delivery of every molecule will vary based on its inherent properties such as size, diffusion coefficient, and individuals' predisposed skin barrier conditions. In

stratum corneum, corneocytes are embedded in a lipid matrix and bioavailability of hydrophilic drugs is low. While lipophilic or semi-lipophilic molecules can penetrate lipid barrier of the outmost layer of the epidermis, large or hydrophilic molecules are able to transverse the stratum corneum after AFL pretreatment.

50.5.2.1 Corticosteroid

Corticosteroid has been a mainstay in the scar treatment. It is mostly known to inhibit inflammatory mediators and promotes remodeling of extracellular matrix. To exert its clinical effect, corticosteroid should penetrate cell membrane to bind the nuclear receptor. Sustained release of corticosteroid can be beneficial because wound regeneration of the inflammatory stages is known to persist for several days after laser irradiation. Triamcinolone acetonide is the most widely used and available as micronized suspensions of corticosteroid crystals. Currently, intralesional injection of corticosteroid has been well advocated in the treatment of both hypertrophic scars and keloids. After its administration, micronized crystals of corticosteroids persist in skin and are released over a period of weeks. However, local injection of triamcinolone actinide is often painful and consistent dosing is difficult to achieve throughout the scar.

Combination treatment of AFL and topically applied corticosteroids demonstrate encouraging results. Application of triamcinolone immediately after AFL can induce synergistic effect of deep penetration into the scar tissue to induce collagen remodeling. Use of relatively low-dose triamcinolone (10 mg/mL) is sufficient to induce clinical improvement in various types of scars including burn, trauma, or surgical scars. AFL-assisted delivery of topical triamcinolone potentially offers an efficient, safe, and effective adjunctive treatment. Corticosteroids available as topically applied formulations demonstrated mediocre effect in scar treatment. There are only few reports used to alleviate symptoms or appearance of hypertrophic scars immediately after surgical procedure [7]. Nevertheless, the combination of AFL and topical corticosteroid application yields successful result for the treatment of keloid without any adverse event [8]. AFL-assisted corticosteroid application is a promising tool with minimal pain and rapid wound healing in few days. Beyond the specific action of the lasers on scar remodeling, the channels that they create can be used to deliver active molecules to potentiate its efficacy (◘ Fig. 50.2). On the other hand, the presence of MTZ-induced channels is transient mostly at presence for 3 to 7 days. Accordingly, disrupted physical barrier of stratum corneum is restored within a week after AFL. Thus, further study is required to determine the optimal dosage of triamcinolone suspension and potency of topically applied formulations.



◘ **Fig. 50.2** **a** A 16-year-old woman with Fitzpatrick skin type IV with hypertrophic scars after facial reconstruction surgery. **b** Patient underwent five sessions of fractional CO_2 laser (eCO_2 Lutronic, Goyang, Korea. 60 mJ, 10% density) combined with topical application of triamcinolone acetonide suspension of 10 mg/mL

50.5.2.2 Other Agents for Scar Treatment

When routinely applied, topical corticosteroids do have risk to cause localized adverse effects such as skin atrophy, pigmentary changes, or telangiectasia. To spare such undesired skin reaction, drugs with immunomodulatory function has been applied in various skin conditions.

5-Fluorouracil (5-FU) is a pyrimidine analog antimetabolite that results in an irreversible inhibition of thymidylate synthase, commonly used for premalignant skin lesions. Laser-assisted delivery of 5-FU has been tested in animal models using various types of laser systems. Pretreatment with AFL resulted in more than 50-fold and 30-fold increase in penetration using Er:YAG and CO_2 system, respectively. In a study comparing the effect of 5-FU and triamcinolone to treat hypertrophic scars, lesions subjected to 5-FU demonstrated comparable results in terms of scar texture and height [9]. Appropriate dosing of 5-FU should be evaluated due to concern for increased systemic absorption with laser-assisted drug delivery, which can expand the adverse effect profile unlike bland topical application.

Atrophic scars result from loss of dermal or subcutaneous tissue during the wound-healing process. Fillers are high-molecular-weight biopolymer developed to provide structural support for volume restoration of skin. On this account, it is unable to permeate through intact epidermis and employed by injection. Laser systems, AFL in particular, can improve atrophic scars by promoting new collagen synthesis after irradiation. Concomitant use of AFL and topically applied poly-L-lactic acid (PLLA) fillers proved to be successful in treating patients with atrophic scars from various eti-

ologies including acne and trauma. Histologic evaluation on cadaveric skin demonstrated the penetration of PLLA to the dermis, albeit large molecular size [10]. Additionally, sustained release by prednisolone encapsulated in PLLA microsphere provided continuous delivery enough to suppress prolonged inflammatory response [6]. Likewise, several bioactive molecules and peptides such as polydeoxyribonucleotide (PDRN) are evaluated for potential application for scar treatment. Recently, enhanced percutaneous delivery of adipocyte and hematopoietic stem cells by AFL systems has been evaluated in scar management.

50.5.3 Other Modalities to Enhance the Effect of Laser-Assisted Delivery

50.5.3.1 Emerging Devices

AFL-assisted drug delivery of therapeutic agents emerging devices is one of the latest strategies to enhance cutaneous bioavailability of topically applied molecules. Notwithstanding that MTZs can empower to bypass the skin barrier, passive uptake through MTZs can be inadequate as the channels are rapidly restored within few days. Furthermore, within few hours after ablation, the depth of columns is gradually shortened by accumulated fibrin and interstitial granulation tissue. Therefore, several physical maneuvers have been suggested to enhance the delivery of active molecules. Ultrasound may temporarily reduce the intact biding of stratum corneum. Acoustic waves by ultrasound may induce cavitation, which increases the penetration of molecules. In animal model, active filling of MTZs was observed by altering the pressure during the topical application of test molecule [6]. Similarly, combination of sonophoresis and iontophoresis with AFL-assisted drug delivery can induce favorable results.

Radiofrequency (RF) devices locally generate heat depending on the local electrical resistance and current density. RF devices deliver thermal energy to the dermis and subdermal tissue, which induces collagen contraction and remodeling by disrupting its structural bond, thereby most commonly applied to the treatment of facial rhytides and skin tightening. Advances in laser and energy-based devices expanded clinical indications of RF devices. Fractionated RF systems are used to improve scar texture, and bipolar fractional microneedle RF systems have shown the resolution of atrophic acne scars. Furthermore, ablative fractional RF associated with acoustic pressure generated by ultrasound was used to increase the delivery of triamcinolone into hypertrophic scars [8].

The use of non-ablative fractional lasers (NAFL) needs to be examined as a less invasive method of laser-assisted drug delivery. NAFL systems create a similar array of microablative columns as does AFLs; the MTZs consist of columns of thermal injury with intact overlying stratum corneum. NAFL systems heat tissue without vaporization, thus being less associated with patient discomfort. Although the epidermis is not fully vaporized, barrier function of the skin in the treated area is transiently impaired allowing for enhanced drug delivery. NAFLs applied alone have confirmed its therapeutic efficacy in skin rejuvenation and various types of scars. NAFL-assisted drug delivery of minoxidil or corticosteroids can be applied to treat alopecia areata. Fractional erbium glass laser (1550 nm) was reported to effectively enhance percutaneous delivery of photosensitizers [4].

50.5.3.2 Limitations

Further investigations are required to establish the safety and efficacy of laser-assisted delivery of molecules as a transcutaneous drug delivery system. The majority of the existing studies have been performed on animal models and additional human studies are needed. Drug permeation through AFL-generated MTZs inevitably raises concern about systemic absorption and potential systemic toxicity. Transdermal delivery is considered relatively safe as the dosage required for the therapeutic effect of a drug is lower than the oral dose and avoids the drug metabolism in the liver. Although most applications of laser-assisted drug delivery have been intended for local effects in the skin, some reports have demonstrated that systemic absorption does occur. Along with increased transcutaneous absorption, a decreased dose should be considered to minimize side-effects that could be local or systemic. Further clinical studies are needed to fully evaluate the safety and efficacy of laser-assisted drug delivery for scar treatment.

50.6 Conclusion

Laser-assisted drug delivery is an evolving technology with many possible applications as a highly targeted customizable method for distribution of drugs within the skin. Current studies have demonstrated that laser pretreatment of the skin can increase the permeability and depth of penetration of topically applied drug molecules. Fractional laser systems can be successfully utilized in the treatment of various forms of scarring with a very favorable safety profile. Fractional photothermolysis, both ablative and non-ablative, can improve the texture of various scars by promoting collagen remodeling. AFL-assisted drug delivery systems offer distinct advantage by enabling the topical medication to penetrate deeper and reach target pathogenic site even for the systemic drug administration. Corroborative efforts with multidisciplinary measure and novel combinations of existing treatments can help ensure optimal clinical and cosmetic results.

Take-Home Message

- Lasers are safe and effective means of enhancing the delivery of topically applied agents through the skin.
- Ablative fractional laser-assisted drug delivery is increasingly used to enhance percutaneous uptake.
- Microthermal zones generated by fractional laser create precise, uniform columns of tissue vaporization, which facilitates delivery of various drugs.
- Ablative fractional laser-assisted corticosteroid delivery may take advantage of the newly formed channels to penetrate uniformly and deeply into the scar tissue. Combination of valuable scar treatment options can create synergistic therapeutic response.
- Laser-assisted drug delivery provides a new opportunity for a minimally invasive modality in scar treatment.

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Emerging Technologies in Scar Management: The Role of Allogeneic Cells

Clarisse Ganier and Sonia Gaucher

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51.1 Background

After skin injury, the wound-healing process has to occur as soon as possible to prevent excessive blood loss and/or infection. In chronic wounds, this normal healing process fails, which results in a pathologic cycle of inflammation and protease release, leading to the development of a pathologic scar. Also, in the healing of large and deep wounds, scar formation is evident. Nevertheless, in some natural cases, such as fetal skin, humans and animals are able to heal scarless due to the fast wound-healing process and/or specific fetal characteristics [1].

Scars caused by burns, chronic ulcers from diabetes, infections, skin cancer surgery, and other genetic or somatic disease could require effective treatment to avoid functional and psychological troubles and even in some severe cases to prevent mortality. Most of the current treatments do not prevent scarring. They first aim to reduce local inflammation.

Herein, we will discuss about emerging technologies in scar management using allogeneic cell therapy. Allogeneic cell transplants offer the possibility of large prefabrication, cryopreservation for instantaneous use, and repeated applications. They also allow the use of fetal cells that show interesting properties. Furthermore, they are applicable for genetic skin diseases inducing severe scars such as dystrophic epidermolysis bullosa. Current research exploring allogeneic cell therapies for scar treatment show that they are mostly locally delivered by grafting and/or by intradermal injections.

51.2 Allogenic Cell Therapy Studied in Scar Management Field

Allogeneic cell therapies combined with scaffolding biomaterials have been employed in tissue engineering approaches for wound care and scar management. We will describe here the cells and their scaffold used in scar management. The common cell types used for scar treatments are fibroblasts and keratinocytes as commercial products for skin regeneration (Table 51.1). The emergence of three-dimensional (3D) printing is gaining commercial interest for large-scale production. Research works on mesenchymal stromal cells (MSCs) therapy for scar management are also increasing and show very promising results.

Table 51.1 Human allogenic cell types used in skin regeneration

Source	Commercial products and their applications	Type of allogeneic cells
Skin	Apligraf® – Venous leg ulcers – Diabetic foot ulcers OrCel® – Partial-thickness burns Clinical trials	Living fibroblasts and keratinocytes
	TheraSkin® – Diabetic foot – Venous leg ulcers Cryoskin® – Chronic nonhealing – Neuropathic diabetic ulcers	Keratinocytes
Neonatal foreskin	TransCyte® – Full-thickness and deep partial-thickness burns – Partial-thickness burns	Dead fibroblasts
	Dermagraft® – Full-thickness diabetic foot ulcers	Living fibroblasts
	Lyphoderm® – Chronic venous ulcer – Partial-thickness burns	Keratinocytes
Fetus	Studied in animal models or involved in clinical trials	Fibroblasts and/or keratinocytes
Bone marrow	Studied in animal models or involved in clinical trials	Mesenchymal stromal cells
Umbilical cord	Studied in animal models or involved in clinical trials	
Adipose tissue	Studied in animal models or involved in clinical trials	

51.3 Human Allogeneic Epidermal Sheets

Epidermal sheets consist of human keratinocytes that are differentiated *in vitro* to give rise to a stratified epidermal layer. They can be combined with other biocompatible substrates (bovine collagen, hyaluronic acid), acellular natural human or porcine materials, or nylon or polyglactin meshes. An example of one product using allogeneic keratinocytes is Cryoskin® that is available from frozen cells on a carrier dressing [2]. A single blind study shows the efficacy of this cell therapy for the acceleration of healing of chronic nonhealing neuropathic diabetic ulcers. In general, the clinical outcome of the epidermal sheet grafts is usually not satisfying because of the nonpermanent character, ultimate rejection, and absence of a dermal component.

51.4 Cellular Dermal Substitutes and Human Dermal Fibroblasts Therapy

In contrast to epidermal sheets, the dermal substitutes are composed either of autologous or of allogeneic dermal fibroblasts. The scaffold for the cells consists mostly

of biomaterials, like benzyl-esterified derivatives of hyaluronic acid (Hyaff-11), polyglycolic acid, or polyglactin. TransCyte® is a comparable product containing a nylon mesh coated with porcine dermal collagen that is seeded with neonatal fibroblasts and fixed to an outer silicone membrane.

The major indication of application consists in transient wound cover after surgery. One of the most successfully bioengineered products is Dermagraft®, an allogeneic cell culture using neonatal dermal fibroblast grown on a biodegradable scaffold. This product showed the capacity to secrete several growth factors, to stimulate angiogenesis, and re-epithelialization from the wound edge, even after cryopreservation and thawing. In diabetic foot ulcers, its efficacy and its safety were demonstrated [2].

In addition, some other clinical trials are ongoing using a medicinal product comprised of viable allogeneic dermal fibroblasts suspended in HypoThermosol®-FRS for remodeling scar contractures from burn patients and from dystrophic epidermolysis bullosa patients. Fibroblasts are from neonatal foreskin, cryopreserved, thawed, and expanded in culture under good manufacturing practice at Intercytex Ltd., UK (► ClinicalTrials.gov, Identifier: NCT01564407 [burn patients], ISRCTN67757229 [recessive dystrophic epidermolysis bullosa patients]).

51.5 Human Skin Equivalent

Skin equivalent is only composed of a culture of keratinocytes growing on dermal substitutes containing fibroblasts. An example of an allogeneic skin equivalent product is Apligraf® consisting of cultured keratinocytes on a dermal layer of fibroblasts within a bovine type 1 collagen matrix (► http://www.apligraf.com/professional/). Apligraf® obtained its Food and Drug Administration (FDA) approval for diabetic foot ulcers and venous leg ulcers applications. This product has been well tolerated in over 150,000 patient applications.

Clinical trials showed that the healing rate of the venous ulcers treated with Apligraf® as well as the healing time was improved. Healing occurs with less fibrosis, which might be because of the construction of the graft itself containing neonatal cells and growth factors/cytokines, stimulating a more fetal-like scarless wound healing. Another product used in clinical trials for the treatment of venous ulcers is OrCel®, a bilayered cellular matrix containing adult epidermal keratinocytes and dermal fibroblasts. Donor dermal fibroblasts are cultured within the porous Type I bovine collagen sponge while keratinocytes, from the same donor, are cultured on the coated, nonporous side of the collagen matrix.

Recently, OrCel® obtained its first FDA approvals for treatment of acute surgical excisions, such as contracture release sites in patients suffering from dystrophic epidermolysis bullosa undergoing hand reconstruction surgery (► https://www.accessdata.fda.gov/cdrh_docs/pdf/p010016b.pdf) and also in burn patients undergoing excision and grafting [2]. *In vitro* skin cells used to make OrCel® skin equivalent are extensively expanded that give rise to a low human leukocyte antigen class II (HLA-II) level of the allogeneic cells. Therefore, OrCel® skin equivalent is well tolerated by the recipient after grafting into wound bed. The company reported in both clinical trial and commercial experience no clinical signs of tissue rejection using the cryopreserved OrCel® product. Resorption appears to take place gradually, with no remnants of the donor cells or matrix being detectable by 2 weeks of posttreatment. Their working hypothesis is that extracellular secretion of cytokines and growth factors by the living cells in OrCel® is the major factor for accelerating wound healing.

51.6 Bioprinting of Skin

The use of three-dimensional (3D) bioprinting has emerged as a flexible tool in regenerative medicine to bioengineer skin substitutes. There are many kinds of bioprinting technologies, but the four more commonly used are inkjet-based printing, extrusion-based printing, laser-assisted printing, and digital light processing (DLP)-based printing—dynamic optical projection stereolithography (DOPsL). Cell viability can be affected by several factors, including bioprinting technique used.

Jorcano laboratory has developed one bioprinter prototype able to print skin cells, soluble factors, and biomaterials in a desired pattern with the help of high-precision Cartesian robots. The printing skin mimics the structural and molecular structure of the human skin [3]. It is the first functional printer to be introduced to the marketplace. To date, there is no allogeneic 3D printed skin used in patients, but this technology raised great hopes for the treatment of scar in the future.

51.7 Injections of Mesenchymal Stromal Cells (MSCs) for Skin Regeneration

MSCs were known to contribute to skin regeneration and to accelerate cutaneous wound healing. MSCs were first isolated from bone marrow in the 1970s by their ability to adhere, proliferate, and develop on a plastic surface, displaying fibroblastic morphology. MSCs are multipotent adult progenitor cells that can differentiate to lineages of mesenchymal cells, including osteoblasts, chondroblasts, and adipocytes. These can be isolated from various adult or perinatal tissues such as adipose tissue or umbilical cord. MSCs have shown positive therapeutic effects in many tissue repair situations

through the secretion of trophic factors. In addition, allogeneic MSCs are well tolerated after injections due to their immune-modulating effects [4].

Many studies have demonstrated that MSCs exhibit a number of trophic functions to enhance skin regeneration, such as promoting angiogenesis, modulating the inflammatory response, and limiting tissue fibrosis [5]. In *in vivo* studies, these cells have been used successfully to limit scar formation. Transplanted allogeneic or xenogeneic MSCs transiently survive in the implantation site; their therapeutic potential in wound healing is associated with their secretion of trophic effects on resident cells. One of these *in vivo* studies using a rabbit model showed that intradermal injection of MSCs can regulate inflammation and prevent the formation of hypertrophic scars. The MSCs underwent apoptosis rapidly in the injected site, between 24 and 72 hours postinjection. They demonstrated that apoptosis has an important role in the activation of the inflammatory regulatory abilities of MSCs through TNF-alpha stimulated protein 6 (TSG-6) [6].

An *in vivo* study showed the efficacy of MSCs and dermal fibroblasts combined to minimize skin hypertrophic scarring [7]. They showed that transplanted xenogeneic MSCs influenced positively fibroblast proliferation, migration, and extracellular matrix deposition and reduced inflammation following wounding. This effect was superior to MSC or fibroblast transplantation alone. This study suggests that MSCs, even if eventually rejected quickly after injection, transplanted with fibroblasts normalize matrix regeneration during wound healing. This promising study provides insight into allogeneic cell therapies as a viable method for antifibrotic treatment and demonstrates that even transiently engrafted cells can have a long-term impact via matrix modulation and effect on other tissue cells.

One of the first randomized, controlled clinical trial will study the safety and efficacy of MSCs in skin scar for the treatment of Cesarean section [8]. Eligible patients received transdermal hydrogel MSCs once a day for six consecutive days. Their outcomes should be available soon (► ClinicalTrials.gov, NCT02772289).

51.8 Promising Embryonic(-Like) Stem Cells Therapy for Scar Treatment

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are defined as pluripotent cells able to self-renew. In the field of skin, those stem cells showed some promising results regarding fibrosis care.

Many *in vitro* and/or *in vivo* studies are ongoing on embryonic stem cells and induced pluripotent stem cells (iPSC) as potentially promising in scar management [9]. As fetal cells, ESCs are thought to possess antifibrotic ability. An *in vitro* study showed the capacity of ESC-derived macrophages to secrete scarless-like secretome to regulate the altered keloid niche and reverse the profibrotic phenotype of keloid fibroblasts [10]. Because iPSCs are similar to ESCs in many features, they have been evaluated in scar tissue repair. An *in vitro* recent study documented that iPSC-conditioned medium may efficiently suppress hypertrophic scar fibroblast activation [11].

51.9 Conclusion/Discussion

The allogeneic cell therapy for scar management shows many advantages: large prefabrication, cryopreservation for instant use, and repeated applications. They also allow the use of fetal cells such as embryonic stem cells. Furthermore, they are applicable for genetic skin disease inducing wound healing without genetic modifications.

Most of current and emerging therapeutics for scar management are using allogeneic fibroblasts and keratinocytes as epidermal sheet, dermal substitute, or skin equivalent. The immune rejection of these adult cells is commonly reported, mostly shown for allogeneic keratinocytes due to different HLA expression and cytokine production. Fetal cells are of particular interest for skin repair due to the high expansion ability, low immunogenicity, and intense secretion of bioactive factors. However, the main cellular effect seems in promoting wound healing through secretion of endogenous and exogenous factors rather than cell survival.

Regarding the viability of allogeneic cells, most of the studies on the literature agree on the fact that allogeneic cells do not survive for a long time after transplantation. But most of their therapeutic potential seems to be based on their secretion of trophic factors such as growth factors, cytokines, and extracellular vesicles at least for MSC therapy and also for dermal fibroblasts therapy. Extracellular vesicles (exosomes, microvesicles, and apoptotic bodies) are secreted by most cells of the organism. These extracellular vesicles are of growing interest among investigators, specially from MSCs across multiple fields, including dermatology as a drug [12]. As MSCs or stem cells, extracellular vesicles demonstrate immunomodulatory properties, accelerate skin cell migration and proliferation, control wound scarring, and improve angiogenesis. Several clinical trials should appear in the future years testing the safety and the efficacy of stem cells and derived products for skin scar treatment.

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New Drugs for Scar Treatment

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_52

52.1 Background

Cutaneous wound healing following injury is a complex biological process involving the orchestration of the immune system, inflammatory pathways, mechanotransduction pathways, and various types of participating cells. In adult humans, the wound repair process results in the replacement of the damaged functional tissue with a patch of cells (i.e., mostly fibroblasts) and disorganized collagen-rich extracellular matrix that is commonly defined as a scar [1]. While scarring occurs in almost all tissues, it is most apparent in the skin. Cutaneous scarring poses a significant psychological and physiological burden on patients, and an estimated $12 billion are spent annually on scar treatments in the USA alone [2]. Additionally, dysfunctional healing and hypertrophic scarring often causes lifelong disability, which has a significant additional economic impact [1, 2]. Over 40 million patients undergo surgical procedures annually, which often lead to the formation of hypertrophic scars (HTSs) resulting in substantial morbidity and disfigurement of the skin. Similarly, scar formation occurring as a result of burns and other forms of trauma leads to severe functional disabilities costing the economy over $4 billion per year [2]. Keloidal scars, which are characterized by excessive fibrosis in areas of the skin with acne or other minor injuries, represent another major fibrotic skin disorder. Several other skin fibrotic diseases such as Dupuytren's disease, psoriasis, and scleroderma lead to cutaneous scarring as well [2].

In current practice, cutaneous scars are treated using corticosteroid injections or cryotherapy, surgical revisions, topical silicone gels, sheets and pressure garments, radiation, and laser treatments [3]. These traditional treatment modalities have shown mixed success and most methods lead only to partial alleviation of scar formation. Further, many of these treatment modalities are associated with other practical issues such as patient discomfort and pain, multiple and frequent visits to the doctor's office, or even higher recurrence of scars [3]. Recent progress in the identification of key signaling pathways involved in fibrosis and scar formation has led to the emergence of new therapeutic agents for scar treatment, with promising results in animal studies. Agents targeting collagen synthesis pathways, cytokines, growth factors, and cytotoxic agents are under investigation for scar therapy. Of these, drugs that inhibit expression of transforming growth factor (TGF)-β1/TGF-β2 or augment TGF-β3 had shown initial promise, but have been shown to be ineffective in later clinical trials as discussed below [3, 4]. Similarly, treatment of scars with interleukin-10 (IL-10), an interleukin that is involved in regulating inflammatory pathways, has shown some promise in treating psoriasis, but has failed to show any significant benefit for other types of scars [5].

A paradigm shift in our understanding of the scar pathophysiology emerged when the role of mechanotransduction in fibrosis was explored. The role of mechanical stress in scar formation had been described as early as in the 1800s, with the description of Langer's lines of skin tension used for surgical incisions to minimize scarring. But recent work elucidating the role of mechanical cues activating inflammatory pathways and scar-promoting cells highlighted mechanotransduction as a central focus of scar pathophysiology [6]. In the past decade, aberrant activation of mechanosensitive skin cells have been shown to underlie abnormal wound healing and scar formation in various skin diseases including hypertrophic and keloidal scars, Dupuytren's disease, and scleroderma [6]. Offloading of mechanical forces during healing of human skin incisions following abdominal surgeries has been shown to be effective in reducing scar formation in Phase I clinical trials [7]. In particular, focal adhesion kinase (FAK), a molecular mediator of mechanotransduction, has been identified to play a key role in fibrosis and scar formation (Fig. 52.1) [8]. Animal studies have shown that pharmacological inhibition of FAK can lead to significantly reduced scar formation and accelerated wound healing [9].

In this chapter, we will review the latest pharmacological therapies that are being evaluated for scar management in the currently available literature. This includes agents that have recently completed clinical trials and drugs that target cellular mechanotransduction pathways.

52.2 Objectives of the Proposed Chapter

This chapter describes the evidence-based new drug therapies introduced in recent scientific literature for scar mitigation and prevention. Although the underlying pathophysiology of hypertrophic scar formation following injury is far from completely understood, over the past decade, advances in our understanding of the cellular and molecular mechanisms by which fibrotic scars develop have paved the way for devising new approaches in scar therapies.

52.3 Description of the State-of-the-Art Historical Evolution: Recent Data

Traditional scar revision technologies include surgical treatment, topical silicone gels, sheets and pressure garments, radiation, and laser treatments [3]. In current practice, intralesional corticosteroidal therapies and antiproliferative 5-fluorouracil therapy are also commonly used to pharmacologically mitigate hypertrophic scars, although their effectiveness is mainly supported

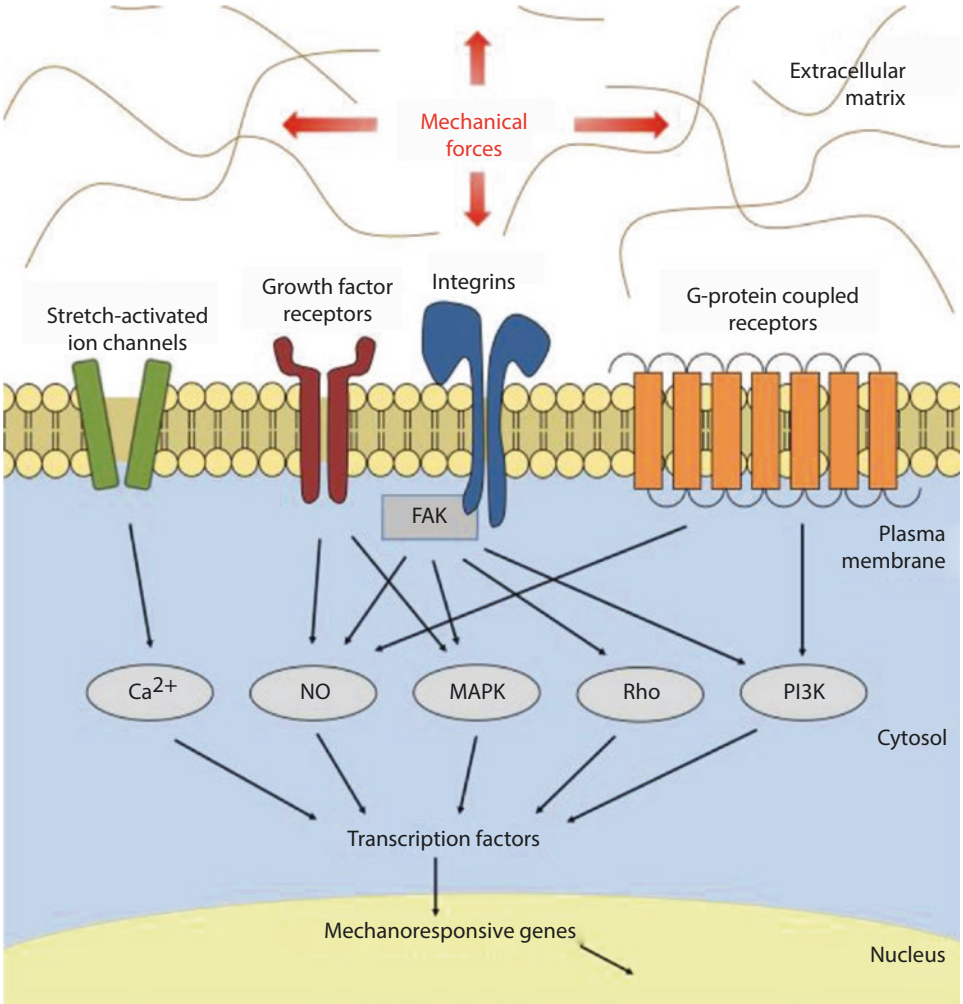

Fig. 52.1 Focal adhesion kinase (FAK)-mediated mechanotransduction. Mechanical forces activate FAK, which activates several downstream effectors and transcriptional factors that mediate cellular mechanotransduction [6]. Source: Mechanobiology in Health and Disease, 1st Edition. Elsevier. © All rights reserved

by case studies and preliminary clinical studies [3]. These treatments are often associated with adverse reactions, such as dermal atrophy or hypopigmentation, leading many patients to seek alternative treatment modalities after prolonged use. Recent studies have investigated new pathways to reveal drug targets such as modulators of wound inflammatory cytokines, growth factors, and mechanomodulatory mediators as potential targets for scar-mitigating therapies [6].

