

Scars

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Abstract

Wound healing occurs as a response to disruption of the epidermis and dermis. It is an intricate and well-orchestrated response with the goal to restore skin integrity and function. However, in hundreds of millions of patients, skin wound healing results in abnormal scarring, including keloid lesions or hypertrophic scarring. Although the underlying mechanisms of hypertrophic scars and keloid lesions are not well defined, evidence suggests that the changes in the extracellular matrix are perpetuated by ongoing inflammation in susceptible individuals, resulting in a fibrotic phenotype. The lesions then become established, with ongoing deposition of excess disordered collagen. Not only can abnormal scarring be debilitating and painful, it can also cause functional impairment and profound changes in appearance, thereby substantially affecting patients' lives. Despite the vast demand on patient health and the medical society, very little progress has been made in the care of patients with abnormal scarring. To improve the outcome of pathological scarring, standardized and innovative approaches are required.

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Introduction

Every injury to the skin is followed by regeneration of the dermis and epidermis in a process known as wound healing. Wound healing is a complex and well-orchestrated series of chronological, overlapping stages that result in wound closure: haemostasis, inflammation, proliferation and remodelling¹. The goal of wound healing is to restore skin homeostasis after injury, and in many cases the normal process of remodelling will take place and result in a normotrophic scar, one that will result in a flat pliable appropriately coloured scar. However, depending on the extent and depth of the injury, wound healing can result in scar formation with varying degrees of severity (Box 1 and Fig. 1). Excessive scars, such as hypertrophic scars and keloid lesions, can form as a result of dysfunction of the wound healing process, after any skin insult that involves the deep dermis, including burn injury, lacerations, abrasions, surgery, piercings and vaccinations¹. Therefore, understanding of the wound healing processes in a range of conditions is essential to provide adequate care and to develop clinically relevant therapies.

Box 1

Scar types according to the international scar classification

- A normal scar is flat and pale without itching and not enlarged.
- An immature scar, frequently observed in children, is a mild transitory elevation of the scar, becoming red, sometimes itching, presenting a slight augmentation of the density. This scar will normalize after a variable period of time, reaching full maturation in 18 months to 2 years in some patients.
- An atrophic scar can develop by a separation of the dermal edge with preservation of epidermis continuity. These scars are often observed in adolescents after skin resection for benign tumours on the back.
- A hypertrophic scar is a scar proliferation staying within the limits of the edges of the initial scar, with progression starting 1 month after the complete healing, growing for 5–6 months and presenting a plateau with a slow decrease of the inflammatory signs, progressing after 1 year (sometimes more) to a stable scar having lost its inflammatory signs. It may be linear after a surgical incision or widespread after burns. Hypertrophic scars are usually red, itching and elevated.
- Keloids are characterized by pseudo-tumour proliferation extending over the edges of the initial wound, and they keep growing in time, some of them reaching high volumes. They are observed more over the thorax, on the earlobes and the neck. Minor keloids form with mild elevation over the scar edges; major keloids form large 3D excessive tumour-like growths that continually proliferate.
- Scar contractures are frequent in burns, with bands of hypertrophic retractile scars limiting joint movement. Their mechanical force is strong enough, when not correctly managed, to impact the growth plates of diaphyseal bones, leading to permanent deformities of limbs as children grow¹⁹⁰.

Hypertrophic scars and keloid lesions are pathophysiologically different; however, it is not always possible to differentiate the two different scar lesions on initial presentation as they can clinically behave similarly and look similar.

Hypertrophic scars usually present in anatomical areas of high tension (pre-sternum) or across joints (areas with the potential of contracture) as firm, red, elevated, pruritic (itchy) scars¹. Hypertrophic scars remain within the boundary of the original lesion, becoming progressively obvious over the first 12 weeks after injury and frequently regress within 2 years².

Keloid lesions can occur at any anatomical site and can be seen in areas of high mechanical stress after any form of deep dermal injury³. Keloid lesions are benign, fibroproliferative, exophytic outgrowths, extending beyond the boundary of the original lesion; they do not regress with time and will often continue to expand locally¹. Keloid lesions are most frequently observed in genetically susceptible individuals and are more prevalent in dark-skinned patients and those with a familial history of keloids⁴. It has been demonstrated that certain ethnic groups such as Black people, Hispanic people and East Asian people suffer more frequently from keloid lesions¹. Although genetic predisposition is a risk factor for initiation and development of keloids, most keloids start with an injury; however, some keloids can start spontaneously or after a minor trauma or even from an infection such as acne⁵. It is hypothesized that the initial physiological response within the individual after injury (for example, inflammation) is the essential component for the development of the scar in an already susceptible individual.