52.4 Transforming Growth Factor-β (TGF-β)

TGF-β expression is involved in almost all stages of the wound-healing process, including wound inflammation, angiogenesis, extracellular matrix synthesis, and tissue remodeling. Various studies have established the important role this wound-growth factor plays in dermal fibroblast differentiation into myofibroblasts and subsequent scar formation across a range of fibrotic diseases [3, 4]. Studies exploring the scarless and regenerative ability of the fetus have pointed toward the possibility that different isoforms of TGF-β could contribute to different stages of wound healing. While TGF-β1 and TGF-β2 are expressed highly in postnatal adults, TGF-β3 is the dominant isoform in fetal wound healing, leading many researchers to identify either TGF-β3 as a therapeutic target to upregulate or TGF-β1/GF-β2 as targets to inhibit for scarless wound healing [3, 4].

Despite strong preclinical outcomes, current TGF-β clinical trials have had disappointing results. Juvista, a new recombinant TGF-β3 product developed by Renovo, had shown promise in early phase efficacy trials but failed to meet primary endpoints in Phase III trials [3, 4]. Renovo also pursued a trial with Juvidex (mannose-6 phosphate), an inhibitor of TGF-β1/TGF-β2 [3]. Juvidex failed to meet its primary goal in a Phase II trial but it did meet a number of secondary endpoints [3]. Other researchers have also explored the clinical potential for a recombinant human antibody to neutralize TGF-β1 to combat systemic sclerosis, but their clinical studies did not prove any difference in efficacy from control during their Phase I/II trials [3]. TGF-β therapy could potentially have confounding results due to its

dual importance in both normal wound healing and also in excessive fibro-proliferation during scar formation. TGF-β receptors are upregulated during fibrosis, and while blocking TGF-β expression seems to prevent fibrosis, it can also lead to chronic, nonhealing wounds. Albeit, TGF-β continues to be an attractive pharmacological target for a wide variety of fibrotic diseases, and newer strategies modulating TGF-β pathophysiology await further investigation.

52.5 Interleukins (IL)

Neutrophils and macrophages, two of the major cell types during the inflammatory phase of wound healing, secrete cytokines such as interleukins (ILs). IL-10 has been shown to regulate inflammatory cell function during wound healing by sequestering pro-inflammatory IL-6 or IL-8 and by regulating the Th1 cell cytokine production [3, 5], leading some research groups to explore the therapeutic effect of administering IL-10 to the wound bed during early wound healing. The previously mentioned Renovo also demonstrated the ability of IL-10 to potentially improve scar healing in human patients during Phase I/II trials administering Prevascar, their recombinant human IL-10 (rhIL-10) product [3]. However, they were unable to pursue Phase III trials after failing the aforementioned Juvidex and Juvista trials. Treatment with rhIL-10 has also been explored in several other clinical trials to potentially combat various inflammatory diseases such as Crohn's diseases and rheumatoid arthritis with disappointing results, but has shown promise in treating psoriasis.

52.6 Mechanotransduction Pathway Inhibitors

During wound healing, mechanical stress plays an essential role in promoting pro-fibrotic cellular events through mechanisms that stimulate inflammatory pathway components leading to exuberant fibro-proliferation. Manipulation of the wound mechanoenvironment with new medical devices that can modulate local biomechanics, therefore, has gained a rapidly growing market for scar reduction of surgical wounds [6–8]. Based on long-standing surgical principles clinically used to minimize scar development, these polymer-based medical devices offload mechanical force to release tension imposed upon healing surgical incisions. In particular, incisions created at high-tension body locations such as the central chest, shoulders, knees, ankles, and/or the back are prone to forming HTS than other body sites. For example, abdominoplasty wounds can develop into wide scars due to their natural high-tension closure, and application of a stress-shielding device on these wounds has demonstrated clear efficacy in mitigating scar formation [6]. This technology successfully led polymer stress-shielding devices to the market, and numerous patients have seen benefits in the clinic.

Despite success on surgical incisions, polymer mechanomodulatory devices are difficult to use on large-sized excisional wounds, burn injuries, and wounds that formed in contoured body areas. Alternatively, noninvasive therapeutics that pharmacologically target key mechanotransduction (cellular machinery that transduces mechanical stimuli to biochemical signals) pathways have also received highlight in recent literature. Currently, a prototype of such therapeutic agents is at the early preclinical development stage with translational potential.

Small molecule-mediated suppressors of pivotal mechanomodulatory proteins have been studied as anticancer agents for many decades. A non-receptor protein tyrosine kinase, focal adhesion kinase (FAK), is a key upstream mediator of the Integrin mechanotransduction pathway and an important inducer of cell adhesion, proliferation, migration, and angiogenesis [8, 9]. FAK is known to be deregulated in cancer and is thought to be a rational target to block tumorigenic activities using pharmacological inhibitors [10]. Because emerging studies have shown that FAK transduces mechanical stress signals to stimulate the activation of the FAK–ERK–MCP-1 signaling pathway and is an important regulator of cancer-promoting pathways [6–8], many pharmaceutical companies have taken effort to develop later-generation FAK inhibitors that display improved pharmacodynamic and pharmacokinetic properties. Clinical trials are ongoing in human cancer subjects, and the therapeutic potential to antagonize stromal solid tumors seems promising to date [10].

In currently available literature, small molecule-mediated inhibition of the kinase activity of FAK has been successfully used to prevent experimental bleomycin-induced lung fibrosis and mechanically induced skin HTS formation [6, 9]. FAK inhibition significantly reduced scar-forming fibroblast migration, myofibroblast production of α-smooth muscle actin, and aberrant collagen extracellular matrix deposition in these studies (◘ Fig. 52.2) [9]. Because wound healing and cancer development share similarities in terms of overlapping mechanisms that promote transformation, proliferation, and survival of cells, FAK inhibitor therapy that can be safely delivered to wound sites would be a new and promising approach to wound and scar management. In most circumstances, cutaneous scar development is a localized event; therefore, this provides rationale and support to develop targeted FAK inhibitor delivery modalities in attenuating scar formation. Localized drug delivery has the advantage of circum-

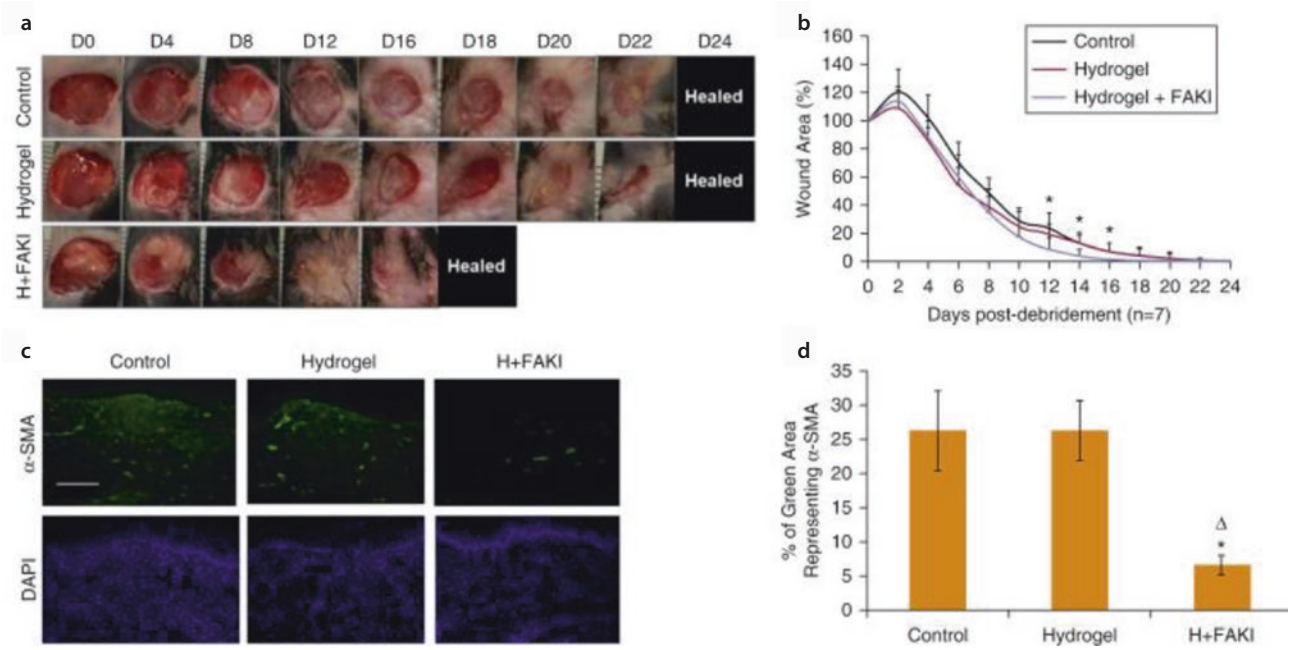

Fig. 52.2 Pharmacological blockade of focal adhesion kinase (FAK) improves wound healing and reduces scarring of murine burn wounds. (**a**, **b**) Mouse contact burn wound healing was accelerated with FAK-I hydrogel treatment. (**c**, **d**) Wound expression of α-smooth muscle actin (SMA) was significantly reduced with FAK-I hydrogel treatment [9]. Source: *Journal of Investigative Dermatology* (2018), Volume 138. Elsevier. © All rights reserved

venting systemic toxicity while maximizing bioavailability and local drug efficiency. Localized topical FAK inhibitor therapy ideally requires drug delivery vehicles that are biocompatible, eliciting no or low immunogenicity. Medicated self-adhesive patches that release therapeutic molecules upon dermal contact may not be suitable for large-sized open wounds, and other topical formulations in the form of topical cream, lotion, or ointment are easily subject to over- or under-dosing if application amount per treatment is not accurately measured. The latter is also problematic especially for therapeutic compounds with potential toxicological effects at the systemic level. Therefore, it is scientifically reasonable to devise a dermal delivery vehicle that can deliver topical FAK inhibitor to wounds and/or scars in a controlled manner. Biopolymers have strong advantages as drug delivery carriers because of their ability to carry bioactive compounds to target tissues and cells and to release compounds over a prolonged duration. Recent studies have used collagen-based bioscaffolds to develop biodegradable hydrogels that release FAK inhibitors in a regulated manner upon direct contact with the skin, which has proven preclinical efficacy in rodent wound models for HTS reduction [9]. Development of relevant drug delivery systems and extensive safety studies on potential adverse effects of each agent will be imperative to successful development of pharmaceutical therapies against fibrotic scar formation.

52.7 Supportive Articles in the EBM Literature

To date, currently available scar treatment modalities, especially for large-sized excisions and burn-related injuries, have not led to successful clinical outcomes, and the future market for new wound healing and scar mitigation therapies remains strongly promising. Recent progress in the identification of new signaling pathways and cellular components implicated in fibrotic scar formation has advanced our knowledge toward developing nontraditional therapies for scar treatment. Promising results in preclinical studies have resulted in many publications from multiple research groups with some therapies already completing human clinical trials. Scientific rationale for these newer therapies is strong; however, clinical development of some of these agents have faced failure during clinical trial phases. TGF-β-based therapies, Juvista and Juvidex, both displayed strong preclinical effects but failed during multiple human trials. IL-10 products also showed disappointing clinical outcomes. A mechanomodulatory agent, specifically localized FAK inhibitor therapy, is in its early preclinical development stage with promising animal data recently published. The more we understand the cellular and molecular mechanisms underlying fibrosis and scar formation, the more therapeutic opportunities will be revealed for scar mitigation.

52.8 Clinical Relevance

Cutaneous scar development of the skin, particularly the formation of HTS and keloidal scars following wound healing, constitutes a major clinical challenge for health care, both in terms of individual suffering and economic burden.

Scar formation can occur at any site of dermal lesion resulting from burn-related trauma, or surgical wounds. Burn patients are particularly prone to severe disfigurement and functional impairment through often extensive scarring, and affected children are the most vulnerable patient group in regard to long-term suffering. HTS formation affects a variety of life quality determinants. Cosmetic disfigurement by scar appearance may strongly diminish a person's self-consciousness, as well as their ability to participate in social activities and professional life, and is often associated with serious physical impairments, especially in the context of scar-induced contractures. Moreover, scars frequently cause secondary illnesses requiring complex multidisciplinary treatment not only by plastic surgeons but also by dermatologists, physical therapists, and psychotherapists. In children, abnormal scars can profoundly limit the potential of physical as well as emotional and psychosocial development during childhood. Therefore, effective scar treatment approaches can critically determine a person's long-term ability to lead a self-determined life.

From the perspective of health care professionals, researchers, and health economists, and for the society as a whole, scar formation is perhaps still an underestimated yet growing burden for the public health. In the United States alone, about 500,000 patients are treated for burn injuries each year, resulting in expenses of about $7.5 billion. Conversely, treatment of scarring is a considerable economic factor, generating a $12 billion annual market with further potential to grow [1, 2, 6].

It is a long-standing clinical observation that the proneness to HTS formation and keloids is considerably influenced by individual genetic traits as well as ethnic risk profiles [6]. Studies showed that about 16% of patients with Hispanic or African ancestry are affected from keloidal scarring, as patients with darker skin color are approximately 15 times more likely to be affected than light-skinned individuals. As the individual recurrence risk of keloids also strongly depends on constitutional determinants, progress in research toward their identification and, ultimately, targeted modulation can immediately affect therapeutic strategies of scar formation in the future. Consequently, scarring is a promising as well as challenging field of translational research into personalized medicine in the field of plastic and reconstructive surgery. Beyond that, the search for novel pharmacological treatments addressing molecular targets in the pathways of wound healing and fibrosis has the potential to improve the lives of numerous patients, and also to generate new products for health care of major economic value.

52.9 Conclusion

Wound healing and repair following injury is a complex and poorly understood process that leads to cutaneous scar formation, which constitutes a significant health care burden. Despite spending billions of dollars every year on scar management, traditional scar treatment modalities have not proved to be effective. Treatment modalities such as corticosteroid injections and radiation can be largely uncomfortable for the patients. Surgical revisions, which are targeted at reducing the wide base of the scar, are associated with high recurrence rates in the absence of other therapeutic strategies. Identification of key signaling pathways that are dysregulated during abnormal wound healing has led to the emergence of a range of new pharmacological interventions that target growth factors, cytokines, and collagen biosynthesis, and have showed promising results initially but have not led to successful outcomes in later clinical trials.

The clarification of the role of mechanotransduction in fibrosis has opened up a new avenue for scar therapy research. Offloading of mechanical forces of surgical incisions during healing has been shown to be effective in reducing scar formation, which further underscores the importance of mechanical signaling in scar development. Specifically, inhibition of focal adhesion kinase, a key regulator of mechanotransduction has been shown to be effective in attenuating scars and accelerating wound healing. Small molecule inhibition of FAK blocks the activation of inflammatory signaling pathways, thus uncoupling mechanical force from pathologic scar formation. This strategy has been employed to reduce scar formation in burn wounds as well as excisional wounds in mice. Taken together, recent findings indicate that molecular strategies targeting mechanotransduction pathways in general and specifically FAK pathway can effectively reduce fibrosis and show promise as an effective and versatile strategy for scar management.

Take-Home Messages

- The underlying pathophysiology of cutaneous hypertrophic scar formation following injury is incompletely understood; however, improved understanding of the molecular mechanisms by which fibrotic scars develop has paved the way for devising new approaches in scar therapies.
- Traditional scar management modalities include surgical revision, corticosteroid injections, and radiation treatment methods. These conventional therapies are often associated with practical issues and higher recurrence rates.
- Recent scientific evidence suggests that mechanical stress plays a crucial role in promoting pro-fibrotic cellular events via pro-inflammatory pathways leading to exuberant cutaneous scar formation and fibrosis.
- New medical devices that can modulate local biomechanics has gained a rapidly growing market for scar reduction of surgical wounds.
- Pharmacological inhibitors of the mechanotransduction pathways are promising evidence-based new scar therapies that block inflammation and pathologic scar formation.

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Emerging Technologies in Scar Management: Remodeling of Post-surgical Linear Scar Using Microplasma Radiofrequency

Wei Liu

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53.1 Introduction

A strategy of remodeling of an existed scar is by changing its tissue architecture that can eventually lead to a grossly non-visible or minimally visible scar. Since some years, mechanical or energetic manipulation of scarred skin has received considerable attention in attempts to improve scar quality. Next to techniques as dermabrasia, CO_2 laser, or microneedling, microplasma technology might represent a new technique in this field [1].

53.1.1 Fractional Microplasma Radiofrequency Technology

There are four formats of matter: solid, liquid, gas, and plasma. With energy, solid can be converted into liquid and liquid into gas. Similarly, gas can also be transformed into plasma with energy input. The fractional microplasma radiofrequency technology (FMRT) employs the energy of radiofrequency to act on nitrogen of the air in the narrow space between the therapy tip and the treated skin, and thus to form a grid of high-energy focal-led plasma sparks, which result in ionization of a portion of the atoms. With this physical effect, the FMRT can cause mild ablation of the epidermis with the formation of micro-channels in a fractional way (Fig. 53.1).

The device we used in the past 13 years for patient treatment was a product from Alma Lasers (Caesarea, Israel) called Pixel^{RF} with both roller and stationary tips. Figure 53.1 demonstrates its working mechanism of the device. In general, this device creates the depth of ablative point in 100–150 μm, and the size of ablative point 80–120 μm in diameter, and heating effect with a unipolar can reach the depth of 1000 μm, depending on the radiofrequency power and pulse duration. However, the ablative depth could reach to the upper part of the dermis with increasing energy, and thus to remodel a superficial layer of dermis. By this way, the FMRT can remodel tissue structure via ablative microchannel of epidermis and controlled thermal modification of the underlying dermis, with new collagen synthesis and collagen remodeling [2, 3]. With this type of working mechanism, the created micropore wound can be healed in 7 days (Fig. 53.2) and thus repeated treatments can be applied.

Although this particular device was used because of its availability to the author at that time, the effect of wound/scar remodeling is also likely to be achieved by other devices such as CO_2 fractional laser or others made by Lumenis, Cynosure, Alma, or Syneron, depending on physicians' clinical expertise (Fig. 53.3).

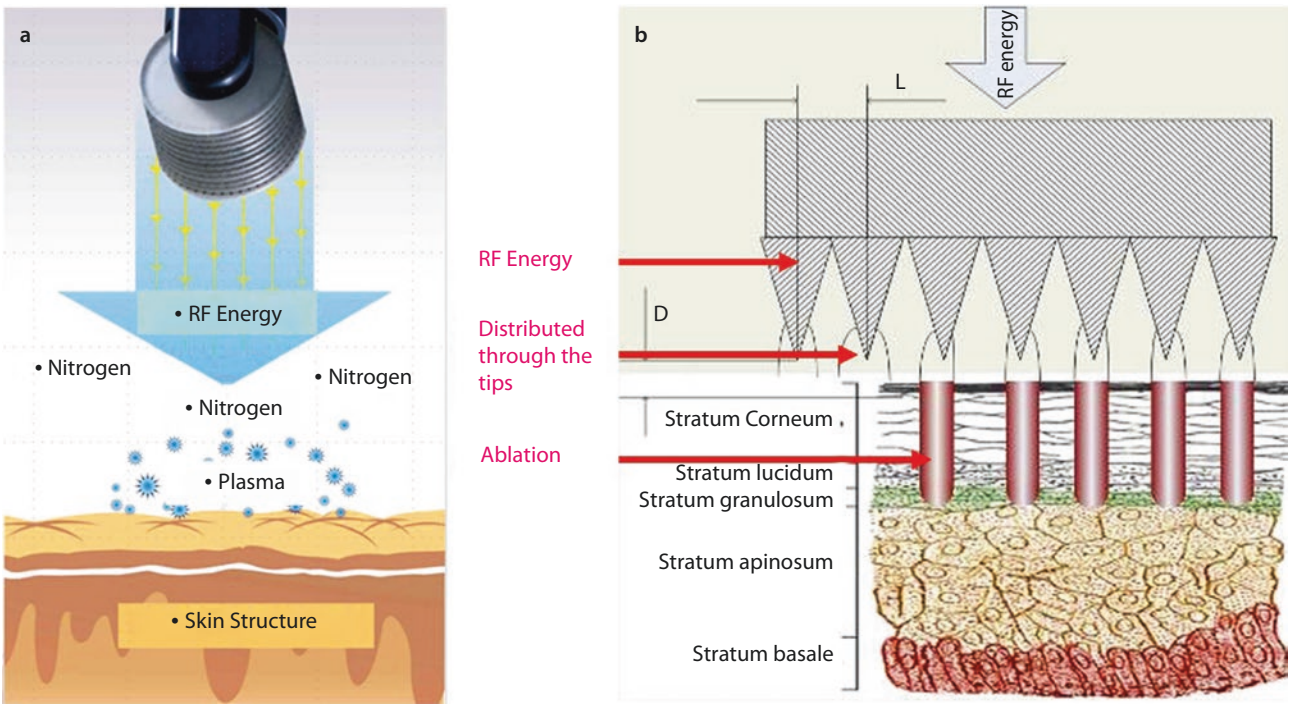

Fig. 53.1 The schematic picture of FMRT working mechanism. **a** Radiofrequency energy acts on nitrogen to create plasma particles. **b** Plasma particles penetrate epidermis in a fractional way. (*Photo courtesy from Alma Lasers*. © All rights reserved)

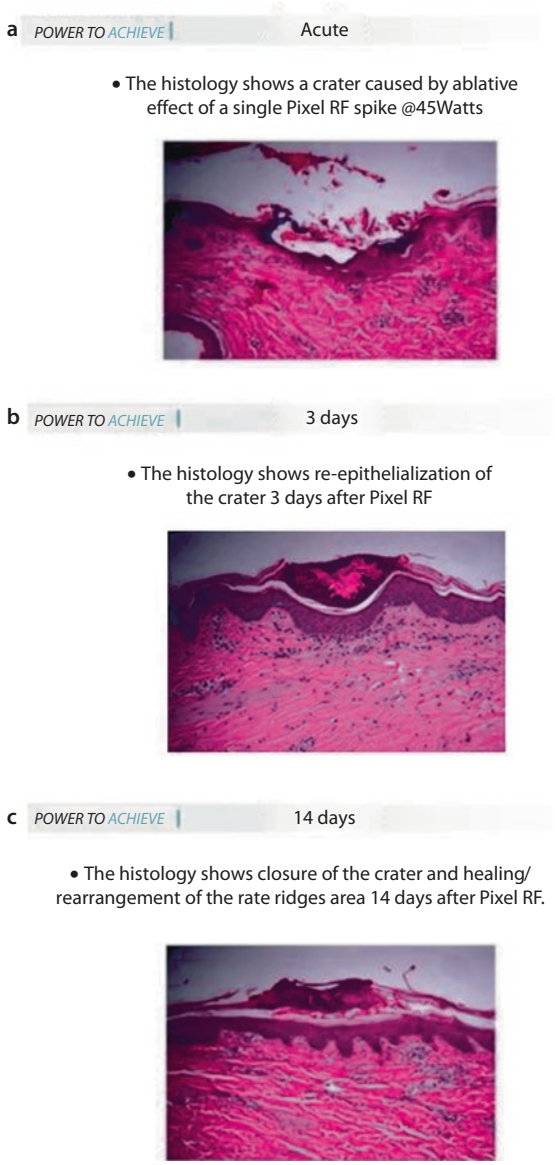

Fig. 53.2 Histological demonstration of microplasma working depth and healing process. **a** Acute wound immediately after microplasma. **b** Healing at day 3. **c** Healing at day 14. (*Photo courtesy from Alma Lasers*. © All rights reserved)

53.2 Procedures: Clinical Protocol for Microplasma-Based Tissue Remodeling (Fig. 53.3)

53.2.1 Pre-therapy Preparation

1. Patients with skin lesions at the treating area should be advised not to receive the treatment before the cure of these lesions, including infectious skin lesions caused by both virus and bacteria, dermatitis, psoriasis, eczema, and urticaria.
2. Patients should be advised for proper management of the micropore wound post-therapy and potential side effects with signed written informed consent.
3. Photography before the treatment. Be sure that it is taken before topical anesthesia and it is in the same conditions of environment such as light, focus, and positions.
4. Topical application of 5% lidocaine hydrochloric gel under plastic wrap for 60–90 minutes before the treatment followed by thorough cleaning and sterilization with 70% alcohol.
5. Non-treated skin should be protected with paper tape surrounding the treated skin if the tip is larger than the area to be treated.

53.2.2 Microplasma Treatment

1. Fractional microplasma radiofrequency treatment was performed with the device of Pixel RF (Alma Lasers, Caesarea, Israel).
2. A roller tip was used with the power setting at 60–90 watts, and 3–4 passes were usually made in different directions.

53.2.3 Post-therapy Wound Care

1. Patients are advised for comprehensive instructions of post-procedure care.
2. Sterile saline cleaning and erythromycin eye ointment were topically applied daily for 6 days to prevent infection.
3. Patients are advised not to be exposed to sunlight to avoid post-therapy pigmentation.
4. Patients are advised to protect the treating area by avoiding scratching or rubbing.

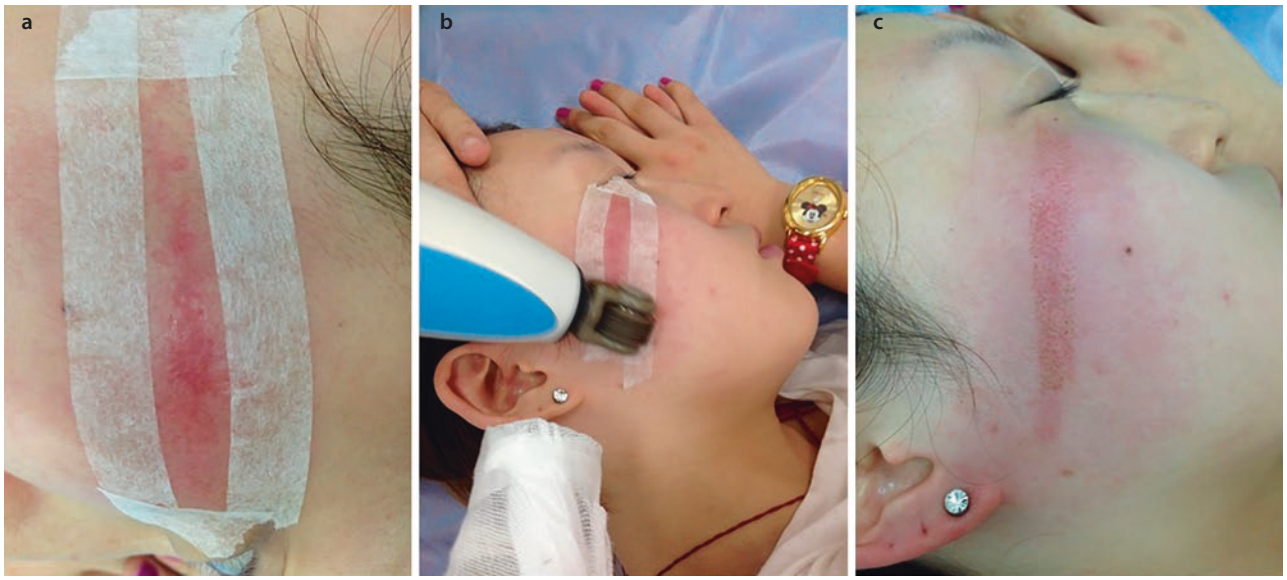

Fig. 53.3 Microplasma procedure. **a** Paper taping is applied to protect untreated skin and 2–3 mm skin surrounding the healed wound tissue is also included in the procedure. **b** A roller tip is applied to perform the procedure. **c** The gross view of the treated wound/skin tissue immediately after the procedure

5. Patients are advised to have the follow-up regularly.
6. In the case of early wound remodeling, anti-tension type or device should be applied before and after the treatment.

53.3 Application Areas for FMRT-Mediated Tissue Remodeling

53.3.1 Microplasma Therapy for Post-scar Revision Skin to Enhance Cosmetic Result

Brief descriptions of the procedures for treating a linear scar for cosmetic reasons are as follows:

1. In general, a patient will visit our clinics and seek a consultation through discussing what a patient is expected and what can be achieved from the procedures. Then the patient will make an appointment for a scar revision surgical procedure.
2. In the surgical procedure, the patient is given a local injection of 1–2% lidocaine for anesthesia. In most cases, a w-plasty procedure will be applied along with the surgical excision of a linear scar to prevent linear tension, which usually causes observable scarring after the scar revision. To reduce wound tension, wound edge flap should be freed before wound closure. In addition, suturing of wound tissue at various levels also helps reducing wound tension, including subcutaneous, dermal, and epidermal tissues. For patients who are prone to scarring, wound irrigation with triamcinolone acetonide (5 mg/mL) or 5-fluorouracil (2–4 mg/mL) or both combined should be applied before wound closure to prevent scar formation.
3. After the surgical procedure, tension-reduction tape (such as 3 M tape) should be applied to keep the wound in a tension-free state. Patients are advised to have the tape changed every 2–3 days and maintained for at least 6 months post-surgery. The stiches are removed at day 5 or 6 post-surgery for head and neck regions, and stich removal can be postponed for 1 or 2 days at other regions. In case of the scar-prone patients who were treated for hypertrophic scar or keloid, an injection of triamcinolone acetonide (5 mg/mL) or 5-fluorouracil (2–4 mg/mL) or both combined with lidocaine into the healed wound can be administered at 1 or 2 months post-suturing.
4. In most cases, Pixel RF microplasma is applied to the healed incisional wound at 8 weeks post-surgery. Generally, the therapy should include 2–3 mm normal skin on both sides of the linear wound. The procedure is usually applied with a roller tip at 60–70 watts with 3–4 passes (Fig. 53.2).
5. Pixel RF microplasma therapy should be repeated for 3–5 times with 8–12 weeks' interval in general and patients should be closely followed up every 4–8 weeks until a linear wound mark and stich marks are completely removed. By this procedure, the linear scar resulting from scar revision procedure can be largely removed and the fine linear scar becomes grossly less visible or non-visible.

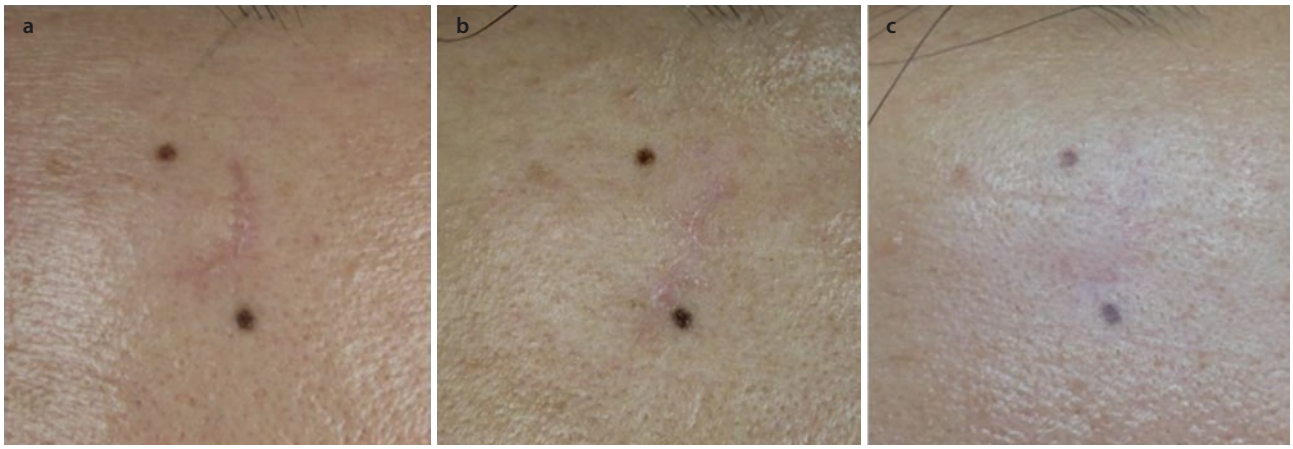

Fig. 53.4 Case presentation of microplasma remodeling of a linear scar resulting from surgical scar revision procedure. **a** Before surgery. **b** The gross view of a linear scar at 8 weeks after the first microplasma remodeling on a post-scar revision scar. **c** After 3 microplasma remodeling, the gross view reveals complete scar remodeling and no visible linear scar at the time points of 8 weeks after the third remodeling

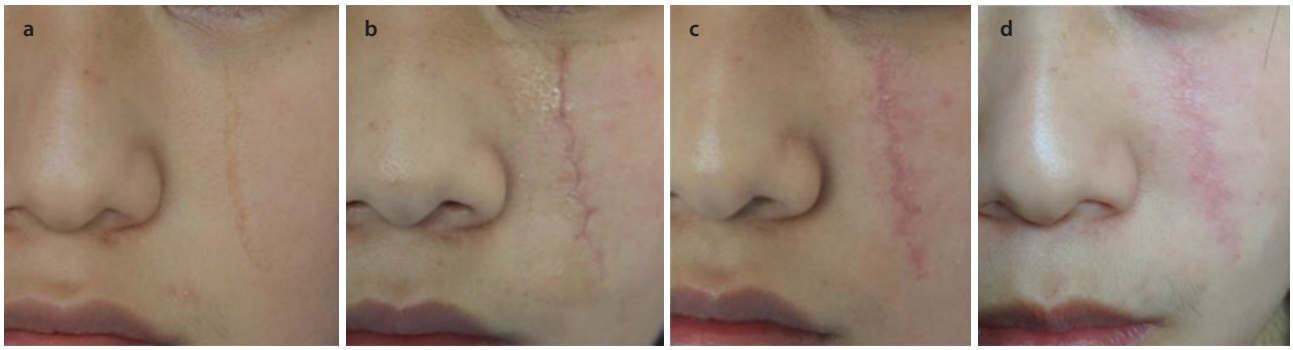

Fig. 53.5 Case presentation of microplasma remodeling of a linear scar resulting from surgical scar revision procedure. **a** Before surgery. **b** The gross view of a linear scar at 8 weeks post-surgical scar revision. **c** Gross view of a remodeled linear scar at 8 weeks after the first microplasma remodeling. **d** After 3 microplasma remodeling, the gross view reveals complete scar remodeling and no visible linear scar at the time points of 8 weeks after the third remodeling. However, erythema resulting from tissue remodeling remains visible

The following are the case presentations.

Case 1

A 32-year–old female patient visited our clinic to request for forehead scar treatment solely for cosmetic reason. Physical examination showed a red-colored linear scar with a length of 2 cm and a width of 0.2 cm. In addition, the linear scar was also a bit elevated and with a few stich marks scar on both sides (Fig. 53.4a). The patient received a scar revision surgery along with w-plasty procedure. After the surgery, the patient wore 3 M anti-tension paper tape vertical to the incision line. Later, silicone gel was also applied topically on the incisional line, and then 3 M paper was used. At 8 weeks post-surgery, she received microplasma therapy with an energy of 65 watts and 4–6 passes of rolling therapy. At 8 weeks after the first treatment, the follow-up photo showed significant improvement of the gross view of her forehead scar, although a fine linear scar remains when observed closely (Fig. 53.4b). Then, the patient received another two treatments with 8 weeks' interval between them. At 8 weeks after the third therapy, the follow-up photo shows no visible linear scar on her head (Fig. 53.4c), and the patient was completely satisfied as the result match her original request of removing her forehead scar completely.

Case 2

A 27-year-old female patient visited our clinic for cosmetic treatment of a linear scar on her left face. Physical examination showed a mature flatten linear scar with a length of 6 cm and a width of 0.5 cm as shown in Fig. 53.5a. The patient received a surgery of scar revision plus w-plasty. The follow-up photo at 8 weeks post-surgery showed an apparent linear scar resulting from scar surgical revision, with which the patient was significantly unsatisfied despite the fact that an original wide and flatten scar has been transformed into a fine

linear scar (Fig. 53.5b). At this time point, microplasma tissue remodeling procedure was applied to the patient with an energy of 70 watts and six passes using a roller tip. Interestingly, at 8 weeks after the first therapy, the linear scar has already been significantly remodeled with the previous linear scar obscured; however, the linear scar remained obviously visible (Fig. 53.5c). Thereafter, the patient was given another two microplasma therapies with 8 weeks' interval between them. At 8 weeks after the third therapy, the follow-up photo showed that a linear scar resulting from scar revision surgery was almost completely remodeled with no apparently visible linear scar (Fig. 53.5d). Due to the thorough tissue remodeling process, in which the tissue structure of a healed linear wound has been significantly changed along with a regenerative skin repair, angiogenesis apparently occurred with manifestation of skin redness (Fig. 53.5d), which will disappear in 3–6 months after the discontinuation of the treatment. The patient was very satisfied with the end result, in which microplasma tissue remodeling played a role significantly more important than the surgical procedure.

53.3.2 Microplasma for Early Wound Intervention to Prevent Scar Formation

With the success of remodeling healed linear wound tissue, we wondered if such a concept could be applied to tissue remodeling of an early incisional wound to prevent scar formation. The scenario is that linear wounds of non-elected surgical procedures such as trauma and wounding are usually difficult to prepare an optimal condition for their healing, and thus these linear wounds are more likely to form an obvious linear scar than the wounds created by elected surgical procedure of scar revision.

Due to the non-optimal healing condition, the wound tissue remodeling procedure should be applied at an early-stage wound. In addition, improvement of wound healing conditions by other wound manipulation methods should also be applied comprehensively including anti-tension, silicone product, drug local injection, or even re-suturing of an already sutured wound. Following are the general principles:

1. When a patient with an acute linear skin wound visits the clinic, proper wound cleaning should be the first consideration. In case of severe wounds or appearance of early signs of wound infection, antibiotics should be applied either locally or systemically or both.
2. Anti-tension tape or device should be applied before and after stich removal, such as 3 M tape, Zipline™ or Neodyne™ or other tension reduction device in order to maximally reduce the tension-induced scarring during wound healing process.
3. Silicone product should be applied as early as possible, such as Dermatix™, Kelo-cote™ or other products. This should be applied along with taping or tension-reduction device and wound tension-free procedure should not be compromised by other procedures.
4. Proper surgical procedures for wound closing is important as a thick scar will be too difficult to be remodeled for achieving a desirable effect. When decided to perform, proper debridement, wound edge preparation as well as fine suturing should all be included.
5. The timing for microplasma procedure can be decided on the basis of the wound condition. If an injured wound is properly managed with a condition similar to that of elected surgical procedure, the remodeling procedure can be performed at time point about 8 weeks post-wound closure to give a wound sufficient time to heal as a very fine linear immature scar, which can be completely remodeled with microplasma procedure. If a wound is improperly closed with a thick linear wound mark and obvious other stich marks, then the procedure should be applied as early as 1–4 weeks post-wound closure.
6. The energy of microplasma remodeling can be adjusted according to the wound condition. For example, a wound of a child or a wound with fine closure technique, then the wound can be treated with a relative low energy; whereas a wound is closed unprofessionally or in a poor condition, a relatively high energy should be applied and the treatment should be repeated until a desirable result can be achieved.
7. The comprehensive scar-reduction management should be continually applied after the remodeling and maintained for at least for 6 months post-wound closure.

The following are the case presentations.

■■ Case 3

A 52-year-old male (Fig. 53.6)was wounded on his left-side face 3 days before, and he came to our clinic for assistance of the wound management in order to prevent severe scarring. Physical examination showed that there was a linear wound on his left-side face with a length of 3 cm. The wound had been closed unprofessionally by single layer suturing with tight knots that would be bound to form a thick linear scar with obvious stich marks after the healing of the wound (Fig. 53.6a). To better prepare the wound closure, the stiches were removed and the wound was re-opened. After thorough

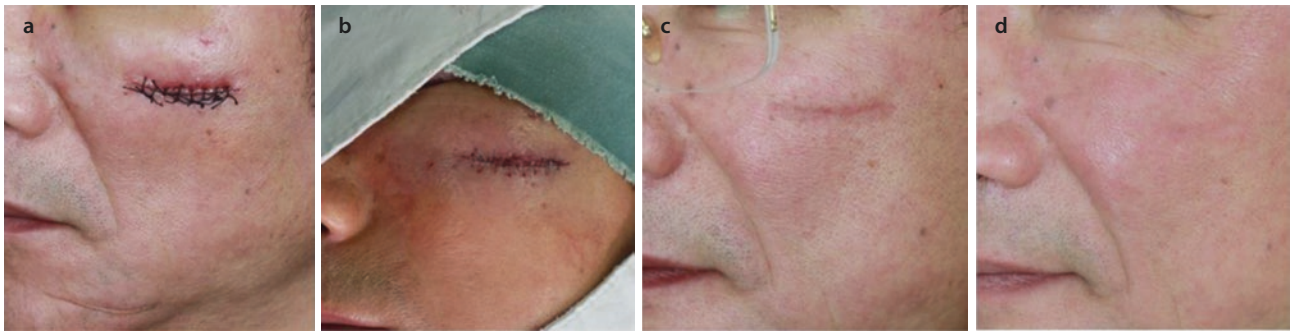

Fig. 53.6 Case presentation of microplasma intervention of an early stage wound to prevent scar formation. **a** The patient has facial wound 3 days ago with unprofessional wound closure technique. **b** The stiches were removed and the wound was reopened. After wound debridement and proper position of wound tissues, the wound was properly closed with fine suturing technique, which paved the way for further tissue remodeling. **c** Gross view shows remodeling of a linear scar at 8 weeks after the first microplasma remodeling. **d** Gross view shows that post-wound linear scar is almost completely remodeled with no visible scar

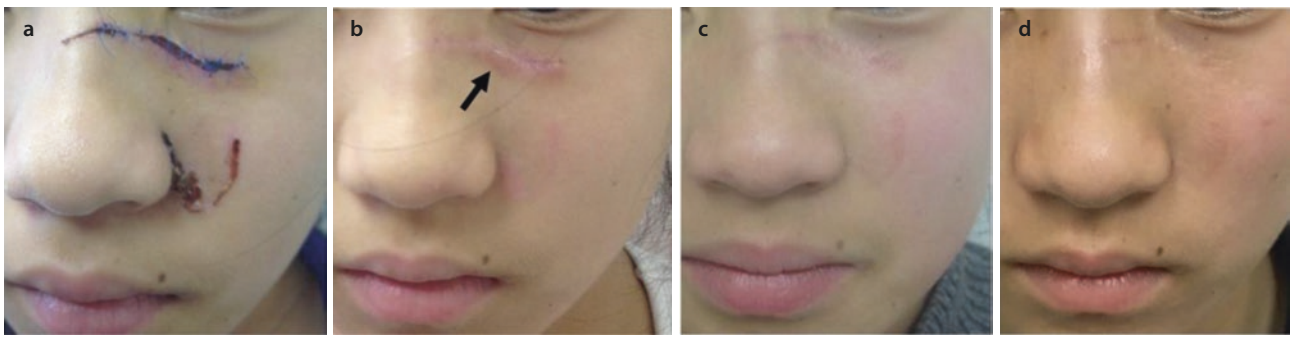

Fig. 53.7 Case presentation of microplasma intervention of an early stage wound to prevent scar formation. **a** The patient has two wounds on her face for 5 days. **b** Early sign of scar formation was observed on her upper face scar at day 12 post-wounding. The arrow shows elevated tissue growth that would develop into hypertrophic scar, and thus a steroid injection was given. **c** Significant improvement of the linear scar was observed at 8 weeks after the first microplasma remodeling. **d** Gross view shows almost complete remodeling of the linear scar except for minor hyperpigmentation caused by microplasma treatment

wound debridement, wound dermal and epidermal layers were properly positioned and closed with fine suturing (Fig. 53.6b). The stiches were removed at day 5 post-surgery and 3 M tape was applied. At 4 weeks post-surgery (31 days after wounding), the patient received his first microplasma remodeling. Eight weeks later (87 days after wounding), the follow-up photo showed significant improved gross view of the healed linear wound (Fig. 53.6c). Then the patient was given the second microplasma remodeling. Eight weeks later (143 day after wounding), the patient was followed up with a photo demonstrating that linear wound mark was almost all removed via tissue remodeling (Fig. 53.6d). The patient was very satisfied with the wound remodeling result.

Case 4

A 11-year-old female was injured on her left-side face and part of nose 5 days before she visited our clinic. She had concern of possible scar formation on her face after wound healing. Physical examination showed that there was a linear scar on her left-side face starting from suborbital region and extending to the left part of the upper region of the nose. In addition, she also had a curved linear wound at the left side of her left ala nasi as shown in Fig. 53.7a. The patient was asked to remove her stiches and to apply 3 M tape for anti-tension purpose. The patient was given COX-2 inhibitor (oral medicine) for 2 weeks to reduce wound inflammatory process. At day 12 post-wounding, there was an early sign of scar formation as raised tissue was observed on the upper wound of her face (arrow, Fig. 53.7b). The patient was thus given an injection of low concentration steroid to inhibit potential scar formation. Four weeks later, several more injections were given with 4 weeks' interval between them. During the time period, taping and silicone gel were consistently applied. At 3.5 months post-wounding, the patient was given the first microplasma remodeling. Eight weeks after the first therapy (5.5 months post-wounding), the scarring was significantly remodeled with obvious improvement of the gross view as shown in Fig. 53.7c. Afterward,

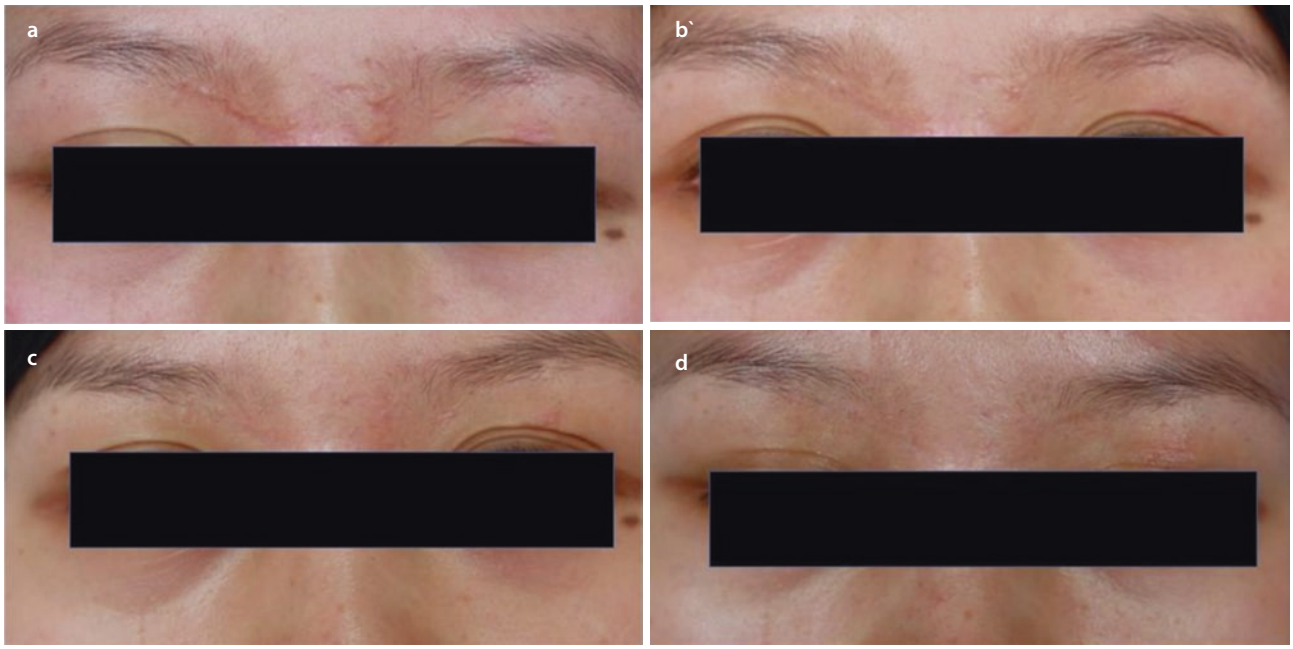

Fig. 53.8 Case presentation of microplasma remodeling of an existed linear scar. **a** Gross view of an existed linear scar at the region between forehead and nose. **b**–**d** Gross view of remodeling the scar at 8 weeks, respectively, after the first, third, and fourth microplasma remodeling. The end result shows almost no visible linear scar in the region

the patient was given three more procedures of microplasma remodeling. The final follow-up photo demonstrated that original scar was barely visible except for minor pigmentation. The patient was extremely satisfied with the results.

53.3.3 Microplasma Remodeling for an Existing Linear Scar

As described previously, scar revision surgery along with microplasma tissue remodeling is a preferred procedure to deal with the significant linear scars in majority cases. However, direct remodeling with microplasma is also a choice for linear scars under certain conditions. These include (1) a superficial linear scar; (2) an irregular shaped linear scar that is difficult to revise with surgical procedure; (3) a linear scar that formed in not too long time; and (4) the scar contains less dense collagen. These linear scars are more likely to be remodeled than other types of linear scars.

The following is a case presentation:

Case 5

A 35-year–old female patient had an irregular linear scar caused by trauma in less than 1 year on the region between forehead and nose (Fig. 53.8a). The linear scar was relatively irregular and superficial and was a bit raised above the skin. Microplasma remodeling procedure was applied using a roller tip with 70 watts for 4–6 passes. Figure 53.8 shows the tissue remodeling results after the first (Fig. 53.8b), third (Fig. 53.8c), and fourth (Fig. 53.8d) microplasma treatments, which demonstrated gradual improvement of the gross view of the linear scar, and the scar was barely detectable at the end of the treatment. The patient was very happy with the end result.

Conflict of Interest No conflict of interest.

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Vacuum Massage in the Treatment of Scars

Peter Moortgat, Jill Meirte, Ulrike Van Daele, Mieke Anthonissen, Tine Vanhullebusch, and Koen Maertens

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Background

Vacuum massage is also known as depressomassage, vacuotherapy, or Endermologie®. It is a non-invasive mechanical massage technique performed with a mechanical device that lifts the skin by means of suction, creates a skin fold, and mobilizes that skin fold [1, 2] as displayed in Figs. 54.1 and 54.2.

Vacuum massage originates from cupping therapy, a traditional Chinese medicine therapy dating back 2000 years or more. A local suction on the skin is created using heat or mechanical forces in order to create vasodilatation. In the late 1970s, Louis-Paul Guitay suffered from severe skin burns after a car accident. During his rehabilitation, he had to endure hours of manual massages every day. This multi-month process was normal practice for burn victims with extensive scar tissue in the late 1970s. Massage sessions typically lasted 3– 4 hours a day and consisted of rigorous routines. The therapist rolled skin and tissue back and forth to regain elasticity. As days grew into weeks, Guitay became dissatisfied with these incessant treatments. They were time-consuming, labor intensive, and he noticed his results varied drastically based on the skills of each individual therapist. Endermologie®, taken from the French term meaning "through the dermis", was Louis-Paul Guitay's way of standardizing massage therapy to maximize the effect of each treatment. He developed a mechanical device to copy the manual massage techniques by means of negative pressure. This method allowed him to perform the massage in a more consistent way and was less time consuming. From then onward, Endermologie® or vacuum massage has been frequently used to treat traumatic or burn scars.

Although vacuum massage was invented to treat burns and scars, very little literature is available on the effects of this intervention. Soon after its development, the device was used extensively in Europe to treat trauma and burn scars [2]. In the course of its use, care providers soon noticed its ability to improve the appearance of cellulite, and consequently most studies mainly focused on lipodystrophy to investigate its working mechanism. The number of studies concerning cellulite is three times higher than those of burns or scars.

The aim of this chapter is to present an overview of the available literature with the physical and physiological effects of vacuum massage. This was done in order to find the underlying working mechanisms of Endermologie® that could benefit the healing of burns and scars. Analyzing the physical and physiological effects of this treatment can increase insights in the influence on the scarring process and may clarify the outcome.

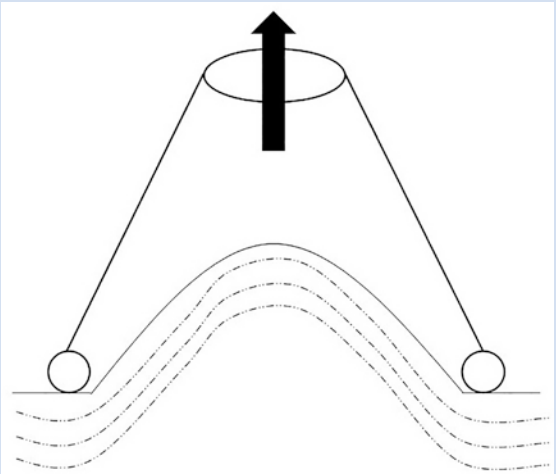

Fig. 54.1 Vacuum massage creates a skin fold and mobilizes that skin fold

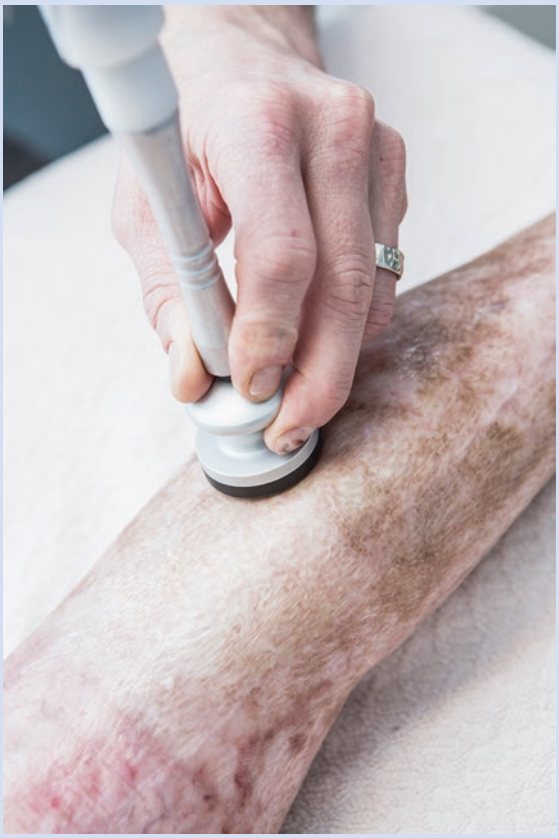

Fig. 54.2 Vacuum massage on scars

54.1 Working Mechanism of Vacuum Massage in Relation to Pathological Scarring

In recent years, there has been an increasing interest in the mechanobiology of scars. The influence of mechanical forces on skin has been examined since 1861 when Langer first reported the existence of lines of tension in cadaver skin [3]. Internal tension in the dermis leads to cell–extracellular matrix (ECM) and cell–cell interactions transferring external mechanical forces into biochemical signals inside the cell [4]. Khan et al. reclaimed the term "mechanotherapy" and presented the current scientific knowledge underpinning how mechanical load may be used therapeutically to stimulate tissue repair and remodeling. It has long been thought that the effectiveness and efficiency of physical therapy would improve if our understanding of the cell biology/biochemistry that participates in mechanics could be improved. Traditional physical therapy focuses primarily on rehabilitation, but recent developments in mechanobiology that illuminated the effects of physical forces on cells and tissues have led to the realization that the old therapy model should be updated. Recent studies showed how mechanotherapies target particular cells, molecules, and tissues. The role of mechanical force in various therapies, including micro-deforming soft tissue techniques, shockwave, vacuum massage, tissue expansion, skin stretching, and tension reduction (tissue targeting) therapies is the subject of numerous ongoing clinical trials [5–7].

All adherent cells including endothelial cells, fibroblasts, and myofibroblasts sense tension originate from the environment. Tension is transmitted via cell–ECM contacts, leading to reorganization of the cytoskeleton and the elicitation of specific signals that modulate gene expression. In skin, alterations of mechanical forces are continuously recognized by cells, and their functions are adapted according to the biological requirements. If mechanical tension is removed, those tissues undergo atrophy, indicating the important role of mechanical signals for maintaining proper functioning of the organism. Obviously, fibroblasts and myofibroblasts are cells implicated in scarring, which is strongly influenced by mechanical tension.

The precise mechanisms by which different cell types transmit mechanical signals are not fully understood. They might involve stretch-activated ion channels, direct interactions between structural and signaling components, or activation of small GTPases. As outlined above, many cooperative interactions exist between integrins and growth factor signaling. In particular, fibroblast to myofibroblast conversion and alpha-smooth muscle actin (α-SMA) expression crucially depend on a combination of mechanical tension and TGF-β. Thus in scarring, generation of tension can induce myofibroblast formation, causing a self-perpetuating loop. A similar autocrine loop is discussed for the induction of collagen synthesis in fibroblasts by mechanical tension. In this case, TGF-β is induced by tension, which in turn activates collagen synthesis via the classic pathways. In addition, fibronectin is induced by the application of cyclic strain to fibroblasts. In parallel, many proteases are downregulated, whereas protease inhibitors are upregulated. As a result of these events, modulation of mechanical tension results in alterations of fibroblast and myofibroblast activity. . Tension directly modifies gene transcription, induces signaling from integrins affecting small GTPases, or induces/inhibits growth factor signaling, which then indirectly affects ECM protein synthesis by fibroblasts/myofibroblasts [8]. By a combination of these mechanisms, mechanical tension induces an activated, contractile fibroblast/myofibroblast phenotype characterized by high levels of synthesis of ECM proteins, low protease activity, and high production of fibrogenic cytokines. Translated into a clinical situation, this means a retractile scar with adhesions between the dermal tissue and the underlying viscera.

The mechanotransduction theories provide possible evidence for several physical non-invasive treatment options. It was suggested that many of the physical scar management methods, including compression therapy, silicone therapy, adhesive tape, and occlusive dressing therapy, are related to mechanotransduction mechanisms. Mechanical compression seems to induce apoptosis and to regulate cytokine release, thus reducing hypertrophic scarring. The effects of mechanical tension on TGF-beta1 and collagen synthesis leads to the hypothesis that brief, moderate stretch of scar tissue seems to downregulate hypertrophy and retraction of scars and could be the best option for splinting, positioning, and postural stretching [9].

54.2 The Effects of Vacuum Massage on Scars

54.2.1 General Effects [1, 10–12]

General effects are defined as the effects inherent to the intervention itself or to the individual who performs the treatment. A number of studies mentioned the measured effects were dependent on the number of treatments. The more the treatment, the higher the effect. After this ascertainment, Adcock et al. also discovered that the principal force applied to the tissue during the therapy depended on the particular type of maneuver performed, with the suction and the roller tension being of minor importance. Moreover, they observed a major decrease of tension in thicker tissue.

In four studies performed, the results showed a setback after a follow-up period without treatment, but one study demonstrated the opposite. All these results are shown in Table 54.1.

Table 54.1 Basic information available in the literature describing effects of vacuum massage on several skin layers

Literature	Etiology	Study design	Targeted skin layer	No. of patients	Assessment	LESS score
Moortgat et al. [16]	Burn scars	CCT	Epidermis/ dermis	48	POSAS, touch pressure threshold, DermaLab elasticity	18
Anthonissen et al. [15]	Burn scars	CCT	Epidermis/ dermis	47	POSAS, Tristimulus colorimetry, trans-epidermal water loss	18
Adcock et al. [1]	Pig skin	RCT	Dermis/ hypodermis	12	Histology	17
Adcock et al. [12]	Pig skin	RCT	Hypodermis	4	Intra-dermal tonometry	16
Revuz et al. [11]	Aging skin	CCT	Dermis	24	Subjective assessment of skin laxity and skin loosening, stereophogrammetry, cutometer	16
Moseley et al. [18]	Scar like	RCT	Dermis/ hypodermis	10	Likert scale, tonometry	16
Lucassen et al. [19]	Healthy skin	Pre/post	Dermis/ hypodermis	19	High frequency ultrasound	13
Watson et al. [2]	Healthy skin	RCT	Epidermis/ dermis	5	Laser-Doppler imaging, lymphoscintigraphy, venous flowmetry	13
Innocenzi et al. [14]	Lipodystrophy	CCT	Epidermis/ dermis	12	Descriptive histology	11
Innocenzi et al. [20]	Lipodystrophy	CCT	Epidermis/ dermis	15	Quantitative histology	10
Ortonne et al. [21]	Lipodystrophy	RCT	Dermis/ hypodermis	30	High frequency ultrasound, fringe projection, skin fold thickness	13
Bourgeois et al. [13]	Scars	RCT	Epidermis/ dermis	20	Subjective assessment of pain, itch, tightness, erythema and skin smoothening, profilometry	13
Monteux et al. [22]	Lipodystrophy	Pre/post	Dermis/ hypodermis	9	Skin fold thickness	11
Marques et al. [10]	Healthy skin	Pre/post	Hypodermis	12	Gene profiling, micro-array	11
Scuderi et al. [23]	Healthy skin	RCT	Epidermis/ dermis	10	Subjective assessment of skin smoothening and skin tone	10
Majani et al. [24]	Scars	Pre/post	Epidermis/ dermis	26	Subjective assessment of skin smoothness, pain, tenderness, oedema and aesthetic improvement, histology	10
Marquez-Rebollo et al. [25]	Scar like	Pre/post	Epidermis/ dermis	70	Number of indurations	10
Gavroy et al. [26]	Scars	CCT	Details not available	606	Test de glissement	7
Lattarulo et al. [27]	Healthy skin	Pre/post	Epidermis/ dermis	34	Laser-Doppler imaging, $tcpO_2$	7
Worret et al. [28]	Scar like	Pre/post	Dermis	10	Subjective assessment of pain, color and elasticity, quality of life, cutometer	7
Delprat et al. [29]	Scars	Pre/post	Details not available	132	Test de glissement	5

RCT randomized controlled trial, *CCT* controlled clinical trial, *$tcpO_2$* transcutaneous oxygen pressure

54.2.2 Physical Effects [13–16]

An improvement of the tissue hardness and the elasticity of the skin were the two most observed effects. However, most of the studies used subjective methods to quantify these effects. Other reported physical effects were decreased skin fold thickness, decreased face volume, improved skin laxity, increased epidermal thickness, and improved skin roughness. Recent studies have shown that elasticity and redness, measured with subjective and objective assessment tools, were significantly improved after 1 year when the scar was treated for 6 months. The results of one study also revealed that the vacuum massage had minimal value as additive treatment to pressure garments and silicone when it concerned redness. For elasticity, on the other hand, vacuum massage + pressure therapy and silicone seemed to perform better than pressure therapy and silicone alone. The results are set out in Table 54.2.

54.2.3 Physiological Effects [2, 10, 13, 15, 17]

An improvement in blood perfusion was noticed in four studies. Fibroblast proliferation was enhanced together with an increase in collagen content. Two studies mentioned an improved venous and lymphatic flow together with increased transcutaneous oxygen pressure. Smoothening of the dermo-hypodermal junction and a decreased dermal interstitial space were also observed. One study mentioned altered gene expression profiles in adipose tissue. In another study, a significant decrease of trans-epidermal water loss (TEWL) was found and indicated a recovery of the skin barrier. After correction for baseline and age of scar, there was evidence for lower mean TEWL values in the vacuum massage group, significant after 3 months ($p = 0.006$). Humbert et al. investigated the histological effects of vacuum massage and discovered an increased migratory ability of fibroblasts together with increased elastin and hyaluronic acid presence which indicated induced remodeling capacity. The upregulation of MMP-9 suggests degradation of the existing damaged ECM to induce remodeling. These findings were somehow confirmed by the study of Meirte et al., where an increased dermal thickness together with a decreased dermal density were already noticed in the first 2 hours after a vacuum massage treatment. These results are shown in Table 54.3.

54.2.4 Mechanical Effects

The suction forces generated by vacuum massage could elicit an array of mechanical forces within the tissues, associated with a relaxation of those mechanical forces. Once stress forces on a wound were relieved, apoptosis of myofibroblasts would occur. This finding implies that vacuum massage may release the mechanical stress associated with scar retraction, and thus induce apoptosis. This can be another plausible theory for its mechanism of action to improve the outcome of (burn) scars.

54.3 Conclusion

Although vacuum massage initially had been developed for the treatment of burn scars, literature reveals little evidence for the efficacy of this treatment. Very few studies investigated the effects of vacuum massage on human models with scars. The heterogeneous population and the wide diversity of study designs make it very hard to translate the previously mentioned results toward the burns and scars population in humans. Although the present study contributes additional evidence for the working mechanism of vacuum massage as an anti-scarring agent, the results should be confirmed by studies on human models. Variations in duration, amplitude, or frequency of the treatment have a substantial influence on collagen restructuring and reorientation, thus implying possible beneficial influences on the healing potential by mechanotransduction pathways. Vacuum massage may release the mechanical tension associated with scar retraction, and thus induce apoptosis of myofibroblasts. Suggestions for future research include upscaling the study design, investigating molecular pathways and dose dependency, comparing effects in different stages of repair, including evolutional parameters and the use of more objective assessment tools.

Table 54.2 Overview of the physical effects of vacuum massage on epidermis/dermis/hypodermis

Paper	Tissue hardness subjective	Tissue hardness objective	Elasticity subjective	Elasticity objective	Skin fold thickness	Scar adhesions	Face volume	Skin laxity	Epidermal thickness	Skin roughness	Color subjective	Color objective
Delprat et al. [29]						Decreased						
Gavroy et al. [26]						Decreased						
Adcock et al. [12]		Decreased										
Revuz et al. [11]				No changes			Decreased	Decreased				
Innocenzi et al. [14]									Increased			
Innocenzi et al. [20]									Increased			
Ortonne et al [21].					Decreased					Decreased		
Worret et al. [28]	Decreased		Increased	Increased							Decreased	
Moseley et al. [18]	Decreased	Decreased	Increased									
Bourgeois et al. [13]	Decreased									Decreased	Decreased	
Monteux et al. [22]					Decreased							
Scuderi et al [23].	Decreased							Decreased				
Marquez-Rebollo et al. [25]	Decreased		Increased									
Majani et al. [24]	Decreased		Increased									
Moortgat et al. [16]			Increased	Increased								
Anthonissen et al. [15]												Decreased

Table 54.3 Overview of the physiological effects of vacuum massage on epidermis/dermis/hypodermis

Paper	Blood perfusion	Dermo-hypodermal junction	Collagen content	Collagen orientation	TEWL	Lymphatic flow	$tcpO_2$	# fibroblasts	Fibroblast phenotype	Dermal interstitial space	Superficial vascular surface	Pain	Itch	Altered gene profile
Lucassen et al. [19]		Smoothened												
Adcock et al. [1]			Increased	Dense longitudinal bands										
Watson et al. [2]	Increased					Increased								
Lattarulo et al. [27]	Increased						Increased							
Revuz et al. [11]				Dense longitudinal bands										
Innocenzi et al. [14]								Increased	Secreting					
Innocenzi et al. [20]								Increased	Secreting	Decreased	Increased			
Ortonne et al. [21]		Smoothened												
Worret et al. [28]												Decreased		
Bourgeois et al. [13]											Increased	Decreased	Decreased	
Marques et al. [10]														Yes
Majani et al. [24]										Decreased				
Moortgat et al. [16]												Decreased	Decreased	
Anthonissen et al. [15]					Decreased									

$tcpO_2$ transcutaneous oxygen pressure, *TEWL* trans-epidermal water loss

Take-Home Messages

- Vacuum massage is a way of standardizing massage techniques to optimize the treatment.
- Mechanotransduction is the presumed working mechanism behind vacuum massage.
- Improved tissue hardness and elasticity are the two most observed physical effects.
- The effect of vacuum massage is highly dependent on the type of maneuver performed.
- The more treatments are carried out, the higher the effect.
- Fibroblast migratory and proliferative capacities are enhanced by vacuum massage.
- Vacuum massage improves scar elasticity, which will probably lead to amelioration of function.
- Vacuum massage may release the mechanical stress associated with scar retraction.

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Shock Wave Therapy for Wound Healing and Scar Treatment

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_55

Background

To influence the evolution of an excessive scar toward a normal scar, several physical treatments exist to manage hypertrophic scarring. Physical treatments include manual and mechanical massage, physiotherapy, thermal therapy, and shock wave therapy. Manual massage has a wide array of beneficial effects on scars such as drainage of edema, reduction of pain, and pruritus and hydration of the skin [1]. Mechanical massage or vacuum massage uses gentle vacuum suction to lift the skin and to create a skin fold [2]. Since scars have a propensity to retract and create contractures in joints, splinting, taping, and posture stretching play a crucial role in the treatment. Thermal therapy includes high pressure showers, thread-like showers, and high pressure water and aims to mobilize the skin, to improve flexibility and to reduce inflammation, pain, and pruritus. All of these techniques are frequently used; however, there is only little supporting evidence [3].

The ideal non-invasive scar treatment should be safe, well tolerated by patients, have low associated complication rates, is easy to apply, cost-effective, and can be used in an outpatient setting. Shock Wave Therapy (SWT) meets all the aforementioned requirements [4–7]. The application of shock wave therapy in scar management (Fig. 55.1) is still in its exploration phase; however, there are some interesting findings [3].

Fig. 55.1 Shock wave application on a scar

55.1 Working Mechanism of SWT in Relation to Skin Defects

SWT converts external mechanical stimuli into biochemical cell reactions (e.g., gene transcription leading to collagen remodeling) in living tissue, supported by mechanotransduction pathways, which result in the activation of numerous cellular events, responsible for the positive effects of SWT on cell metabolism and cell cycle [8]. Moreover, as in some other mechanotherapies applied in clinical practice, the main action of SWT seems to focus on inducing tissue regeneration and matrix remodeling *in vivo* [9]. Fibroblasts are the major mechanoresponsive cells in connective tissue, and are therefore the main target of SWT [10, 11]. Fibroblasts play a crucial role in remodeling of the extracellular matrix (ECM) by synthesizing and organizing connective tissue components, and there is a strong believe that SWT has a modulating effect on these actions and could therefore be of interest in scar prevention and management.

Sukubo et al. (2015) described the beneficial effects of SWT on macrophage behavior. SWT does not activate resting macrophages and seems to modulate macrophage activity in the inflammatory phase of wound healing. It inhibits the M1 (pro-inflammatory) activation in the initial inflammatory phase and enhances the M2 (anti-inflammatory) activation in the late inflammatory phase [12]. SWT can also regulate inflammation via TLR3 pathway in three phases. In an initiation phase, it induces a pro-inflammatory reaction mediated by cyclophylin A and IL6. There is a suppression of inflammation in the middle phase and in the limitation phase, there is a late anti-inflammatory effect mediated by IL10 [13]. Both findings indicate that SWT, applied in the wound healing stage or in the early stage of scar development, could prevent pathological scarring.

Non-randomized clinical data suggest that SWT is beneficial in terms of improved skin elasticity and revitalizing dermis in females with cellulite [14]. Fibrillar adipose tissue fibrosis looks very similar to dermal scarring [15], so the outcomes of clinical trials investigating cellulite could be transferred to pathological scarring [2]. MR imaging has shown that fibrous septa, visualized in 97% of the area with cellulite depressions, are markedly thickened in cellulite afflicted areas. Shockwave energy might weaken the fibrous septa, and thus the afflicted skin becomes smoother [14]. There is evolving experimental data suggesting SWT activation pathways in adipose-derived stem cells [14].

Delayed wound healing might be considered as one of the main reasons to develop hypertrophic scars. SWT has repeatedly proven to be effective as a wound-healing modality by decreasing time to full wound closure [4, 5, 16, 17]. From the mechanobiologic point of view, it has been described that the neoangiogenic capacity could be related to the inhibition of endothelial cell apoptosis, occurring in the very early phase after SWT stimulation (first 3 hours), as an initial response to the mechanical stimulus. More in detail, it seems possible to detect some "preparatory" signals, such as downregulation of the genes involved in cell cycle, adhesion and apoptosis, probably correlated to an upcoming detachment of endothelial junction [9]. After a low-energy SWT treat-

ment (800 shocks, 1 Hz, 0.03 mJ/mm^2), mRNA expression and protein levels of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) were significantly upregulated. Furthermore, the SW therapy enhanced phosphorylation of caveolin-1 and the expression of HUTS-4 that represents β1-integrin activity. These results suggest that caveolin-1 and β1-integrin are involved in the SW-induced activation of angiogenic signaling pathways [18].

We can summarize that the overall effect of SWT is an improvement of tissue homeostasis, accompanied by an improvement of the tissue self-healing abilities.

55.2 SWT Dose Effect Relationship

For a full treatment outline, the energy flux density (EFD), the number of pulses, the pulse frequency, and the number and interval of treatments are the most relevant parameters [5]. Differences in these parameters can lead to varying outcomes, emphasizing the dose dependency of these mechanotransduction events [9]. High-energy SWT can suppress cell growth, while low-energy shock waves might enhance cell proliferation [19]. SWT applied with an EFD of 0.01–0.03 mJ/mm^2 can modulate the inflammatory pathway in which macrophages are involved [12], and with an EFD of 0.08 mJ/mm^2 SWT can regulate inflammation via the TLR3 pathway. The EFD for soft tissue indications is typically in the range of 0.08–0.25 mJ/mm^2 [4], while scars and fibrosis are treated with an EFD ranging between 0.15 and 0.33 mJ/mm^2. SWT settings of 0.22 mJ/mm^2 and 1000 pulses seem to be ideal for fibroblast viability and growth [20]. Fibroblast viability was also influenced by the number of pulses. The higher the number, the more risk for cell destruction [11]. Each cell type seems to be responsive to SWT but probably with different optimal device settings and ranges of mechanical stimulation, thus developing different biochemical effects [8]. A study by Lee et al. showed that the EFD plays an important role in the targeting of specific mechano-signaling pathways, with 0.12 mJ/mm^2 being the optimal dose for activating the mTOR-FAK pathway [21] and 0.10 mJ/mm^2 showed the best results for inhibiting TGF-β1/Smad pathway [22] (◘ Table 55.1).

55.3 The Effects of Shock Wave Therapy in Soft Tissue Defects

55.3.1 The Effects of SWT in Wound Healing

Wound healing after SWT is characterized by an upregulation of the angio-active factors such as nitric oxide (NO) and vascular endothelial growth factor (VEGF) leading to induced angiogenesis [17], vasodilatation, increase in vascular and capillary density, and increased local blood flow. NO and VEGF are extremely important, both in early stage and late stage healing [5, 7, 9, 11, 17]. It has been suggested that an aspect of the early gene response of endothelial cells to SWT is characterized by a decreased apoptosis and stimulation of the extracellular matrix metabolism [5, 9]. SWT will lead to reduced tissue necrosis in wound healing by increasing cellular proliferation and procollagen production [11, 23]. In terms of timing, vasodilatation is noticed at an early stage (first 3 days) and neovascularization at late-stage post intervention [17]. In a clinical trial investigating the efficacy of ESWT to heal chronic therapy-refractory ulcers, the underlying molecular mechanisms were also studied *in vitro* [24]. Fibroblasts reorganized in a radial and star-shaped clustered manner and had large "stress" fibers. Cluster formation of fibroblasts was dose dependent, meaning that more applications lead to higher clustering. Shock waves also induce upregulation of 67 genes for keratinocytes and 652 genes for fibroblasts, suggesting that SWT mainly targets fibroblasts [24]. The upregulation of Vimentin on mRNA level leading to a visible reorganization of the cytoskeleton provided yet another proof for mechanotransduction as working mechanism for this intervention.

Besides "general wound healing," SWT has specifically been proven effective in burns. First, SWT applied upon donor site healing burn wounds shows a significantly shorter time to complete epithelialization [25]. Second, burn area perfusion has been evaluated with Laser Doppler Imaging before and after SWT and showed a significantly increased perfusion after extracorporeal shockwave therapy treatment [26]. The review of Antonic et al. suggested that SWT may decrease the need for surgical intervention and associated morbidities in patients with severely deep partial- or full-thickness

◘ **Table 55.1** Suggested SWT settings for electro-hydraulic devices when treating wounds or scars

	Energy flux density	Number of pulses	Pulse frequency	Treatment interval	Number of treatments
SWT for wound healing	0.03–0.20 mJ/mm^2	500–1000	4–6 Hz	1× per week	1–3
SWT for scar treatment	0.15–0.33 mJ/mm^2	800–1500	4–6 Hz	1× per week	8–12

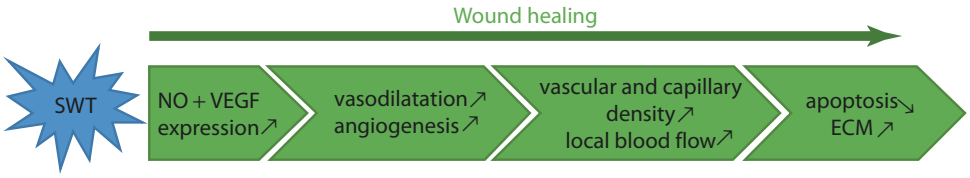

Fig. 55.2 Cascade of wound-healing processes after SWT

burns [4]. Joo et al. demonstrated that ESWT significantly reduced burn scar pruritus severity and activities-of-daily-living disturbances compared to a control group who received sham treatment. The EFD ranged between 0.05 and 0.20 mJ/mm^2, which seemed useful for pruritus in burn scars [27]. The authors hypothesized that ESWT targeted "neurogenic inflammation," which is an inflammation caused by the release of substances (e.g., SP and CGRP) from primary sensory nerve endings. Nerve fiber loss and the depletion of neuropeptides might decrease inflammation, and thus may decrease itch [28]. A recent meta-analysis showed that ESWT had better therapeutic outcomes on acute and chronic soft tissue wounds when compared to Conventional Wound Therapy (CWT) [29]. The meta-analysis showed that ESWT statistically significantly increased the healing rate of acute and chronic soft tissue wounds 2.73-fold (odds ratio, OR = 3.73, 95% confidence interval, CI: 2.30–6.04, $P < 0.001$) and improved wound-healing area percentage by 30.45% (Standardized Mean Difference (SMD) = 30.45; 95% CI: 23.79–37.12; $P < 0.001$). ESWT reduced wound-healing time by 3 days (SMD = −2.86, 95% CI:-3.78 to −1.95, $P < 0.001$) for acute soft tissue wounds and 19 days (SMD = −19.11, 95% CI: −23.74 to −14.47, $P < 0.001$) for chronic soft tissue wounds and the risk of wound infection by 53% (OR = 0.47, 95% CI: 0.24–0.92, $P = 0.03$) when compared to CWT alone. Serious adverse effects were not reported [29] (Fig. 55.2).

55.3.2 The Effects of SWT in Scar Management

Fibrous tissue can be reduced by SWT (at the origin) during wound healing processes, but it can also be remodeled in a second phase of scar formation. Primary data show that height, pliability, vascularity, and pigmentation, all relevant scar parameters, show improvement after SWT [6, 30]. The change in these physical and physiological parameters will probably lead to amelioration in function, which is, for example, demonstrated by an increase of passive ROM reported in a study on retracting hand scars [30]. Subjective pain measures also show a decrease in pain at the scar site after SWT [6, 30].

On a histopathological level, the effects of SWT on fibrosis are plural. A downregulation of alpha-SMA expression, myofibroblast phenotype, TGF-β1 expression, fibronectin, and collagen type I are measured. A significant increase in dermal fibroblast-like phenotype with low contractility and high migratory ability, small vessel density and precursors of extracellular matrix components, probably leads to new and thinner collagen fascicles and parallel orientation to the dermo-epidermal junction [30–32]. Synergistic alterations in pro- and anti-fibrotic proteins (TGF-β1 and MMP-2, respectively) suggest a reduced capsule formation after silicone implantation [33]. One study compared ESWT to triamcinolone injections for the treatment of keloids. ESWT showed comparable functional outcome, together with comparable total sum of scores for POSAS patient scale and POSAS observer scale clinically. A significant reduction in collagen fibers and increased expression of MMP-13 degrading enzyme could be seen when compared to intralesional steroid injection [34]. Zhao et al. demonstrated positive results on planimetric scar characteristics and inhibition of TGF-β1/Smad signaling pathway with Radial Extracorporeal Shockwave Therapy [22], as well as decreased Scar Elevation Index, fibroblast density, and α-smooth-muscle-actin expression in hypertrophic scar tissues of a rabbit model [35].

The most promising results in the research for the effects of SWT on scars were presented as preliminary data of an ongoing randomized placebo controlled trial investigating the effects of SWT in the management of hypertrophic scars. The results of the objective assessments showed a statistically significant better performance of the intervention group for elasticity assessed with cutometry [36] (Table 55.2).

55.4 Conclusion

All the presented findings are fundamental knowledge for further investigation of SWT to reduce the fibrous component in regenerating and remodeling tissues. The dose dependency of the treatment effects remains understudied. Energy Flux Density, number of shocks, shock frequency, and treatment interval and number are all important parameters in the choice for the most suitable device settings, in relation to the indication. Future studies should include these parameters as covariates to determine the right-specific approach for each scar. The full potential of SWT in wound healing, scar treatment, and cellulite certainly needs further unraveling.

Table 55.2 SWT effects on wound healing, scar formation + remodeling, and cellulite

Effect of SWT on	Changes in histopathological parameters	Physical and physiological changes
Wound healing	Stimulation of the ECM metabolism Upregulation of cell-cycle regulatory genes Reorganization of the cytoskeleton	Angiogenesis Vasodilatation Increase in vascular and capillary density Increase in local blood flow Decrease in apoptosis Reduction of tissue necrosis
Burn wound healing		Shorter epithelialization time Increase in perfusion
Scar formation and remodeling	Downregulation on alpha-SMA expression, myofibroblast phenotype, TGF-β1 expression, and fibronectin Decrease in collagen type I Upregulation dermal fibroblast-like phenotype Increase small vessel density (ratio type I/type III collagen) Increase in precursors of ECM components Synergistic alterations in pro- and anti-fibrotic proteins	Formation of new and thinner collagen fascicles Reduced capsule formation Decrease in height Increased pliability Normalization of vascularity and pigmentation Amelioration of function (range of motion) Decrease in pain
Cellulite	Decrease of serum malondialdehyde and plasma protein carbonyls Release of lipid peroxidation products influence adipose-derived stem cells	Weakening of the fibrous septae Smoothening of skin

Take-Home Messages

- SWT meets all the requirements for the ideal non-invasive scar treatment.
- Mechanotransduction is the working mechanism behind SWT.
- SWT induces tissue regeneration and remodeling *in vivo*.
- Inflammation can be modulated by SWT.
- Low-energy SWT induces cell proliferation, while high-energy SWT suppresses cell growth.
- SWT can decrease time to full wound closure and reduces the risk for tissue necrosis.
- SWT may improve scar elasticity, which will probably lead to amelioration of function.
- There is a high dose–effect relationship when treating soft tissue defects with SWT.

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Effectiveness of Corticosteroid Tapes and Plasters for Keloids and Hypertrophic Scars

Rei Ogawa

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_56

56.1 Introduction

In Japan, corticosteroid tapes and plasters have long served as a first-line therapy for keloids and hypertrophic scars. Pediatric patients are particularly responsive to this type of treatment. This may reflect the fact that children have thinner skin than adults and the steroids are therefore more easily absorbed. The postoperative application of corticosteroid tapes/plasters also significantly prevents the development of keloids and hypertrophic scars after surgery.

External corticosteroid preparations are classified into five classes on the basis of their vasoconstrictor activity and their clinical effect, namely, Group I (Strongest), Group II (Very strong), Group III (Strong), Group IV (Mild), and Group V (Weak). Steroid tape is available in the following three countries in different preparations. In the UK, the commercially available formulation comprises a fludroxycortide-impregnated tape (4 μg/cm^2) [1]. Fludroxycortide tape is a Group III preparation. The USA has a steroid tape preparation that contains 4 μg/cm^2 flurandrenolide, which is also a Group III preparation [2]. In Japan, two steroid tape formulations are available, namely, the Group III preparation found in the UK (4 μg/cm^2 fludroxycortide tape) and a 20 μg/cm^2 deprodone propionate tape. Deprodone propionate tape is considered to be a Group I or II preparation [3] (Fig. 56.1). In our experience, deprodone propionate tape (Eclar® plaster) is the most effective tape for the treatment and prevention of keloids.

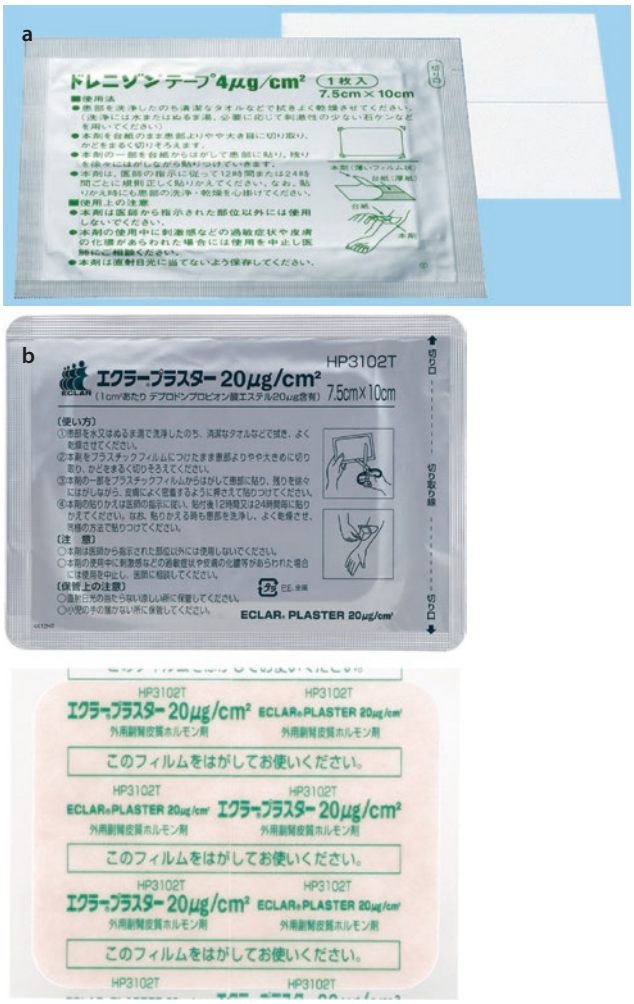


Fig. 56.1 The steroid tapes and plasters that are available in Japan. **a** Fludroxycortide tape (Teikoku Seiyaku CO., LTD., Kagawa, Japan). **b** Deprodone propionate plaster (Hisamitsu Pharmaceutical CO., LTD., Saga, Japan)

56.2 Difference Between Steroid Tapes/Plasters and Steroid Injection

Corticosteroid injections rapidly reduce the volume of keloids and hypertrophic scars. However, the downsides of corticosteroid injections include pain (caused by the injection itself) and difficulties associated with contraindications such as pregnancy, glaucoma, or Cushing's disease [4]. These problems can be overcome by using steroid tapes/plasters. Most pediatric and older patients can be treated by steroid tapes/plaster alone due to their thinner skin, which means that the steroids are easily absorbed.

Corticosteroid tapes/plasters can also be used in combination with other therapies such as corticosteroid injection. This is particularly suitable for adults with keloids and hypertrophic scars. The patients can apply the steroid tape/plaster every day in their homes and undergo the injection when they can go to the hospital. In our hospital, we succeeded in reducing the number of hospital visits of patients with pathological scars by adopting this approach. Indeed, many patients now only come to our hospital every 3–4 months.

56.3 Typical Usage of Steroid Tapes/Plasters

Steroid tapes/plasters should be changed every day. Important tips regarding the treatment of keloids and hypertrophic scars with steroid tapes/plasters are as follows. First, the patient should continue to use the tapes/plasters until the elevated mass becomes flat and soft. The patient must also cut the tape according to the shape of the keloid or hypertrophic scar. Second, once

the mass has become flat and soft, the use of steroid tape/plaster should be stopped, even if the scar is still red. This reflects the fact that if the patient continues to use the tape just because the scar is still red, capillarectasia will occur. This is because the steroid treatment thins the structures supporting the blood vessels.

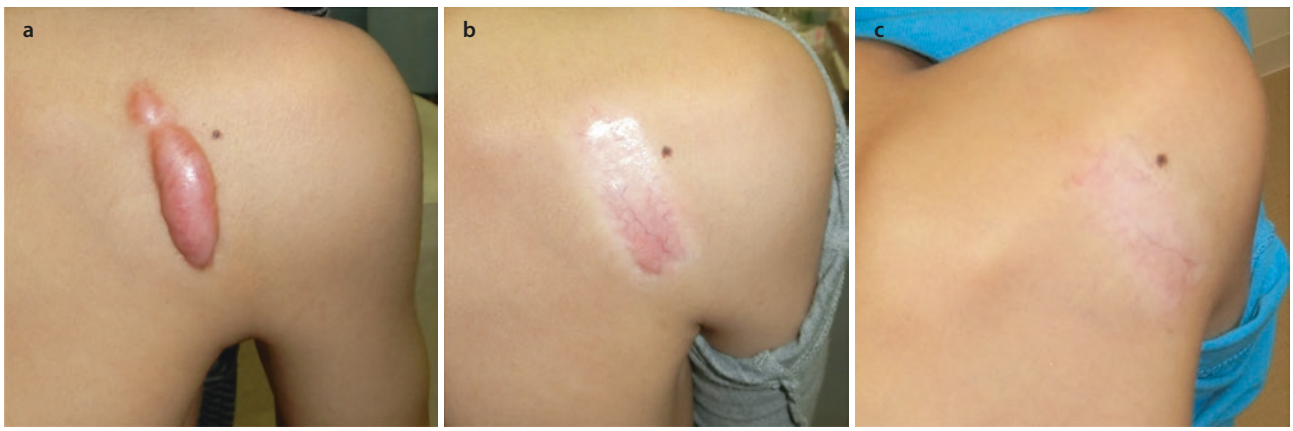
56.4 Difference Between Deprodone Propionate Plaster and Deprodone Propionate Ointment

At this stage, deprodone propionate plaster is the strongest steroid tape/plaster in the world. Deprodone propionate plaster was launched by Hisamitsu Pharmaceutical Co., Ltd., Saga, Japan in July 2001. Since the deprodone propionate in this plaster is at a concentration of 20 μg/cm^2, each 7.5 cm × 10 cm sheet contains 1500 μg of the steroid. The product sheet states that of the 910 cases, 24 (2.64%) exhibited side effects to this plaster. The main side effects were capillary dilation (nine cases, 0.99%), contact dermatitis (five cases, 0.55%), skin atrophy (four cases, 0.44%), and hair folliculitis (four cases, 0.44%).

Deprodone propionate ointment is considered to be a Group III preparation: thus, it is 1–2 ranks weaker than deprodone propionate tape. This is because of differences in the action time and how much steroid is absorbed. When choosing between deprodone propionate ointment or deprodone propionate plaster, it should be noted that to cover the 75 cm^2 area of one deprodone propionate plaster, one must apply 0.125 g of deprodone propionate ointment. This is because the product sheet states that 0.5 g of the ointment can coat an area of 300 cm^2. However, since the ointment consists of 0.3% of the active ingredient, 0.125 g of ointment will only contain 375 μg of deprodone propionate. This is one-quarter of the amount of one tape (1500 μg). Therefore, deprodone propionate ointment will only have the same effect as 24-hr/day deprodone propionate plaster if the ointment is applied to the affected area 4 times a day and is covered with an occlusive dressing technique (ODT) using, for example, a polyurethane film.

56.5 Therapeutic Effect and Usage of Steroid Tape Preparations

In adults, deprodone propionate plaster is a more effective therapy for pathological scars than other steroid tapes. However, in pediatric patients, the therapeutic effect of the other tapes is sufficient (◘ Fig. 56.2). This is indicated by our observational study [3] on the use of fludroxycortide tape in 30 adults and 30 pediatric patients with hypertrophic and keloid scars. The adults were, on average, 37 years old (range 23–67 years), while the pediatric patients were, on average, 7.2 years old (range 2–15 years). Each patient had one scar that was treated with the tape. The scars were on various body sites, including the trunk and extremities. The scars were over 1 year old and the tape was used for at least 1 year for 24 hr/day. The results after 1 year of treatment were judged by using the Japan Scar Workshop Scar Scale 2015 (JSS) [5]. The results suggest that the fludroxycortide tape improved the scars of 20% of the adult patients and 80% of the pediatric patients. After 1 year of fludroxycortide tape usage, the 24 unresponsive adults were switched to 24 hr/day deprodone propionate plaster treatment. Of these 24 cases, 17 (70.8%) exhibited scar improvements 1 year later. Thus, we conclude that adults require a stronger tape to obtain similar responses as children in terms of scar maturation. Thus, deprodone propionate plaster is better for adults, while fludroxycortide tape is sufficient



◘ **Fig. 56.2** Effect of fludroxycortide tape on a scapular keloid of a 9-year-old boy. **a** Before treatment commenced. **b** Sixteen months after starting treatment. **c** Twenty-six months after starting treatment

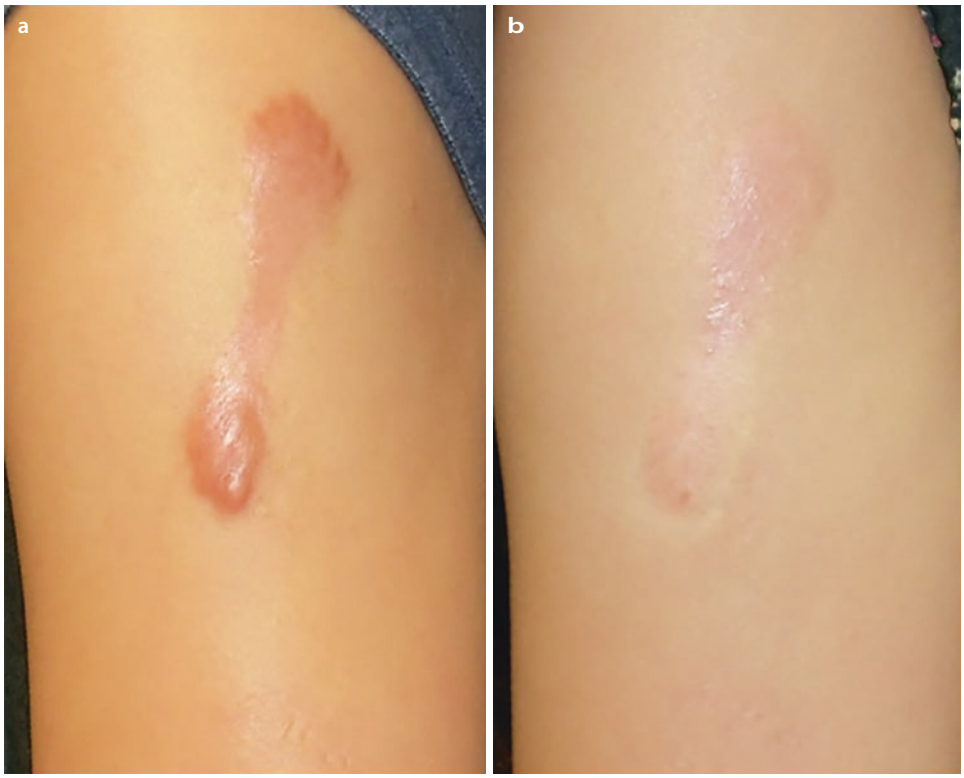


Fig. 56.3 Effect of deprodone propionate plaster on an upper arm keloid of a 25-year-old female patient. **a** Before treatment commenced. **b** Twelve months after starting treatment

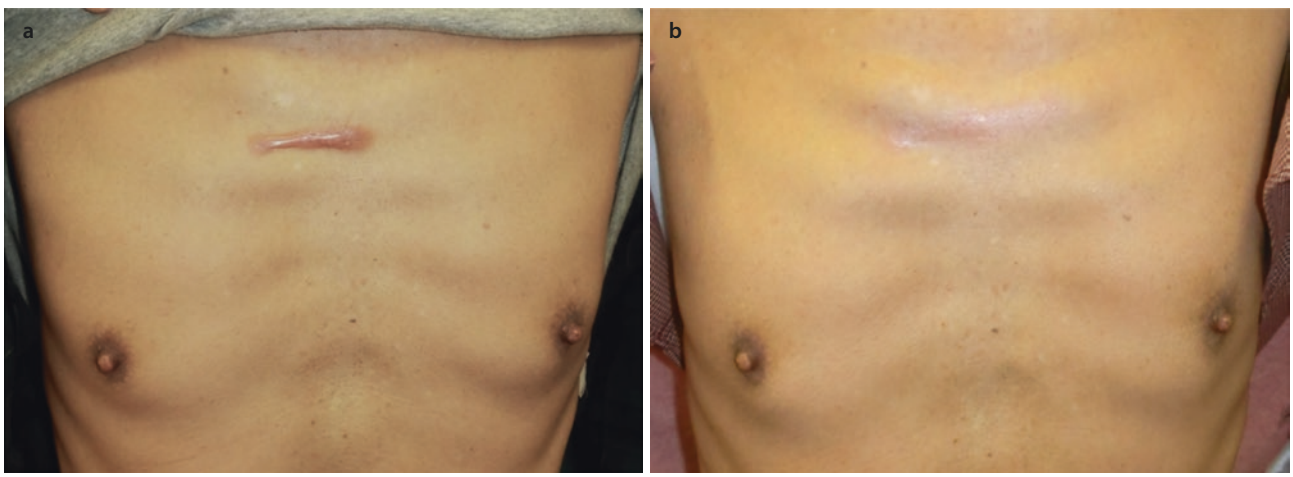


Fig. 56.4 Effect of deprodone propionate plaster on an anterior chest wall keloid of a 68-year-old male patient. **a** Before treatment commenced. **b** Twelve months after starting treatment

for pediatric patients (Figs. 56.3, 56.4, and 56.5). The side effects in our study consisted of contact dermatitis in three adults. None of the children exhibited any side effects.

Steroid tapes/plasters can also be used to prevent recurrence after keloid and hypertrophic scar resection (Fig. 56.6). My empirical experience is that starting 24 hr/day deprodone propionate plaster treatment 1 month after surgery appears to suppress recurrence. Further research is needed to test this hypothesis. It should be noted that we currently routinely use deprodone propionate tape combined with radiotherapy as a postoperative adjunct in surgically treated keloid cases to reduce the recurrence rate. In our experience, this combination reduces the postoperative keloid recurrence rate to less than 10% [6].

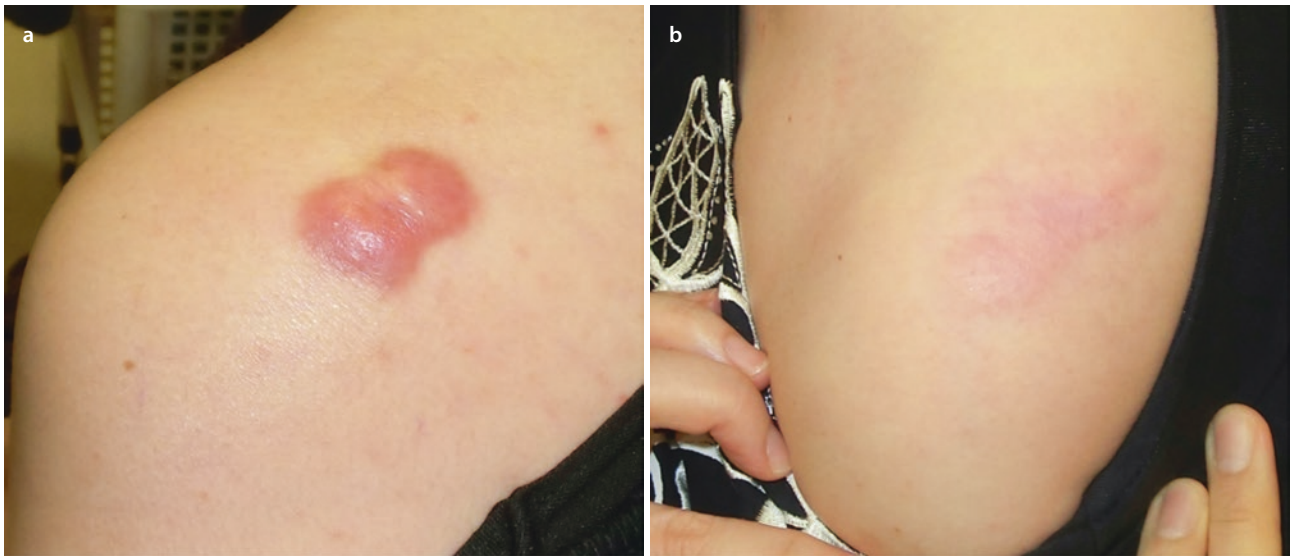


Fig. 56.5 Effect of deprodone propionate plaster on a shoulder keloid of a 49-year-old female patient. **a** Before treatment commenced. **b** Thirty-six months after starting treatment

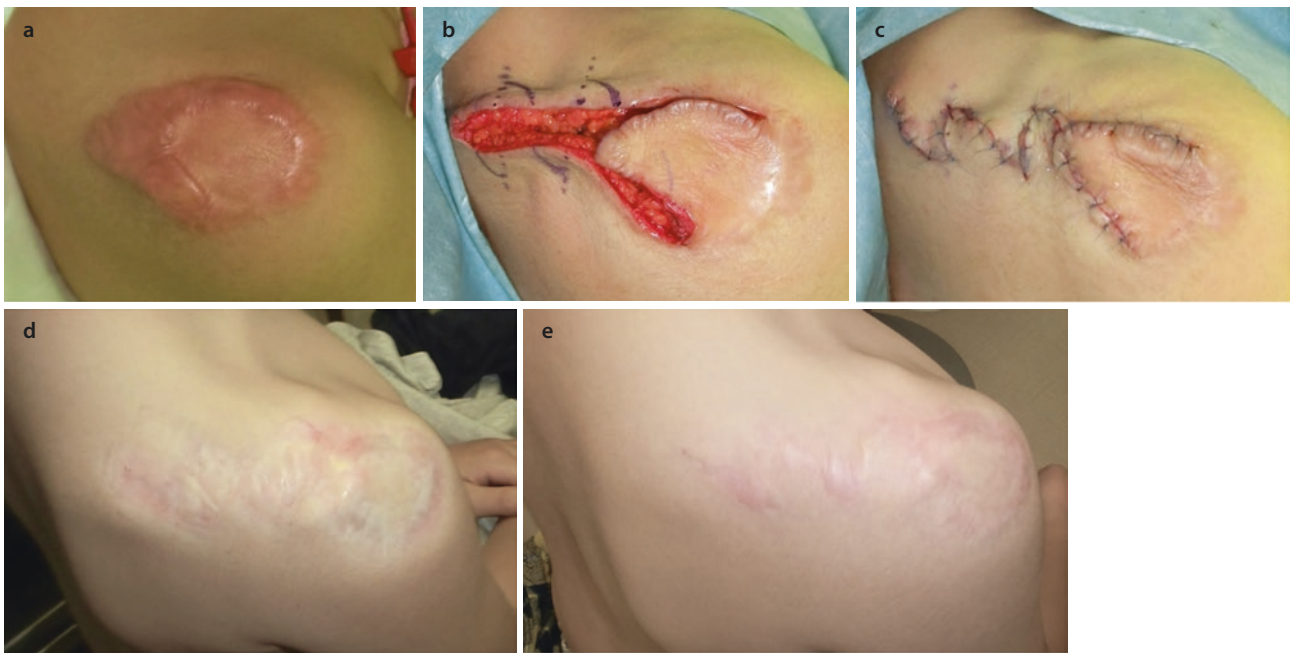


Fig. 56.6 Effect of surgery and postoperative deprodone propionate plaster treatment on a shoulder keloid of a 9-year-old boy. **a** Before treatment commenced. **b** Intraoperative view. **c** View immediately after surgery. **d** Twenty months after surgery. **e** Thirty-six months after surgery

56.6 Side Effects of Steroid Tapes and Plasters

Contact dermatitis is the most common problem associated with the use of steroid tapes/plasters. According to the product sheets, the frequencies of contact dermatitis during fludroxycortide tape and deprodone propionate plaster treatment are 16.7% and 0.55%, respectively. This is consistent with our impression in clinical practice. Thus, deprodone propionate plaster associates with a lower incidence of contact dermatitis. There are two types of contact dermatitis, namely, irritant contact dermatitis and allergic contact dermatitis. One can reduce the possibility of the former by decreasing the frequency with which the tape/plaster is replaced and by reducing the duration of application. Thus, the risk of irritant contact dermatitis may be decreased by various strategies, including replacing the tape/plaster every

24–48 hours, only wearing the tape/plaster overnight, or applying the tape/plaster for 1 day and then using ointment on the next day. In the case of deprodone propionate plaster, we have the impression that mild contact dermatitis is suppressed by the effect of steroid itself. If, however, allergic contact dermatitis develops, it often arises 1–3 months after the start of use. Since it can produce strong pruritus and reddens the skin, it can hamper the continuous use of the tape.

Take Home Messages

- In Japan, corticosteroid tapes and plasters have long served as a first-line therapy for keloids and hypertrophic scars.
- Pediatric patients are particularly responsive to this type of treatment, because children have thinner skin than adults and the steroids are therefore more easily absorbed.
- The postoperative application of corticosteroid tapes/plasters also significantly prevents the development of keloids and hypertrophic scars after surgery.
- Deprodone propionate tape is the most effective tape for the treatment and prevention of keloids.

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Suture Edge Tension Control Technologies for Scar Improvement

Luc Téot, Sergiu Fluieraru, and Christian Herlin

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_57

57.1 Background

Suture management after closure has been considered as highly important in the prevention of enlargement and infection. The rupture of skin integrity, the surgical dissection, and subsequent trauma of the underlying structures may cause local inflammation, edema, dehiscence, and infection. In this context, new technologies were developed and recently validated. The aim of this chapter is to highlight the role of mechanotherapy in prevention of postoperative complications on the suture line. This chapter is designed for surgeons facing surgical procedures at risk of infection or dehiscence or willing to reduce the scar enlargement after surgery on a visible area.

57.2 Introduction/Objectives

The tension exerted on the edges after cutaneous excision surgery has been demonstrated as a source of inflammation and potential complications, like local infection, scar enlargement when skin edges are, even minimally, separated [1, 2]. Keloid generation as well as hypertrophic scarring has been related to mechanical forces in experimental and clinical studies confirming the importance of mechanical control in the prevention of pathological scars especially in Asia [3]. Several techniques have recently been described on the basis of the principle of immobilizing the suture edges after surgery [1].

Globally a better understanding of scar mechanics has been under way for several years [2]. This has made it possible to multiply the compression strategies offered by compression garments or Orlen® (Professional Plastics, Fullerton, CA) plates, particularly in burn scars [4]. Translational research has been stimulated and the optimization of mechanical devices exploiting mechanical forces has been developed, especially in the field of wound healing [5].

A recent study [6] on cadavers measured the forces of tension exerted on the edges of sutured skin and the underlying aponeurosis. These measurements can be considered as a basis for measuring the reapproximation forces of the edges in human clinical practice. A three-dimensional simulation model allowed for reproducing the in vivo tension experienced by the skin, the phenotype of fibroblasts from keloid scars, their matrix synthesis capacity under tension, and in vivo skin tension measured on volunteers. It has been demonstrated that the induction of tension modifies the expression of the genes linked to the mechanical tension of the fibroblasts. This mechanical regulation makes it possible to understand that an increased synthesis of collagen occurs in the scar via the fibroblasts when tension is exerted strongly on the edges. The therapeutic interest of this hypothesis serves as a basis for the development of medical devices opposing edge tension.

57.3 Description of the State of the Art, Historical Evolution, and Recent Data

Applying materials over the suture after surgery is a longtime practice.

In the 2000, the first international consensus [7] on scar management emphasized the positive role of silicone but did not pay too much attention to the adhesive tapes, the first cheap device supposed to limit tension on the suture edges.

57.3.1 Silicone Devices

Silicone gels and tapes have been used since 1986 in prevention and treatment of hypertrophic scars and keloids. Although there have been multiple randomized controlled trials evaluating the efficacy of silicone gels [8], the overall quality of evidence is limited [9].

Silicone gels remain the most reported technique in the successive guidelines published since 2002. Silicone is not per se exerting any tension on the skin edges but may contribute to skin moisture.

57.3.2 Reinforced Suture Materials

During recent years a resorbable barb suture was developed, aiming at distribution of tension along the wound, providing a stronger wound edge approximation. The device was made of slowly resorbable material acting as a barber suture, due to obliquely distributed regular cuttings in the core of the device, preventing longitudinal movements on the suture line. The system was proposed as a drastic change in the suturing methods with a single-layer closure facilitated versus a 2-layer closure. Scar revision including large resection, prevention of shearing forces consequence on flap edges, and situations where the suture line may be exposed to mild to moderate tension were indications for the device [10].

Adhesive sutures. Used since decades long term, these paper tapes are placed over the skin edges to maintain a minimal pressure. Forces exerted on the suture are low, the adherence of the paper embedded with glue being solubilized or detached either by the exudation liquids or by the movements. Reiffel could demonstrate some superiority when adhesive sutures were placed longitudinally on the edges instead of transversally as a scale [11].

Self-adherent smart silicone has been proposed as a solution offering a permanent pressure exerted on the skin edges by a smart technology using adherent silicone covering the suture, isolating the suture from any external contamination. A mechanomodulating polymer device was utilized to manipulate the mechanical environment of closed cutaneous wounds in red Duroc swine, by

applying tension to the edges through physical means (silicone with pretensioning of axial fibers inserted in the layer) [12]. (EMBRACE®). During a surgical procedure, surgeons strive to make incisions that follow the relaxed tension lines on the body, so-called Langer lines. This strategy is used because tension is well known to increase scarring. The Embrace® device (Neodyne Biosciences, Newark, CA) is designed to shield the healing incision from the natural tension that is inherent in any break in skin that must be pulled together to close a wound. Previous preclinical and first-in-human data initially demonstrated that this mechanism of action was effective in scar mitigation in both pigs and humans.

A prospective RCT in scar appearance was conducted on 36 healthy subjects during the post-operative period after abdominiplasty. Embrace® device was used fon the left part of the scar, and control (surgeon's optimal methods) on the right part. Result was significant on the scar appearance at 12 months after 5 weeks of application (Visual analog scale (VAS) $p = 0.027$, Patient and observer scar assessment scale (POSAS) subject $p = 0.02$, and surgeon $p < 0.001$) [13].

57.3.3 Adjustable Tensors

Another system to reduce skin tension across an incision line is the Zipline® system (ZiplineMedical-Stryker). The originality of the system is its ability to bring the two edges together and set the skin tension. This technique has been used since years in suturing the final epidermal layer as well as in restraining the suture edges movements during the postoperative period, results being linked to the compliance of the patient to wear an hydrocolloid based adhesive, covering the adjustable tensors, with a potential risk of allergy. The system may be used as an alternative to superficial sutures.

The medical device (Zipline®) has been developed and is used clinically as a wound closure technique as an alternative to sutures in many surgical procedures.

The medical device is made up of two adhesive carboxymethylcellulose strips, which have a central reinforcing core made up of polyurethane fibers, placed on the suture edges. These strips are interconnected by tensors formed of a polyurethane thread made up of nodes that are regularly distributed along the wire and finished by collars allowing easy grasping for tensioning. The entire set resembles a ladder with an adjustable length of bars. This tensor is firmly fixed and connected to the central core of polyurethane fibers of one of the two strips and placed transversely to bridge the scar zone. The tensor passes from the opposite side into a collar, and the nodules serve as blockers to maintain the desired tension. The distance between the two strips at rest is 1.5 cm and can be reduced to 0.5 cm. This movement is reversible, allowing for a true adaptation of the tension based on local needs and the wishes of the surgeons. The system can be positioned immediately after surgery and maintained in situ during subsequent weeks (Fig. 57.3).

The tension adjustment makes it possible to avoid even minimal edge spacing, which is a source of bacterial penetration and secondary infection. Moreover, the separation movements exerted longitudinally by the natural movements of the body are blocked, and this limitation serves as a transverse but also longitudinal immobilization. This is an essential factor in wound healing, limiting local inflammatory phenomena. Once the tension is stabilized, the loops are cut at their base.

In the author series of 21 clinical cases of skin excision [14], Zipline® was used after tumor resections, scar revision, or flaps. The tension exerted on the edges was variable and Zipline® was able to maintain the suture line outside of the transverse and longitudinal mechanical stresses. The results obtained in this series showed a maintenance of the linear scar measuring less than 0.5 cm permanently after 2 months of application. No local inflammation or secondary enlargement was observed after 2 months.

The anatomical sites were multiple and dependent on the necessities of the surgery. Most areas were located on the shoulders and back, regions known for their dermal fragility and problematic scarring. Maintaining a linear scar on these regions is difficult, especially in young women, after nevus resection. The skin's natural mobility, its thickness, and the forces exerted produce areas of known risk.

All patients underwent cutaneous resection during surgery, with skin loss between 4 cm × 3 cm and 8 cm × 14 cm. The postoperative scars were either straight or slightly curvilinear, and the maximum effect seemed to be obtained when the system was applied to rectilinear scars (Figs. 57.1, 57.2, 57.3, and 57.4). Table 57.1 summarizes the population studied and the amounts of skin resected during surgery. The system was applied for an average of 42 days, with three changes on average.

The evaluation of the scar was performed by three independent evaluators. The average follow-up was 6 ±3

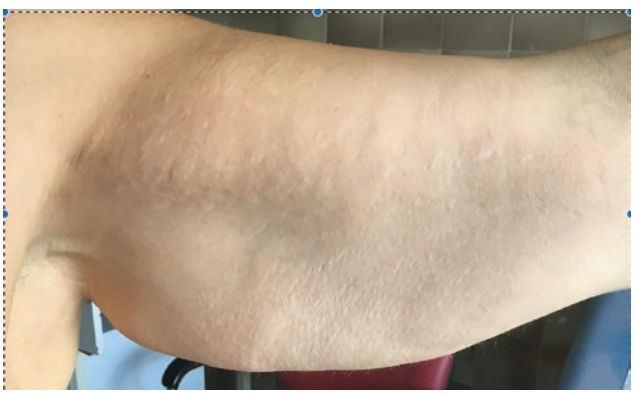

Fig. 57.1 Right arm presenting excessive fat volume (postbariatric surgery)

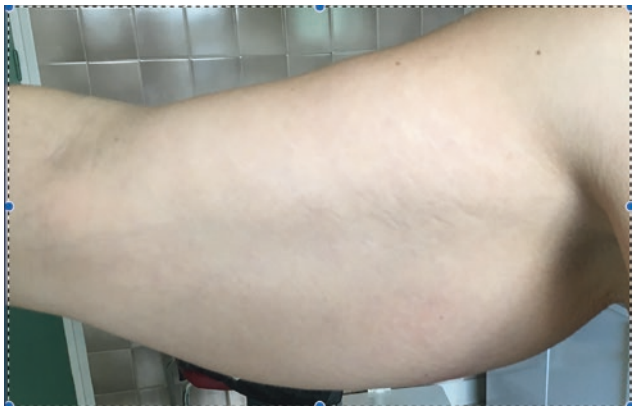

Fig. 57.2 Left arm presenting excessive fat volume

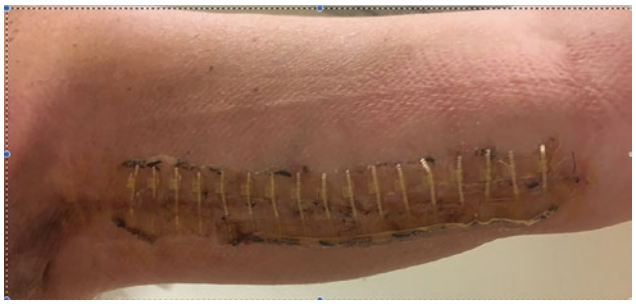

Fig. 57.3 Right arm 2 months after fat reduction and suture edge control

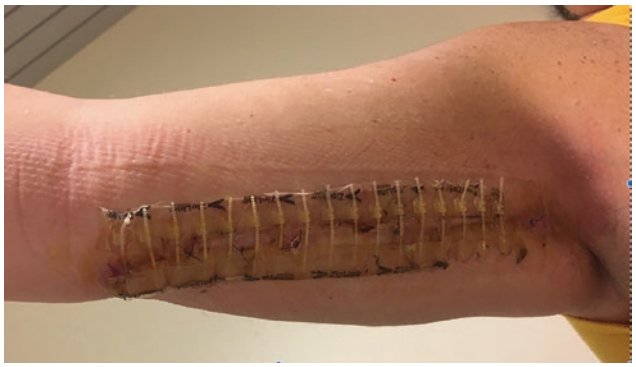

Fig. 57.4 Left arm 2 months after fat reduction and suture edge control

months. The results were considered positive when the scar remained linear without secondary enlargement after 6 months.

Zipline® could be proposed as a skin closure system and as an alternative to epidermal suturing. However, it has not yet been used as a tool to maintain mechanical tension after suturing during cutaneous resection.

The distraction forces exerted on a suture line are caused by the patient's movements. The Zipline® system creates an immobilization of the micromovement-generating forces on the suture edges, which are sources of disunion and scar enlargement. Thanks to the polyurethane core and its staggered arrangement on the adhesive strips, any type of movement can be prevented because it opposes both transverse and longitudinal forces. This compression can be considered dynamic, and it prevents the widening of the suture, regardless of the movement to which it is subjected.

Several clinical trials reporting the effects of Zipline® have recently been published [15–19]. These trials report the product's good capacity to be used in the final closure of wounds. In our series, it appears that maintenance in place for several weeks on the skin serves to limit postoperative mechanical tension and to minimize scars, even in areas in tension and after keloid excision.

Zipline® has been proposed in multiple disciplines like orthopedic surgery in mobile areas like knee or shoulders and in plastic surgery after cutaneous excision for scar revision, cutaneous tumor excision, and loss of cutaneous substances due to chronic wounds such as pressure sores.

57.3.4 Closed Incision Negative Pressure Therapy

Several recent studies demonstrate the value of isolating the wound from any source of external contamination and of keeping it under slight tension.

In recent years, the indication for negative pressure wound therapy (NPWT) has been extended to include treatment of closed surgical incisions (incisional NPWT, iNPWT). Some of the first studies were case series and observational studies [20] using one of the exist-

Table 57.1 Closed incision NPWT clinical indications

CiNPWT clinical indications	Thoracic surgery	Caesarian section	Orthopedic surgery	Postskin grafting	Pilonidal sinus
PICO®	x	x	x	x	x
Avelle®		x	x		x
Prevena®	x	x	x	x	x
Nanova®	x		x	x	

ing NPWT devices (VAC®; KCI, San Antonio, Texas, USA) [21, 22] designed for open wounds. Two simplified NPWT devices became commercially available in 2010 (Prevena™; KCI) and 2011 (PICO™; Smith & Nephew, Hull, UK). These NPWT devices consist of a single-use battery-powered negative-pressure therapy device, an easy-to-place dressing, and either a very small and easily portable canister, or no canister at all. In the latter case, the liquid is removed by evaporation through a semipermeable dressing. The mechanisms of action of this closed incision management have been supported by biomechanical studies:

Biomechanical testing could experimentally demonstrate that a pressure of 80 mmHg applied over a suture was enough to prevent 55% of tissue deformations compared to a situation when no NPWT dressing is applied [23]. Other authors suggested increased blood flow, decreased lateral and shear stress at the suture lines with decreased risk of wound dehiscence, and increased lymph clearance with reduced formation of hematoma/seroma [24].

A recent meta-analysis was conducted by Strugala et al. [25] on the impact of prophylactic use of a specific design of NPWT device on surgical site complications. Articles were identified in which the specific single-use NPWT device (PICO°, Smith & Nephew) was compared with standard care for surgical site infection (SSI), dehiscence, or length of stay (LOS). Risk ratio (RR) ±95% confidence interval (CI) (SSI; dehiscence) or mean difference in LOS ±95% CI was calculated using RevMan v5.3.

Combining all 16 studies, there was a significant reduction in SSI of 58% from 12.5% to 5.2% with NPWT (RR 0.43, [95% CI 0.32–0.57], $p < 0.0001$). Similar effects were seen irrespective of the kind of surgery (orthopedic, abdominal, colorectal, or cesarean section), although the numbers needed to treat (NNT) were lower in operations with higher frequencies of complications. There was a significant reduction in dehiscence from 17.4% to 12.8% with NPWT (RR 0.71, [95% CI 0.54–0.92], $p < 0.01$). The mean reduction in hospital LOS by NPWT was also significant (−0.47 days, [95% CI −0.71 to −0.23], $p < 0.0001$). The significant reduction in SSI, wound dehiscence, and LOS on the basis of pooled data from 16 studies shows a benefit of the PICO single-use NPWT system compared with standard care in closed surgical incisions (Table 57.1).

Another study focused on the interest of CiNPWT after post-SSI revision of orthopedic implants [26] for total hip arthroplasty (THA) due to septic loosening in the presence of active fistula. They were treated with a PICO® device for NPWT, in combination with the standard treatment for prosthesis infection. Resolution of the infectious process and healing of the surgical wound without complications were considered promising results, confirming the interest of the system in most of the surgical disciplines (plastic surgery, thoracic and cardiac surgeries, and colorectal surgery) [27, 28]. The system has also demonstrated efficiency in stabilizing skin grafting.

57.4 Conclusion

The recent development of technologies proposing a mechanical restriction of micromovements on the suture line, with or without negative pressure, tends to demonstrate some evidenced benefits. These techniques are presently used in several surgical disciplines and proposed for at-risk situations in long and difficult procedures and also for minimizing the scar visibility and preventing enlargement as well as volume changes.

Take Home Message

This chapter expoes the interest of mechanotherapy during the post operative period in prevention of pathological scarring and in prevention of postop dehiscence and infection. Several techniques, from adhesive sutures to sophisticated machines applying on the suture edges a negative pressure, have already demosntrated an interest in decreasing the surgical site infection rates. These techniques are exposed and detailed.

Postop mechanotherapy seems adapted in patients at risk of developing local co:plications.

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Scars from a Clinical Perspective: Commented Clinical Cases

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Hyperpigmented Scar

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58.1 Medical History

A 23-year-old healthy Caucasian patient suffered from a deep dermal burn (IIb) 2 years ago due to contact with an open fire. Despite initial professional burn care and aftercare using silicone-based products, the patient developed an elevated hypertrophic scar in an area of 18 × 12 cm with an approximate height of 1 cm on her left lower leg. Repetitive treatments with cryotherapy and intralesional injections with triamcinolone acetonide at the local university hospital did not result in significant improvements; however, as a side effect of the treatment, brownish hyperpigmentations appeared in the treated area. At initial presentation in our clinic, the patient did not complain about any pain except some tension and pruritus but was severely disturbed by the appearance of the scar (◘ Fig. 58.1).

Questions to Medical History

- What is the rationale for the formation of postinflammatory hyperpigmentations after the initial therapy?
- Which therapeutic alternatives exist?
- Are there any medical precautions that should be considered for initiating any additional therapy?

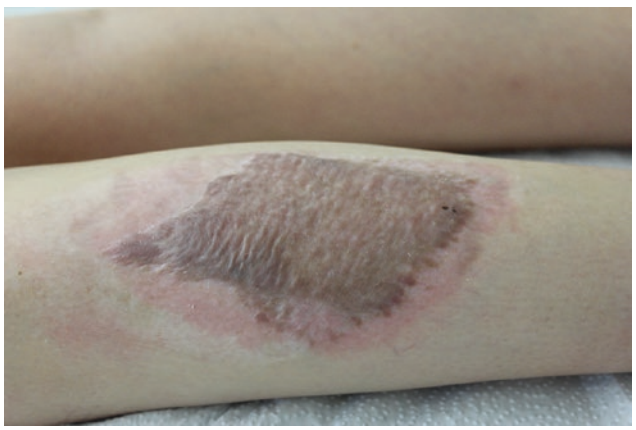
58

Intervention 1

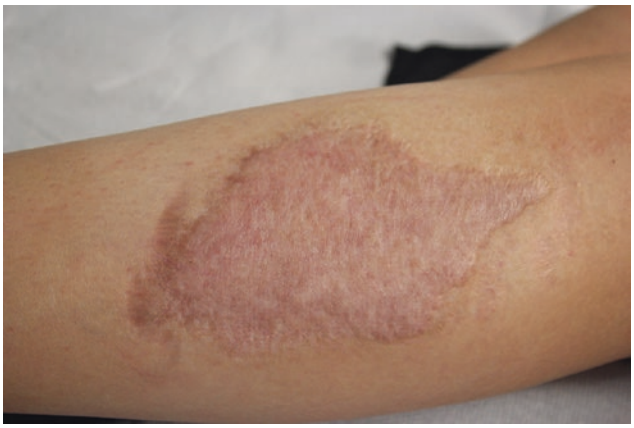
One pass using a Q-switched ruby 4 mm/4 J (Asclepion) under local anesthesia cream. Aftercare with fusidic acid and a class III steroid containing cream.

Interventions 2–6

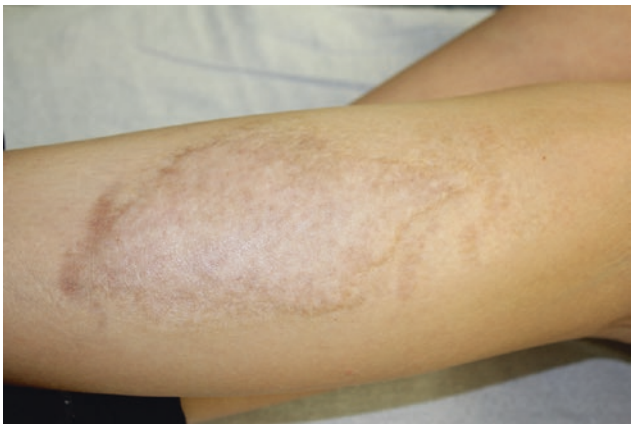
Eight weeks later significant improvement of hyperpigmentation and some minor flattening (◘ Fig. 58.2), five additional sessions with fractional CO_2 (Lumenis, UltraPulse, SCAAR FX 60–90 mJ, 1–3%, 300 Hz) under local anesthesia cream, additional 5-fluorouracil (5-FU) 50 mg/cc for drug delivery on the scar surface. Wound dressings with gauze, fusidic acid, and a class III steroid containing cream. Repetitive treatments approximately every 4–6 weeks apart.



◘ **Fig. 58.1** Baseline situation: elevated hypertrophic scar in an area of 18×12 cm with an approximate height of 1 cm on the left lower leg at initial presentation. Surrounding erythema due to mild reaction to the local anesthesia cream applied prior to the laser therapy



◘ **Fig. 58.2** Presentation 8 weeks after initial Q-ruby laser treatment



◘ **Fig. 58.3** Presentation 12 weeks after last laser treatment

Questions Interventions

- Why use the Q-ruby first before initiating therapy with fractional CO_2?
- What is the rationale for the time intervals in between laser sessions?
- Potential risk of laser therapy?
- Why combination with 5-FU?

Intervention 7

Another pass using a Q-switched ruby 4 mm/4 J (Asclepion) under local anesthesia cream. Aftercare with fusidic acid and a class III steroid containing cream. Final results 12 weeks after last treatment shown in ◘ Fig. 58.3.

Discussion

Hyperpigmented scars are relatively common; however, most frequently scar therapy is directed toward reducing possible symptoms like pruritus, pain or tension, and reduction of excess scar tissue through various

approaches. Nevertheless, using nanosecond or picosecond lasers with wave lengths of 532, 694, 755, or 1064 nm known from laser tattoo removal or treatment of benign pigmentated skin lesions do have potential to improve appearance of hyperpigmented scars. In our case, treatment using a q-switched Ruby laser has been chosen as initial therapy simply due to the fact that the hyperpigmentation was the main concern of our patient. The hyperpigmentation was most probably a response to previous cryotherapy sessions; however, in darker-skinned patients, hyperpigmentations of scars are frequently seen without any previous therapy. Alternatively, a hydrochinone-containing cream may be used, but they are often less effective compared to respective laser treatments [1]. Caution should be paid to possible melanocytic lesions, which can easily be ruled out through dermatoscopy and should be excluded from laser therapy.

The use of fractional CO_2 lasers for the improvement of hypertrophic scars has been demonstrated in numerous studies. Combining deep fractional ablation with high fluences and a low density to stimulate dermal matrix remodeling with superficial smoothening of the scar through ablation of individual scar strands, followed by extensive fractional surface ablation, has been shown to greatly improve widespread hypertrophic scarring [2–4]. On a molecular basis, the heat radiated into the treated tissue results in the activation of heat-shock proteins, predominantly from the HSP-70 family, as well as the alteration of remodeling factors like matrix-metalloproteases and antifibrotic isotypes from the transforming-growth factor beta family (TGF-β) [5, 6]. Although these processes have not yet been fully elucidated, clinical studies have shown a normalization of the dermal matrix architecture following fractional CO_2-laser treatment [7, 8]. Its combination with triamcinolone acetonide or 5-FU appears to further improve results and, in our experience, seems to minimize the total number of sessions necessary to achieve satisfying results [9, 10]. We usually allow the scar tissue to settle in between laser sessions for 4–8 weeks as scar tissue needs time for remodeling. While hypertrophic scars usually respond very well to fractional lasers, some caution should be paid when treating keloids as here, activation of the keloid with further enlargement is relatively frequently seen.

Take-Home Message

- Different scar types do benefit from combinational therapies. Interestingly, hyperpigmentations of scar do respond relatively well to QS-ruby or picosecond lasers.

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Clinical Case Reports: Scar Prevention by Laser Treatment in Mastopexy With Implant

Vincent Hunsinger, Martin Lhuaire, Ibrahim Dagher, and Laurent Lantieri

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_59

59.1 Introduction

Breast ptosis is one of the most common conditions treated by plastic surgeons with more than 100,000 operations each year just in the USA. While its causes are not clearly defined, age, history of significant weight loss, higher body mass index (BMI), larger bra cup size, the number of pregnancies, and smoking history are known to be significant risk factors [1]. Treatment consists generally in mastopexy and/or breast augmentation with implant fitting. The mastopexy procedure is generally considered a reliable aesthetic procedure with less than 2% of unsatisfactory breast shape [2]. In addition to operative risks related to any surgery performed under anesthesia, some complications specific to breast plasty and breast implant may occur such as hematoma, infection, wound healing delay, wound dehiscence, necrosis of the areola, necrosis of the skin, disruption of the implant and silicon leakage, rare case of anaplastic large cell lymphoma, and poor quality of the scars, including hypertrophic scar or keloid [1]. The overall complication rate of mastopexy reaches 10% and the most represented complications are scar related, with 3% of hypertrophic or unaesthetic appearance [2]. The patients' perspective is also essential when evaluating scar cosmetic appearance as it might differ from the ones of the surgeon [3, 4]. In particular, their expectations at short term (inflammatory stage) and long term (1 year) are of equal importance as they usually wish to regain a normal appearance skin as soon as possible and desire sustainable results [3, 4]. To minimize the aesthetic impact of surgical scars, many different strategies have been identified, such as compressing devices, sun protection, silicone dressing, or laser treatment [5, 6]. According to the recent guidelines, prevention of abnormal scar formation should always be a first priority [5–7]. Preventive measures adapted to the patients' risks and needs (possibly including combined therapies) and early intervention are well recognized for their positive outcomes [5–7]. In particular, laser therapy seems to gain each year broader and broader application in this field [8]. Ten years ago, a new approach based on a preventive treatment of scars called Laser-Assisted Skin Healing (LASH) was developed by Pr Mordon (INSERM U703; University of Lille Nord, France), and clinically evaluated by the teams of Pr Magalon (Department of Plastic and Reconstructive Surgery, APHM, Marseille, France) and Dr. Capon (Plastic and Reconstructive Surgery Department of Pr Martinot and Pellerin, CHRU, Lille, France) [9]. Performed immediately after surgery, a laser shot induces a controlled elevation of skin temperature, which activates the overexpression of chaperone proteins (Heat Shock Protein 70) [9, 10]. These proteins then activate tissue regeneration by shortening the inflammatory stage of the wound healing process and hasten scar maturation [9]. This technique, performed during the earliest stage of the healing process for a maximum impact, gave promising results. In 2016, a new laser system was marketed on the basis of this LASH technique. The 1210-nm laser diode (UrgoTouch®, Laboratoires Urgo Medical, Chenove, France) was an automated, portable laser providing a controlled elevation of skin temperature, due to its scar control system technology. The wavelength of the system allows its use on patients with all skin phototypes, including Fitzpatrick scale phototypes V and VI. The performance and safety of this new device were assessed in a 1-year follow-up double-blinded randomized controlled trial (RCT), undertaken on patients undergoing breast reduction: The "SLASH" study [11]. This high-quality-level study was conducted in France and coordinated by Pr Casanova at the University Hospital of Marseille. A total of 40 women (with phototypes II to VI) undergoing bilateral breast reduction were enrolled by the five surgeons involved in the study and treated with the portable 1210-nm laser on one randomly assigned breast, while the controlateral one was used as the study control. The unique laser-treatment session was performed on the suture incisions, in the operating room, while the patient was still under the general anesthesia. According to the results of this clinical study, based on both subjective assessments (with the validated modified Observer Scar Assessment Scale (mOSAS) score) and objective measurements (with software analysis of three-dimensional [3D] pictures of the scars) the 1210-nm automated laser system provided significant improvements of the cosmetic aspect of the scars at short term (6 weeks), medium term (6 months), and long term (12 months) (Fig. 59.1). These aesthetic improvements, notably in terms of volume, surface, and roughness, were strengthened with the blind expression of patients' preference for their laser-treated scars. Of note, in the subgroup of dark skin-type patients (phototypes V–VI), the results also favored the laser treatment, with 53% and 16% mean reductions of the scar volume and surface, compared to the control scars.

I have personally used this laser treatment (Fig. 59.2) in many different indications in my current practice and I propose to report here two cases of breast hypotrophy and ptosis treated by mastopexy with implants associated with the laser treatment.

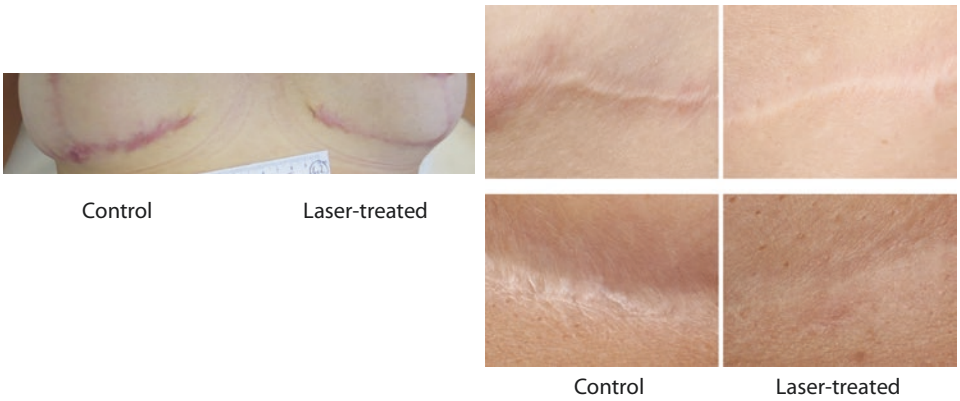

Fig. 59.1 On the left, a two-dimensional (2D) photograph of the inframammary scars of a patient, 6 months after her breast-reduction procedure. The horizontal scar of one breast was randomly assigned to receive in the operating theatre, the day of the surgery, the laser treatment while the other scar of the controlateral breast was used as a control. On the right, 3D photographs of internal or external extremities of the scars treated or not with the laser in two different patients, 12 months after the procedure. (Reproduced from the double-blind RCT "SLASH" with the courtesy of Pr. Casanova, coordinator of the clinical trial)

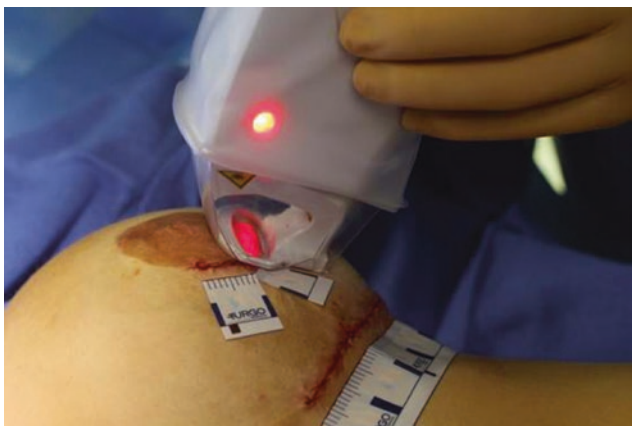

Fig. 59.2 The 1210-nm laser diode laser system UrgoTouch® procedure. The laser treatment (only one pass over the incision) is performed in the operating theatre, when patients are still under general anesthesia. The target cutaneous zone is secured by the application of safety strips containing high-technology microchips. These microchips enable the laser shots and prevent any overdose. The sterile strips are positioned along the sutures just before the laser shot. The laser shot duration is determined and controlled by the laser software itself, based on the patient's skin temperature detected by the embedded pyrometer of the device. This technology ensures the automatic discontinuation of the shot when the target skin temperature (53 ± 3°C) is reached, ensuring both patient safety and reproducibility of the shots. Neither preliminary parameter settings nor adjustments are required for laser shots. A training to the laser is received before its first use

59.2 Case Report Number 1

Description

A 37-year-old woman with bilateral breast hypotrophy and ptosis was seen in consultation seeking for breast lift. Physical examination revealed 85C-sized breasts with grade 2 ptosis based on the Regnault classification (Nipple areola complex [NAC] 2 cm below the submammary fold) and asymmetry (with a left breast more voluminous and ptosic than the controlateral one). The patient (1.70 m, 58 kg, BMI 20) had recently lost 15 kg and reported a previous 95C breast size. She had three children and no prolonged breastfeeding period. The patient had no history of surgery, allergy, or medications, but was a current smoker.

A bilateral breast lift with retropectoral implants and laser treatment was proposed to the patient. The benefits and risks related to the procedure were explained, together with the necessity to quit smoking, before the patient gave her written consent.

Methods

The surgery was performed in November 2017, under general anesthesia and orotracheal intubation. The patient had received antibioprophylaxy and perioperative compression stockings and she underwent preoperative marking. A similar procedure was followed for both breast. Infiltration of local anesthetics (narope-

ine 7.5 mg/mL + xylocaine/adrenaline 1%) was done in the targeted zone. The incision on each breast was made under the future nipple-areola complex flap, with a glandular transection, until it reached the pectoralis muscle. The retropectoral area was dissected to develop the submuscular pocket at the implant size and a sizer was used for the mastopexy. The breast was lifted using inverted-T scar and a superior NAC pedicle technique. The round micro-textured breast implants prefilled with silicone gel were then placed in its pocket (LSM RM 345, Sebbin) and the satisfying shape and volume of the breast were checked. Surgical incisions were sutured according to local standard procedures, using common surgical sutures (Monocryl™ 3/0 and 4/0 and Vicryl™ rapide 4/0, Ethicon) compatible with the laser use, according to the laser manufacturer's instructions.

The safety strips of the laser were positioned along the sutured incisions. The laser shot duration was determined and controlled by the laser software itself, based on the patient's skin temperature detected by the embedded pyrometer of the device. The laser treatment procedure was rapid and went unremarkable. After the laser treatment, the sutured incisions were secured with 2-octyl cyanoacrylate adhesive (Dermabond®, Ethicon) and covered by a dry dressing, before adding the postoperative compressive bra.

Postoperative care recommendations included daily shower and dressing change after cleaning of the sutured incisions with an antiseptic solution. The patient was asked to wear postoperative compression bra for 4 weeks after the surgery and received a prescription for analgesics. Sport activity resumption was allowed 3 months after the surgery.

Results

No complication was reported during the procedure and the early postoperative course. One month after the surgery and the laser treatment, the cosmetic aspects of the scars were already satisfying and the patient was pleased with this short-term outcome (Fig. 59.3).

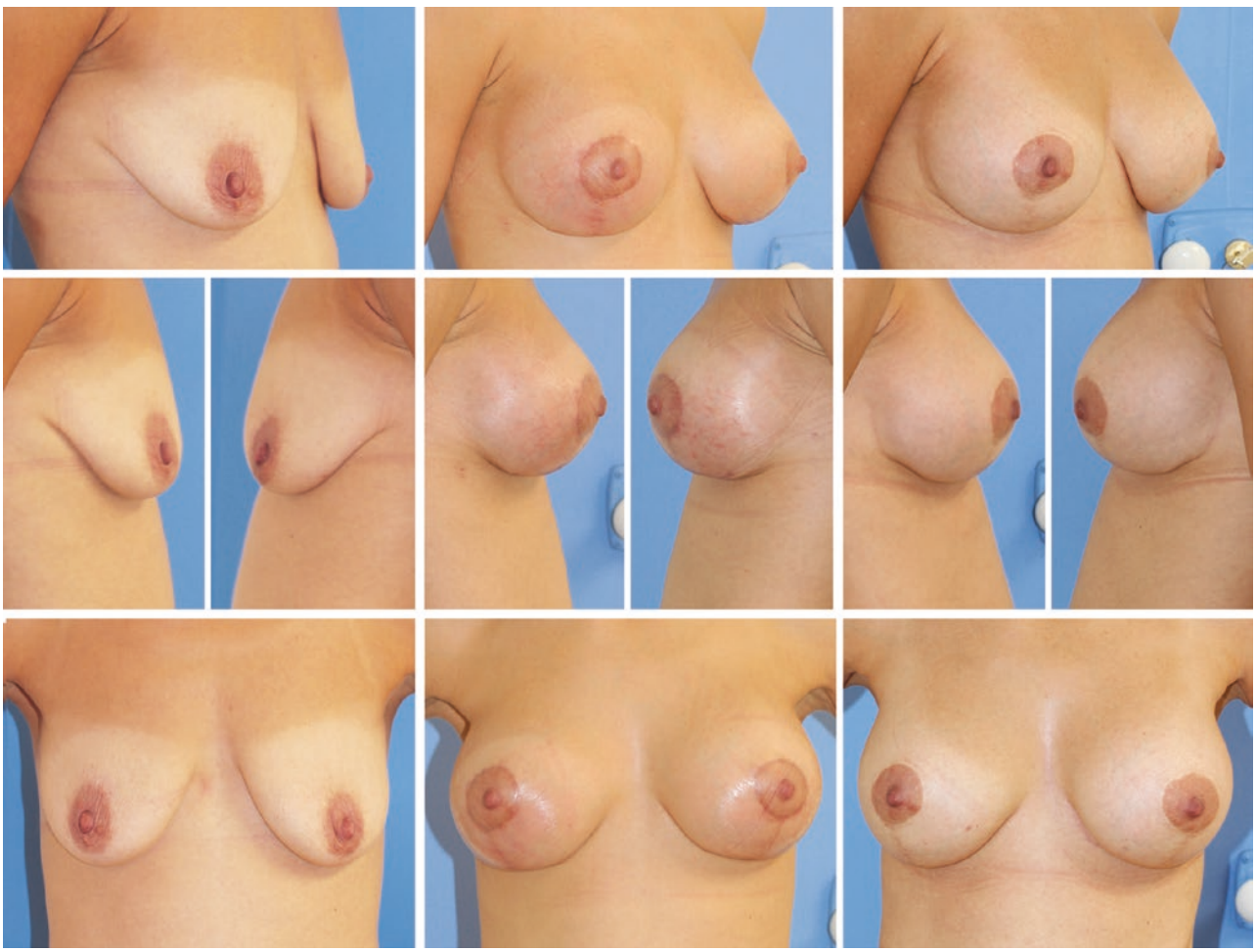

Fig. 59.3 Eighteen months' follow-up of the patient: anterolateral, lateral, and anterior views of the preoperative ptosis and of the breasts 1 month and 18 months after the surgery and the laser treatment

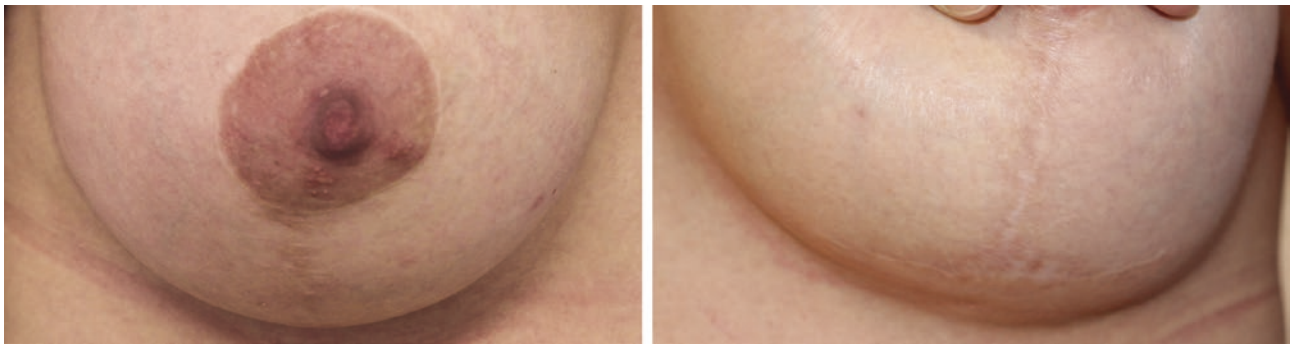

Fig. 59.4 Enlarged photographs of periareolar and vertical scars of each breast, 18 months post-surgery

At the 18-month postoperative visit, the horizontal, vertical, and periareolar scars became very discreet and the patient expressed her complete satisfaction for her new breasts (Figs. 59.3 and 59.4).

59.3 Case Report Number 2

Description

The second case report relates to a 26-year-old woman (1.64 m, 60 kg, BMI 22) seen in consultation for breast lifting after weight loss. The patient presented a bilateral breast hypotrophy and grade 2 ptosis (NAC 1 cm below the submammary fold). The breasts were asymmetric (more voluminous and ptosic left breast). The patient currently had B-cup breasts and wanted a breast augmentation to reach plain C-cups. The review of the medical and surgical history of the patient revealed a sleeve-gastrectomy in March 2013, no allergy, no particular familial medical history, and no current medications, but she was a current smoker. A bilateral breast lift with retropectoral implants and laser treatment was proposed to the patient. She was informed that she had to quit smoking and the benefits and risks related to the procedure were explained to her. The surgery was scheduled in January 2018, once the written consent of the patient was obtained.

Methods

The surgery was performed under general anesthesia and laryngeal mask. The procedure was globally similar to the one reported in Case 1. The glandular transection reached the pectoral muscle plan. The submuscular area was dissected to develop the implant pocket. Inverted-T incision and superior NAC pedicle technique was used and the round micro-textured breast implants prefilled with silicone gel were positioned in their pocket (LSM RS 270, Sebbin, for the right breast, and LSC 72330, Sebbin, for the left breast). The shape and volume of the breasts were checked and judged satisfying. The surgical sutures and laser treatment were performed as previously described. After the laser treatment, the sutured incisions were secured with steri-strips and covered by a dry dressing, before adding the postoperative compressive bra. The global procedure (including surgery and laser treatment) lasted 2 hours. The drains were removed the day after the surgery. Postoperative care recommendations were similar to the ones given in Case 1.

Results

No complication was reported during the procedure and the postoperative course. Two months after the surgery, the interest of an early laser treatment on the inflammatory stage of the wound healing process was noticeable. At the 12-month postoperative visit, the scars were barely detectable. The cosmetic aspects of the scars were very satisfying and the patient was pleased with the results of the procedure, at both the short-term and long-term visits (Figs. 59.5 and 59.6).

59.4 Discussion

To my knowledge, this is the first time the use of the automated 1210-nm laser diode UrgoTouch® is reported in mastopexy associated with retropectoral implant. The short- and long-term cosmetic results reached after a unique session, realized in the operating theater the day of the surgery, were very satisfying from both the surgeon' and the patient's point of view, and consistent with the results reported in the "SLASH" RCT conducted in the breast-reduction indication.

I first tried this laser treatment in October 2016 in a revision of breast and abdominoplasty in a patient of dark phototype skin presenting at my consultation with very wide scars. The aesthetic outcomes of the scars at 10 months were very satisfactory and the patient said that she was happy with the result obtained. Subsequently, I have treated the scars of more than two hundreds of patients in different indications: secondarily to breast

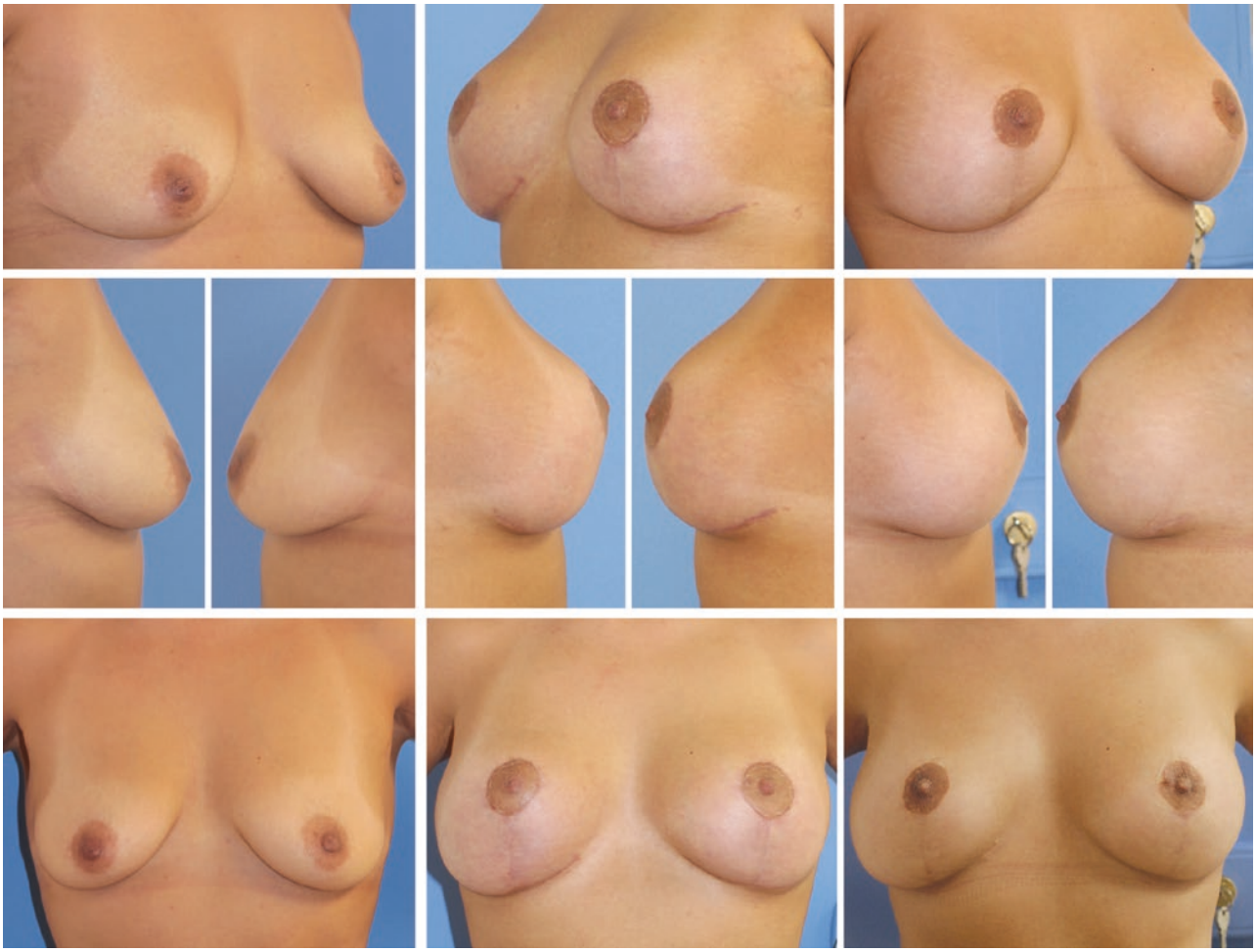

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Fig. 59.5 Twelve months' follow-up of the patient: anterolateral, lateral, and anterior views of the preoperative ptosis and of the breasts 2 months and 12 months after the surgery and the laser treatment

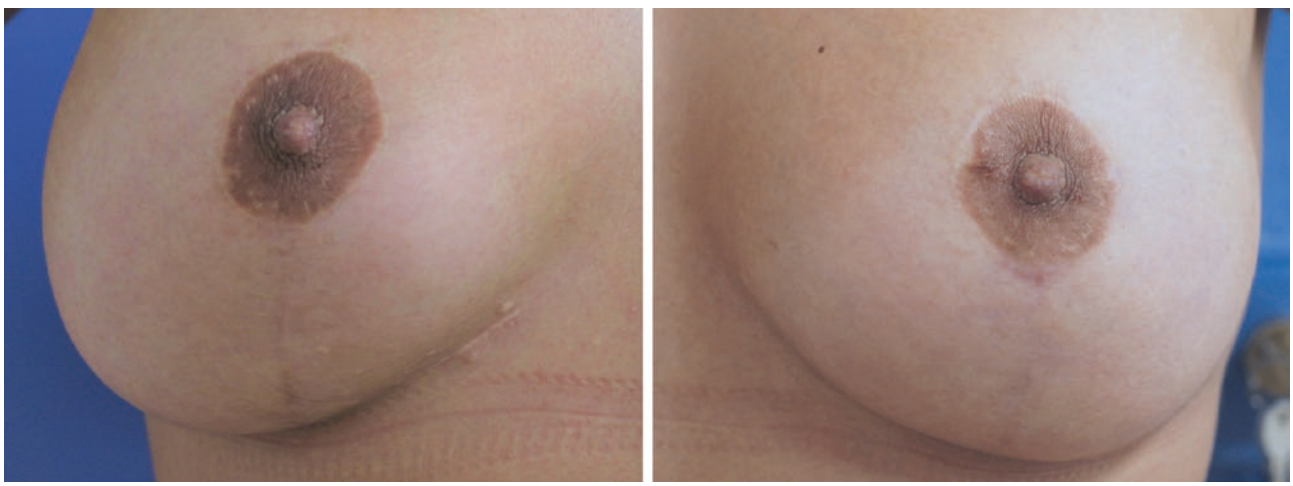

Fig. 59.6 Enlarged photographs of periareolar and vertical scars, 12 months post-surgery

augmentation operations [12], breast plasty, ptosis cure, prosthesis repair, abdominoplasty, brachioplasty, body lift, or gynecomastia, without any particular complication. The laser procedure takes a minimum amount of time (a few minutes, depending on the length of the scars), and I agree with the surgeons of the "SLASH" study who have judged the portable laser very easy to use. Indeed, the absence of parameter setting or adjustment really simplifies this type of procedure.

I always explain the limits of the procedure to my patients during the consultation prior to the surgery and laser treatment, in order to clear unrealistic expectations. Consequently, till today, none of my laser-treated patients were dissatisfied and their testimonials, collected in postoperative consultation or on my medical office's website, are all very positive. While this laser treatment can potentially be offered to all my patients, at the beginning I mainly proposed this procedure to patients with skin at risk or anxious by the scar result of their future operation, but now, it often happens that patients arrive at consultation demanding for it. The contraindications of the use of the laser 1210-nm laser diode UrgoTouch® are available in the manufacturer's instruction for use.

Reflective Questions

- Are there predetermining factors and risk for abnormal scarring?
- What are the guidelines for prevention and treatment of surgical scars and laser treatment?
- What are the contraindications for laser treatment?
- What is the position of laser procedure in your scar prevention strategies?
- How long does a laser treatment take? What formation is required for laser use?

Take-Home Messages

- Different strategies have been identified to minimize the aesthetic impact of surgical scars and prevention of abnormal scar formation should always be a first priority.
- The performance and safety of the automated, portable, 1210-nm laser diode UrgoTouch® treatment reported in real-life practice are consistent with the ones established in the randomised controlled trial SLASH.
- An early and unique laser-treatment session with UrgoTouch® significantly improves the cosmetic aspect of the surgical scars.
- Patients treated with the laser procedure expressed their satisfaction both at short-term and long-term follow-up visits.

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Burn Hypertrophic Scar in Pediatric Patients: Clinical Case

Roohi Vinaik, Joel Fish, and Marc G. Jeschke

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60.1 Background

60.1.1 Incidence of Hypertrophic Scars

Hypertrophic scarring has a greater incidence in darker skinned individuals and predominately occurs in American Indian/Alaskan Natives, followed by African Americans and Asians [1]. The highest risk of pruritus occurs in the latter population. Additional risk factors include young age, female gender, and those with wounds in particular anatomic locations such as shoulders, anterior chest, neck, upper arms, and cheeks. In the total patient population, hypertrophic scarring occurs in between 30% and 90% of burn patients, with a majority of these cases occurring in children [1]. The incidence rate of burn hypertrophic scars increases proportionally with the time to healing, with a recent study demonstrating that scarring risk is multiplied by 1.138 for every additional day needed for wound healing in pediatric patients, highlighting the need for rapid healing in scar prevention [2].

60.1.2 Prevention

Patients have a higher risk of development of hypertrophic scars in wounds that take longer than 3 weeks to heal. A study of 500 pediatric scald burns demonstrated that time to healing is a strong predictor of scarring, with similar results seen in a retrospective review of 59 pediatric patients and 41 adults [3]. Therefore, acute wound care is critical in ensuring rapid healing. Care for burn wounds includes early tangential excision and coverage with a split-thickness autografts, skin substitutes, or temporary xenografts or allografts. Since delayed healing may result from infection, topical application of antimicrobials may help prevent wound colonization. While time to healing is a strong predictor of scarring, patients can still develop hypertrophic scars despite healing earlier [2]. This highlights the importance of improving therapeutic strategies in addition to prevention.

60.1.3 Burn Depth

One of the ways to accurately treat burn scars is to reliably treat them in a timely fashion and determine burn depth accurately. Many modes of burn depth assessment have been used, including biopsy, thermography, and vital dyes, among other examples. The most widely used method for scald burns is the laser Doppler scanner, which was shown to improve prediction of the level of burns that will or will not heal by reepithelialization at 3 weeks.

60.1.4 Chapter Objectives

In this chapter, we discuss management options for pediatric hypertrophic scars. In addition, we provide a palmar hypertrophic scar case with a 5-year follow-up and list the interventions, which consist of laser therapy in combination with serial casting, grafts, and local flaps for treatment of scar tension. Objectives of this chapter include understanding risk factors for hypertrophic scar development, therapeutic options available, and rationale for particular treatment options in pediatric patients.

Clinical Case

A 3-year-old Filipino male initially presented to the clinic with a palm burn from a fireplace contact injury. The care of this wound consisted of once weekly dressings with a closed dressing technique to minimize pain and allow for undisturbed wound healing. The child remained as an outpatient for the entire course of acute care. The deep wound took a full 3 weeks to heal and the patient developed a right palmar contracted hypertrophic scar (Fig. 60.1). The patient presented with a raised, pruritic scar that remained confined within the boundaries of the wound area, as indicated in Fig. 60.1.

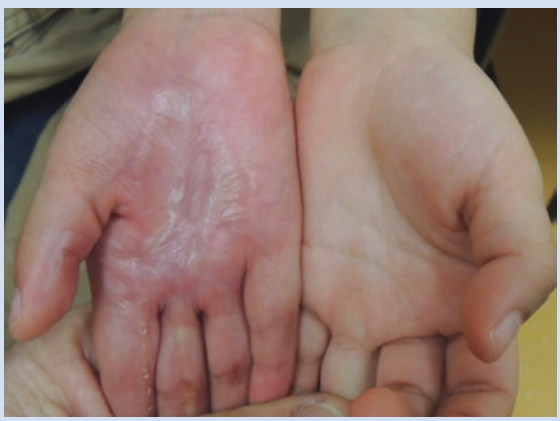

Fig. 60.1 Right palmar hypertrophic scar

Questions to the Medical History

- What are the primary risk factors for hypertrophic scarring in this patient?
- Is ethnicity a primary predetermining factor for development of hypertrophic scars?
- What are the features indicating that this is a hypertrophic scar as opposed to a keloid?
- Is this scar likely to progress over time?

Immediate Postintervention Situation

The patient presented with a scar contracture, which is one of the major detrimental effects of hypertrophic scars. Contractures of nonmatured scars can result in significant functional and developmental impairment and are frequently seen with scar hypertrophy. Conservative approaches guided by physical or occupational therapists have proven to be beneficial in these patients. Initially, scar massage in conjunction with moisturizers is commonly employed [3]. This may decrease pain, pruritus, scar thickness, and erythema, and moisturizers themselves decrease transepidermal water loss. Currently, scar massage and moisturizing with water-based lotions are the mainstay treatment for burn hypertrophic scars in children. Another approach is serial casting, which is used in burn patients to increase range of motion and prevent patient interference with the wound, an important concern in pediatric patients. With these considerations in mind, the patient was treated with conservative measures, including serial casting and scar massage three times a day. This treatment commenced immediately after the skin had healed in a verified burn center with rehabilitation specialists trained to treat this condition.

Contractures particularly in pediatric patients are challenging to treat. Distraction techniques and training of parents are challenges, along with the fact that the treatments are repeated multiple times daily, making this a difficult task for the children and their caregivers. In addition to treatment by serial casting/splinting to maintain the position, surgical correction may be indicated to restore function, especially if the patient has a persistent hypertrophic scar (>1 year). Techniques include scar-lengthening flaps and skin grafts, which are often delayed until the scar has matured unless the contracture interferes with the normal development of the child (use of the hand).

Intralesional corticosteroids such as triamcinolone acetonide are an option for treatment of hypertrophic scars and keloids [1, 3]. Corticosteroids can reduce pruritus and are effective in combination with cryotherapy in older hypertrophic scars and large keloids. In general, the corticosteroid is injected into the papillary dermis every 2–4 weeks until the scar is flattened. Although intralesional steroids are a common treatment for hypertrophic scars, they are rarely used for pediatric burn hypertrophic scars. They have limited utility due to the small dose that can be administered. In addition, the child needs to be sedated for the procedure in many cases. So, intralesional injections are usually reserved for small areas that are slow to settle after the majority of the burn hypertrophic scars have been treated.

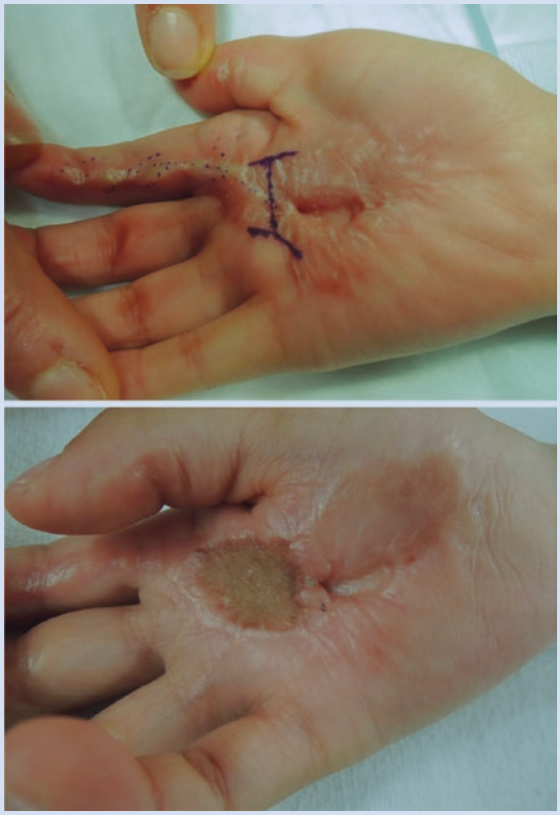

Fig. 60.2 Surgical revision and grafting of the scar

At this point of treatment, the patient's palmar contracture had stabilized. However, therapists were noting difficulty with grasping objects in the affected hand and significantly reduced palmar measurements compared with the other hand. As a result, the patient's scar was treated by surgical revision and grafting after the initial conservative measures (Fig. 60.2).

Questions for Intervention

- What is the advantage of serial casting in this patient?
- Are there any alternative conservative rehabilitative strategies?
- Are these conservative strategies effective?
- In addition to the points mentioned earlier, what are other potential detrimental effects of intralesional injections?

Late Postintervention Situation

Surgical revision is necessary in such refractory cases, and correction of linear hypertrophic scars can be done by tension-releasing techniques. Typical surgical techniques for hypertrophic scar contractures include Z- and W-plasties. Z-plasties are a scar-lengthening technique that can relieve tension and mitigate contracture, improving range of motion, while W-plasties can minimize the appearance of prominent linear scars [4]. Several rounds of surgical releases, especially when combined with other techniques such as laser therapy, can facilitate successful rehabilitation of scars without excision. Lasers initiate an inflammatory response and induce moderate damage to local vasculature, resulting in local hypoxia and remodeling [3, 4]. This, in turn, results in reduced scar erythema, pruritus, pain, and scar texture and stiffness [5]. Lasers can be further subdivided into ablative or nonablative types. Ablative lasers reach their dermal targets by ablating the epidermis, which increases the risk of further scarring and other complications. As a result, traditional ablative lasers are no longer used. However, an exception is the fractional carbon dioxide (fCO_2) laser, which is regarded as an ablative laser but can be considered as an alternative to the conventional ablative CO_2 laser [5]. Alternatively, nonablative lasers can target dermal chromophores while preserving the epidermis, minimizing complications. There are several types of lasers that are used in the treatment of hypertrophic scars. These include pulsed dye laser (PDL), alexandrite and diode lasers, intense pulsed light (IPL), erbium:glass (er:glass), infrared neodymium:yttrium aluminum garnet (Nd:YAG), and nonablative fractional lasers 1550 or 1565 nm (NAFL). However, these nonablative lasers have a relatively shallow penetration depth, limiting their use to certain anatomical locations or shallow scars in the case of Nd:YAG and NAFL. Decision for which type of laser to use is dependent on scar characteristics, pain, and scar texture and stiffness [5]. The procedure itself is short and requires minimal additional rehabilitation, an advantage over surgical interventions, especially in younger patients.

A year after the initial surgical revision and grafting, the patient had laser treatments combined with Z-plasties (Fig. 60.3). This was followed by additional Z-plasties 5 years later. Several rounds of surgical releases combined with laser therapy facilitated successful rehabilitation of the patient's scar.

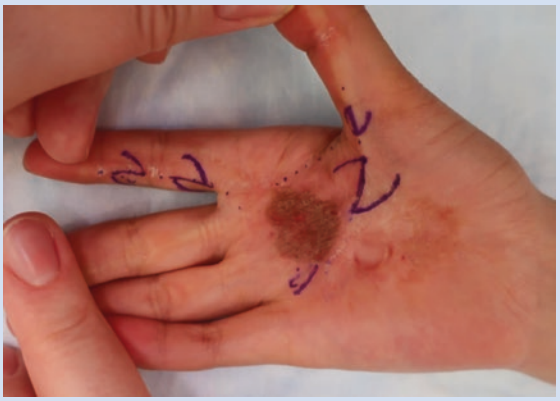

Fig. 60.3 Treatment with Z-plasties and laser therapy

Questions for Intervention

- Why was this surgical management of this patient delayed?
- What are the reasons for a surgical intervention at this point in treatment?
- What is the purpose of Z-plasties?
- What are the potential consequences of laser treatment in this patient?

Answers

The primary risk factors for burn hypertrophic scars determined from the patient's clinical history are young age and increased time to wound healing (>3 weeks). While there is a higher incidence in Asians compared to Caucasians, hypertrophic scarring in general primarily occurs in darker skinned individuals and American Indian/Alaskan Natives [1]. Although hypertrophic scars and keloids have similar underlying mechanisms, they can be distinguished by certain clinical features. Hypertrophic scars are erythematous, pruritic, raised lesions that remain confined within the boundaries of the wound area, as indicated in Fig. 60.1. In addition, the scar did not progress, unlike keloids, which continue to evolve over time.

The patient has limited range of motion and use of his hand due to scar contracture. Initial management with serial casting is beneficial in improving range of motion and softening the scar due to pressure. Casting provides pressure and stretch for an entire week giving caregivers a break, after which the cast is split and massage and stretching are resumed. The hand is placed back in the splint in between stretches, and the therapy

is stopped after 2 or 3 weeks. Alternate options like compression therapy are used to reduce scarring by decreasing blood flow and collagen remodeling at the site of injury, and few studies have shown that it can possibly increase scar pliability and thickness. However, there is minimal evidence regarding effectiveness of these strategies [3]. In addition, they may be difficult to attain due to the poor patient compliance. Techniques such as intralesional injections are avoided in these patients due to the need for repeated painful injections and side effects such as lipoatrophy, altered pigmentation, and blistering.

Surgical management was necessary to allow for normal developmental use of the hand. This was dictated by review with a skilled rehabilitation team that followed the child's developmental needs. Surgery is typically delayed until the scar has matured since early intervention is associated with high recurrence rates and morbidity [4]. Here, rounds of Z-plasties combined with other treatment modalities (e.g., lasers) help relieve tension and improve range of motion. Potential consequences of laser therapy in this patient are hyperpigmentation and discomfort, the latter can be managed with topical anesthetics, oral or intravenous sedation, or nerve blocks to improve treatment tolerance [4].

Take-Home Message

- Burn hypertrophic scars in children are challenging, with multiple modalities of treatment. Children pose special considerations and, in addition to the scars, developmental stages and growth often dictate the treatments.

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Clinical Case: Earlobe Keloid

Luc Téot

Contents

61.1 Medical History – 524

Further Readings – 526

L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_61

61.1 Medical History

A 23-year-old Asian-origin young male came after a long period of keloid of the left ear, secondary to a minor trauma during childhood. The patient was treated by three sequential surgical excisions followed by a recurrence, the last one being followed by YAG laser.

The patient abandoned the possibility to be adequately treated by any therapy during 7 years and was examined at the clinic (Figs. 61.1 and 61.2).

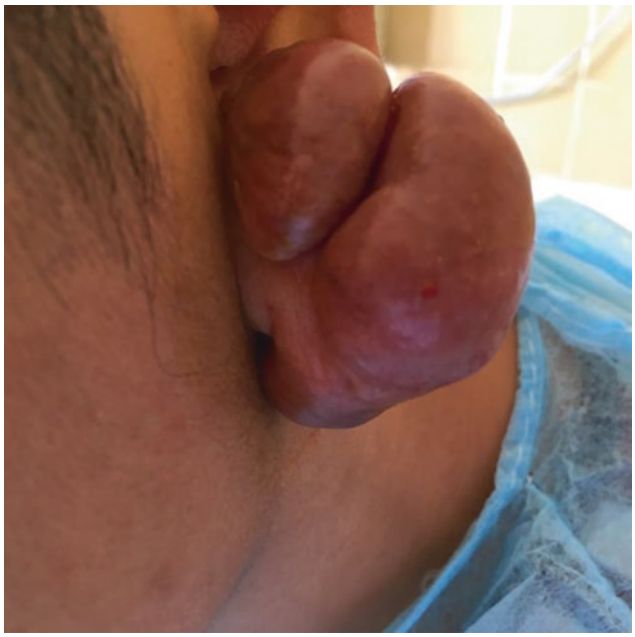

Fig. 61.1 Earlobe keloid at presentation (anterior view)

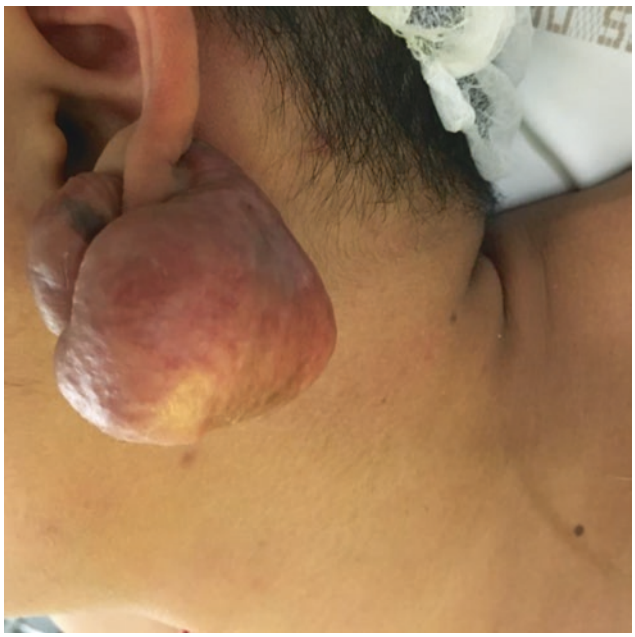

Fig. 61.2 Earlobe keloid at presentation (posterior view)

Questions to Medical History

- Is Asian origin a predetermining factor for earlobe keloid?
- Is keloid growing permanently or does it stop with age?
- Is there any guideline for surgical management of keloid?

Intervention 1

A series of 10 5-FU injections (5 mL) at a dosage of 50 mg/mL was administered at 3 weeks of interval.

The procedure was standardized as follows:

- EMLA cream application 2 hours before injection
- MEOPA (hilarant gas able to disconnect the patient from pain) administration during injection
- Hypnose adjuvant therapy during injection (hypnose works to deviate the attention of the patient and present a growing interest particularly on patients submitted repeatedly to painful stimulation) (Figs. 61.3 and 61.4)

Questions: Procedure 1

- Why 5-FU injections instead of corticosteroid injection?
- What is the rationale of the dose (50 mg/mL)?
- How painful is the procedure?

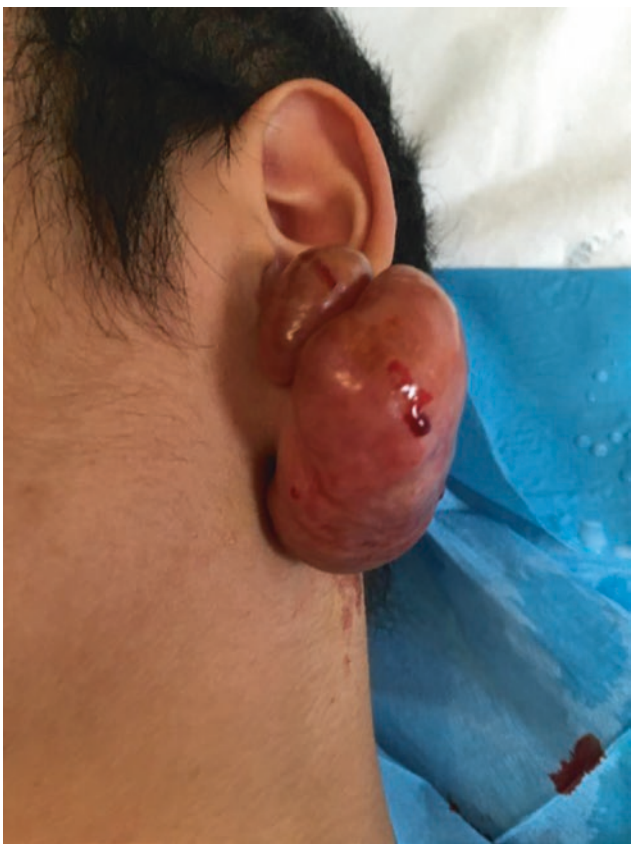

Fig. 61.3 Inflammatory aspect during 5-FU injections (anterior view)

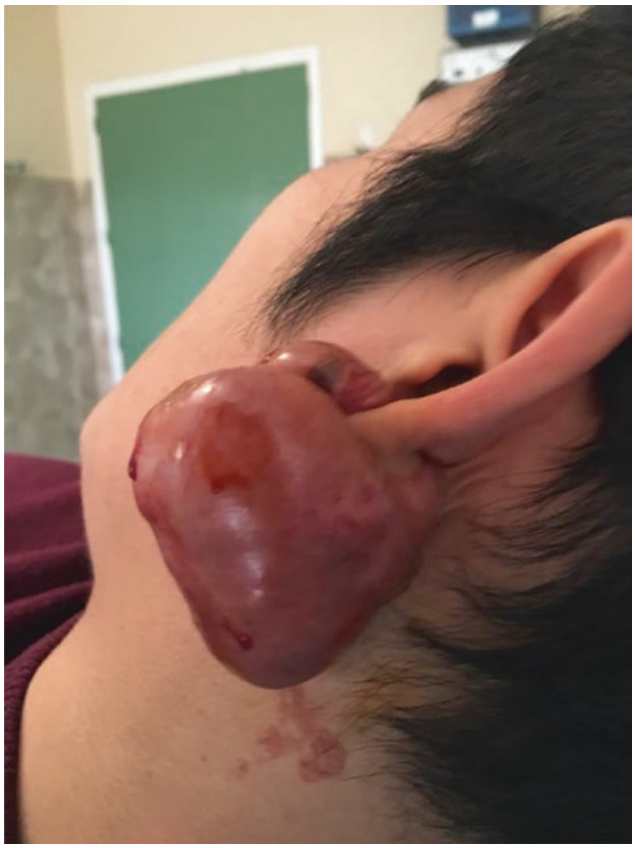

Fig. 61.4 Inflammatory aspect during 5-FU injections (posterior view)

Intervention 2

A surgical excision was administered with reconstruction of the earlobe with a combined approach anteriorly and posteriorly to the earlobe. A compression was made at fashion to ensure the mechanical situation during the 12 months postoperative period. The results were good with no recurrence. The scar presented redness after 3 months postoperation and then this inflammation was resolutive with time (Figs. 61.5 and 61.6).

Late Postintervention Questions

- Why to choose not to apply any postoperative therapy?
- What about the loss of substance of the ear?
- Is there a need for complementary surgery?
- Is further surgery contraindicated?

Answers

The prevalence of earlobe keloid is higher in the Asian skin than in the Caucasian skin even if the global risk of keloid is higher in the black-skin population. Keloids are, contrary to hypertrophic scars, growing permanently, reaching enormous sizes when left apart without adapted treatment.

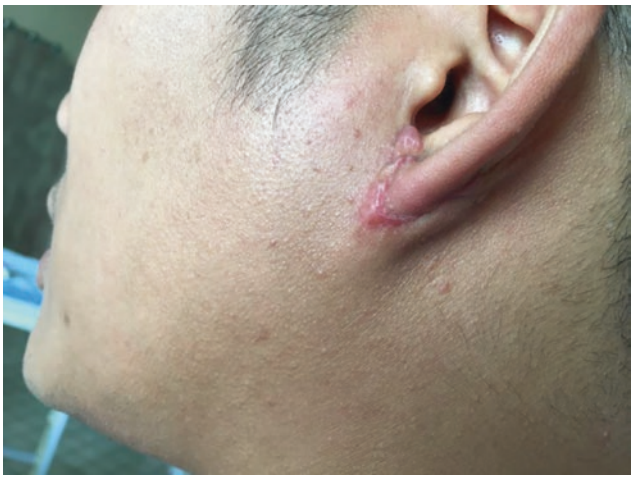

Fig. 61.5 Aspect of the ear 3 months postopertion, and some inflammation is still present

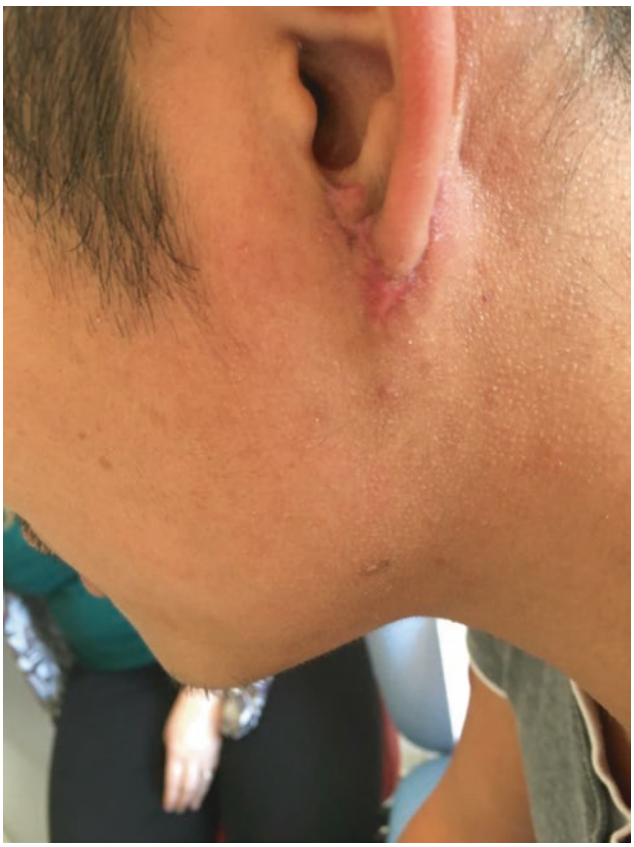

Fig. 61.6 Aspect at 14 months postoperation: the scar is stable and no recurrence occurred

Guidelines of surgical scar management mention the need for a combination of techniques, and most of them are being proposed after surgery (radiotherapy, cryotherapy, laser). Cryotherapy has also been proposed as an alternative to surgery. In this case the preoperative management using antimitotic agents

was proposed to limit the fibroblast postoperative proliferation 5-FU is used at a high dose (50 mg/mL) as suggested by several authors without systemic complications and the rhythm of injections (every 3 weeks) limits the risk of local skin necrosis.

This strategy limits the risk of recurrence after surgery and is proposed as a new option, in combination with preoperative injections and a close checkup of the local situation during 1 year.

The major inconvenience is pain induced by the injection, and pain management needs combined therapies (EMLA, MEOPA, Hypnose). During the surgical procedure the loss of substance of the earlobe had to be treated by reapproximation of the edges, a source of limited cosmetic difference compared to the contralateral side, but the patient refused to be reoperated, considering the high risk of worsening of the scar and of recurrence of the keloid.

Take Home Message

This clinical case reports the interest of a combined strategy using sequential intralesional chemotherapy before surgery in order to limit the rebund effect in highly proliferative ear keloids.

Further Readings

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Scars After Breast Reconstruction

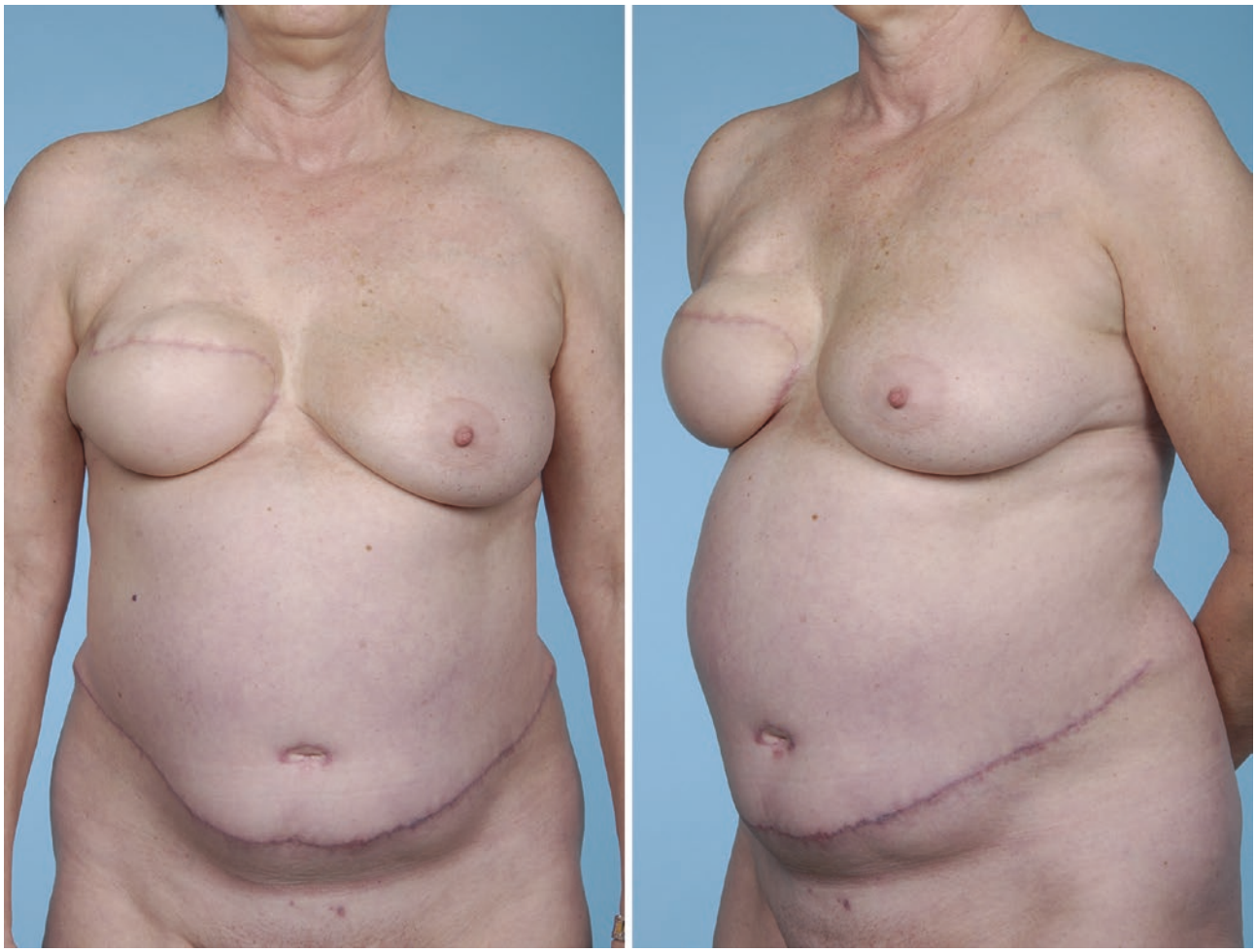
Wouter B. van der Sluis

Contents

62.1 Conclusion – 530

References – 530

L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_62



Medical History

A 47-year-old woman visited the outpatient clinic because of a scar on the right breast. She previously underwent deep inferior epigastric perforator (DIEP) flap breast reconstruction after nonskin, non-nipple-sparing mastectomy, chemo- and radiotherapy, because of breast cancer. She had attended her oncological regular check-ups without problems. She now complained of a painful scar on the right breast, which she also found unaesthetic.

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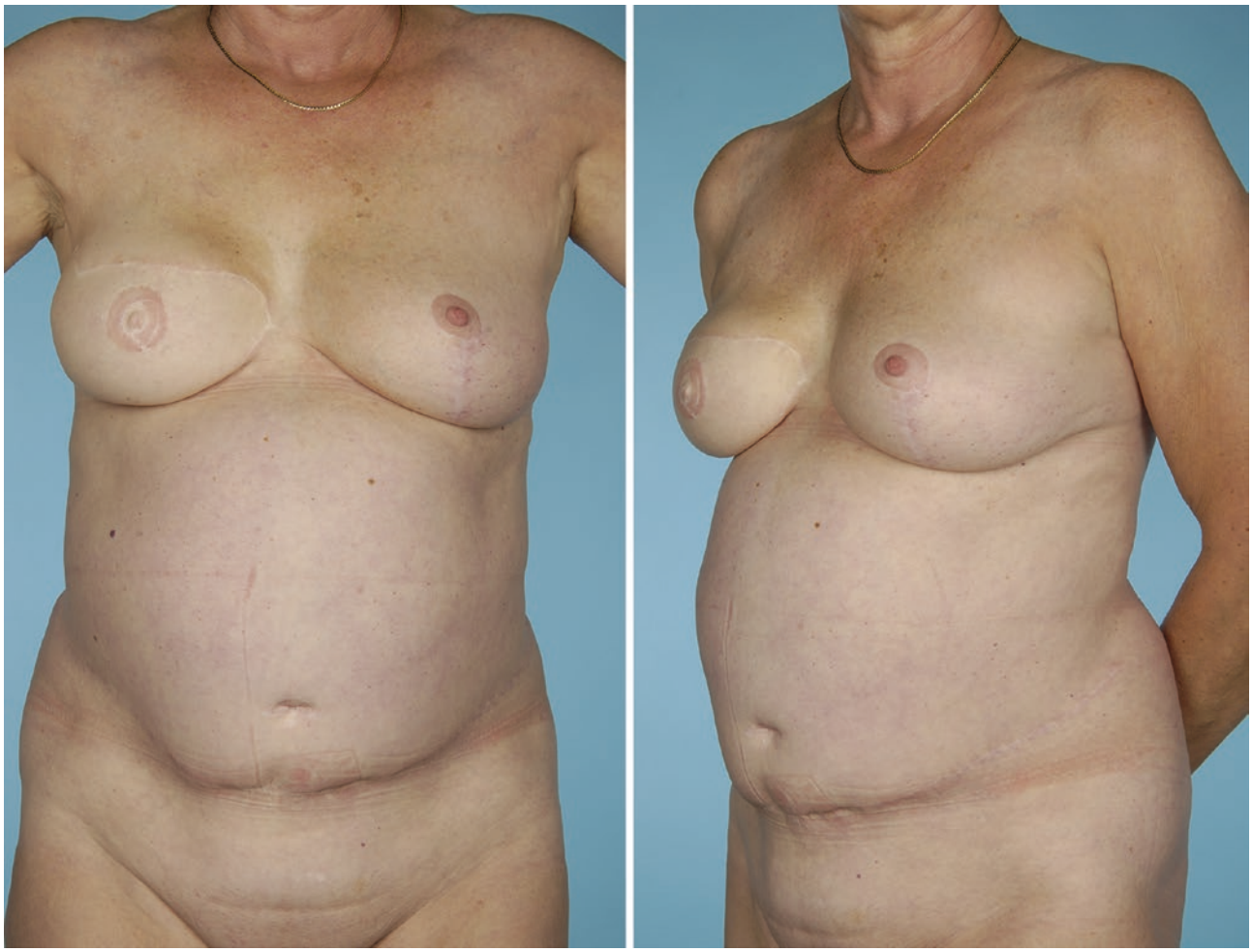
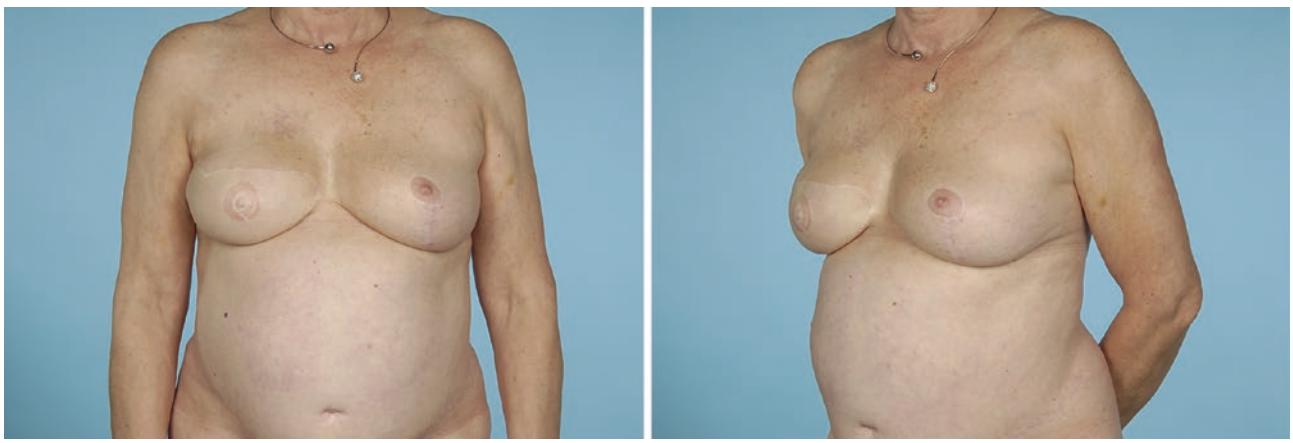
Questions (4 max)

- Q1. Which anatomic areas need to be examined as well during outpatient clinic consultation?
- Q2. Define the problems in terms of anatomy.
- Q3. What could be a (non-)surgical approach of the problem?
- Q4. What should always be checked in postoncological patients before surgery?



Immediate Postintervention Situation

In one surgical session, a donor-site dogear correction, scar lipofilling, and contralateral breast reduction were performed. Liposuction was used to correct the excess of fat at the region of the abdominal scar. The same fat was used for lipofilling of the upper pole of the right breast and the right breast scar. Nipple tattooing was performed at the outpatient clinic.



With 24 months of clinical follow-up, the patient was fully satisfied with the end result.

Argumented answers and explanation according to the five references (cited later): 20 lines

- Q1. Which anatomic areas need to be examined as well during outpatient clinic consultation?
- A1. The contralateral breast, the donor-site scar, and possible donor sites for future fat harvesting.

- Q2. Define the problem in terms of anatomy.
- A2. There is volume asymmetry between the left and right breasts. Right breast: lack of nipple, irregularities, and volume deficit of upper pole. Donor site: dogears, scar irregularities, and scar hypertrophy.

- Q3. What could be a nonsurgical approach of the problem?
- A3. Silicone application on all hypertrophic scars.

- Q4. What could be a surgical approach of the problem?
- A4. Donor-site dogear correction, nipple plasty or tattooing, scar lipofilling, contralateral breast reduction, or a combination of these strategies.

- Q5. What should always be checked in postoncological patients before surgery?
- A5. If they have attended routine oncological checkups.

62.1 Conclusion

There are different surgical options for breast reconstruction: immediate or delayed prosthesis-based reconstruction, oncoplastic reconstruction, fat grafting, and free or pedicled flap reconstructions [1–4]. Different techniques leave different scars on the breast. Nonsurgical approaches for breast scarring after reconstruction are silicone application and/or corticosteroid injections. Physical examination should always include examination of the contralateral breast, the donor-site scar, and possible donor sites for reconstructive purposes. There is a great role for autologous fat grafting in these reconstructive procedures. Other (minor) corrections can be performed simultaneously.

Take-Home Message

- Scar problems after various types of breast reconstruction are common. Many different corrections can be combined in one or multiple sessions.

References

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Atrophic Scars: Reinforcing the Flap Mattress Using Adipocyte Transfer in Paraplegic Patients at Risk of Pressure Ulcer Recurrence

Luc Téot

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63.1 Medical History – 532

References – 533

L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_63

63.1 Medical History

A 28-year-old man became paraplegic after a car accident 10 years ago. He presented repetitive pressure ulcers on the sacrum and the ischions, with successive surgical procedures (flaps, negative pressure, and skin grafting) on both sides.

He was successfully treated on the left side using a rotation flap for an ischiatic pressure ulcer, allowing to restart verticalization. The seated position was allowed after 2 months, progressively allowing a 12-hour-a-day seated position. The flap was followed every month and a progressive crushing of the fat under the ischial tuberosity was noted for a long time, with transient signs of redness appearing 1 year after surgery (Fig. 63.1) A Coleman technique using 300 cc of fat was proposed.

Questions to Medical History

- What is the rationale of using fat transfer in a patient who seems not to respect the postoperative restrictions?
- How to calculate the volume of fat to inject?

Intervention 1:

One year later, a Coleman technique was proposed and administered, using 300 cc of fat obtained from the abdomen by liposuction. The fat was centrifugated 3000 t/min during 3 min, and then the substratum was extracted and used as a filler (Fig. 63.2). The patient was authorized to remain seated 1 hour a day after 2 weeks and then progressively 1 hour more each month, till 12 hours a day.

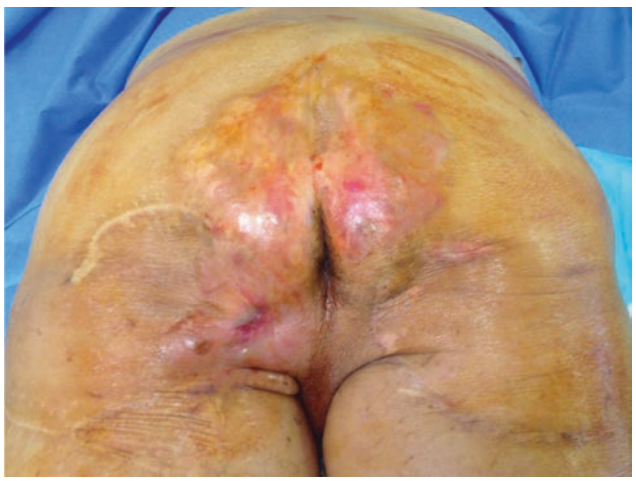

Fig. 63.1 Paraplegic patient operated 1 year before using a rotation ischial flap on the left side. The fat mattress under the flap skin begins to crush, exposing the patient to the risk of recurrence

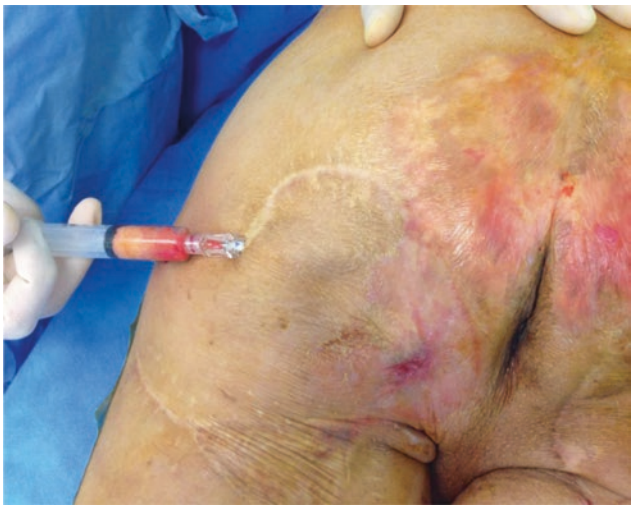

Fig. 63.2 Fat injection 300 cc, under the flap skin in the most exposed area when the patient is seated

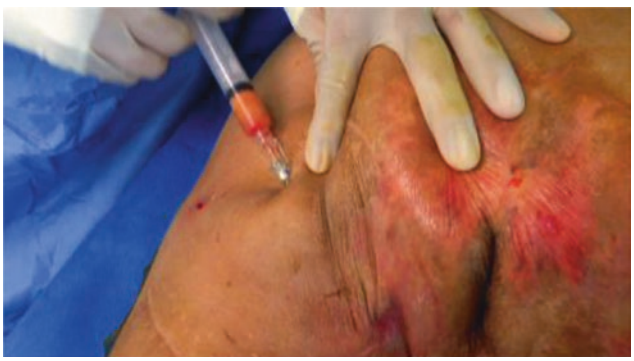

Fig. 63.3 A second 450 fat injection was administered 1 year later

Question Intervention 1

- Is there a risk to inject a large fat volume under a suffering skin?
- Which postoperative protocol is given to the patient in order to prevent the recurrence?

Intervention 2:

The patient was followed regularly, and a second injection was done 1 year after the first one (Fig. 63.3), in order to compensate a recurrent diminished fat volume. The injected fat volume was increased to 450 cc. The patient was informed to limit his seated position to a maximum of 6 hours a day and to check every day the ischial area, the cushion was reanalyzed and changed.

The patient did not present any recurrence after 2 years of follow-up.

Question Intervention 2

- Has the patient been informed about the risk of recurrence?
- How to adapt the behavior of the patient during the postoperative period in order to prevent the recurrence?

Answers

Fat transfer has been proposed since a long period of time as a filler [1], and used alone or in combination with PRP [2]. However, the literature suggests that transplanted adipocyte stem cells bring some mechanical properties [3] and help to regenerate the subcutaneous tissues [4], a reason why injections can be administered even under a lightly suffering skin. In this case the postoperative pressure applied over the flap and then over the fat injected area was too high and the patient was not correctly following the protocol. A second chance was given after some alarming signs of suffering on the ischial area had appeared. The volume of injected fat was increased and the therapeutic education provided to the patient was enhanced. The patient was particularly encouraged to limit the daily seating, which he finally accepted, a crucial point to prevent another recurrence.

Take Home Message

Adipocyte stem cells have provided some evidence in scar improvement. This chapter introduces the use of adipocyte derived fillers in scars presenting adherence to the underlying structures or depressions compared to adjacent areas. The use of fat grafting prepared with simple techniques is now considered as a useful adjunctive technique in resurfacing pathological scars.

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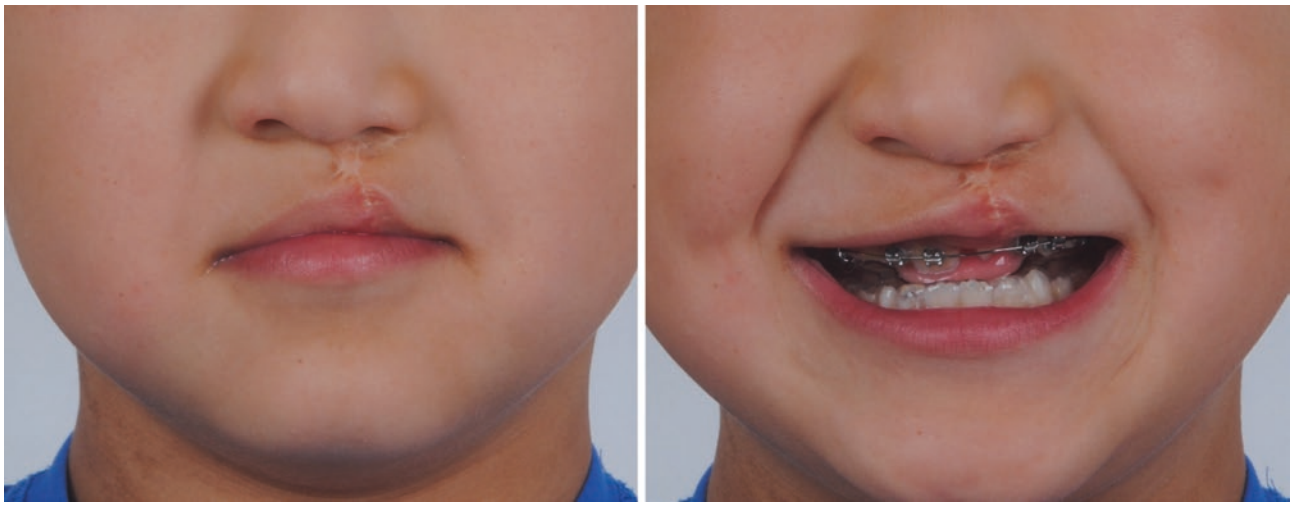
Secondary Lip Correction in a Cleft Lip Patient

Wouter B. van der Sluis and Johan P. W. Don Griot

Contents

Suggested Reading – 537

L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3_64



Medical History

A 11-year-old male visited the outpatient clinic with his parents because of unpleasing esthetic result after surgical correction of unilateral cleft lip and palate in China. There are no additional operative data available. The cleft palate and lip were not part of a genetic syndrome. There were no other comorbidities.

He stated that he was not pleased with the aesthetic result of the cleft surgery and that the main problem for him was asymmetry of the perioral area. There were no functional complaints in the domains of speech, eating, and/or drinking.

Questions (4 max)

- Q1. Define the problem in terms of anatomy
- Q2. What is the Rose–Thompson effect?
- Q3. What would be the surgical approach to this problem?
- Q4. What (non)surgical methods can be chosen to optimize postoperative scarring?

64

Immediate postintervention situation: Correction of these deformities in children is best performed under general anesthesia. Intubation is performed using an RAE (Ring-Adair-Elwyn) tube, which is a prebent tube that facilitates adequate reach of the operative area. The operative area is marked using skin marker that does not wash away or fade out during sterile exposition and surgery. The operative region is infiltrated with a mix of lidocaine and adrenalin.

The scar was excised using a concave excision pattern, making use of the Rose–Thompson effect. With one additional Z-plasty, adequate scar length was achieved. Reconfiguration of misaligned lip mucosa was achieved in the same session. The subcutaneous plane was closed using resorbable sutures. The skin was closed using skin glue.

Argumented answers and explanation according to the five references (cited later): 20 lines

- Q1. Define the problem in terms of anatomy.
- A1. Postoperative scar contracture of philtral scar with subsequent effect on nose and lip esthetics. Also, misalignment of lip mucosa was observed.

- Q2. What is the Rose–Thomson effect?
- A2. The effect of scar lengthening by using concave excisions of the scar, which is subsequently closed in a straight line

- Q3. What would be the surgical approach to this problem?
- A3. Use of the Rose–Thompson effect in combination with one or multiple Z-plasties or a combination of these strategies. An alternative approach might be using fat grafting of the scar; however, this probably provides a less predictable result.

- Q4. What (non)surgical methods can be chosen to optimize postoperative scarring?
- A4. Injecting the orbicularis oris with botulinum toxin, silicon application in the postoperative phase, using glue instead of sutures for tissue approximation.

Take-Home Messages

- Cleft lip scars influence lip, philtrum, and nose aesthetics.
- In secondary lip correction, cleft surgeons typically make use of the Rose–Thompson effect, one or multiple Z-plasties, or a combination of these strategies.

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L. Téot et al. (eds.), *Textbook on Scar Management*, https://doi.org/10.1007/978-3-030-44766-3

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