These excessive scars have substantial effects on patients, and can cause pain, pruritus, contractures (tightening of skin and/or abnormal bands of the scar) and recurring infections³. Excessive scars affect a patient's quality of life (QoL) and mental health long term⁶. In the UK alone, the cost in the public health-care system for clinical management of skin scarring and wounds is US\$155 per inhabitant, based on the price level of 2018 (ref. 7). This adds up to \$10.3 billion annually in the UK and, based on numbers of inhabitants, the US equivalent would be five times higher. However, despite the burden on health-care systems and the negative affect on patient QoL, challenges remain in developing consistently effective treatment strategies for the care of patients with keloids and/or hypertrophic scars.

This Primer provides a comprehensive introduction to scars, including epidemiology and the mechanisms of wound healing and how this creates scar tissue in place of the original skin barrier. This Primer also discusses several diagnosis methods used to classify the type of scar as well as grade its severity. Finally, the Primer discusses the vast number of treatment options and how scarring affects a patient's everyday QoL.

Epidemiology

There are no accurate data on how many individuals are affected by scar formation each year. It is estimated that annually, 310 million people undergo surgery, most of which is performed in high-income countries⁸. Further estimates indicate that 143 million additional surgical procedures would be required in low- and middle-income countries, but are not performed owing to inaccessibility of surgical treatment⁹. Scar formation is a relatively common postoperative complication; however, the prevalence of post-surgical pathological scar formation is not a standard-of-care outcome measure.

An international survey showed that >85% of scars were caused by either an accident or general or orthopaedic surgery¹⁰. Other causes were

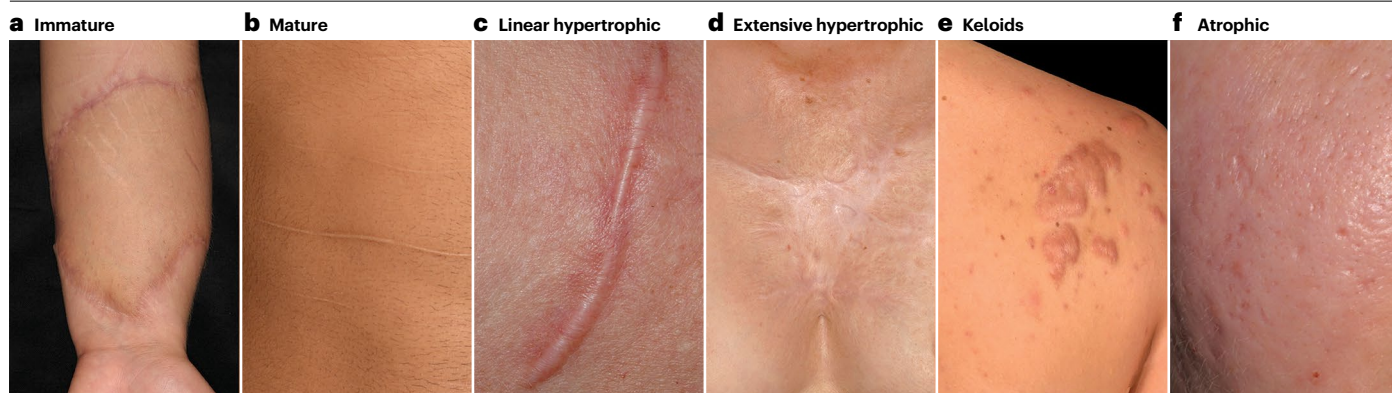


Fig. 1 | Presentation of various scar types. Immature (panel a), mature (panel b), linear hypertrophic (panel c) and extensive hypertrophic (panel d) scars, keloids (panel e) and atrophic scars (panel f). Reprinted with permission from ref. 189, Wiley.

skin excision, restorative surgery or cosmetic procedures. Scar formation can also occur after burns¹¹ or as a consequence of skin conditions such as acne; 95% of individuals with acne are affected by scars¹².

Keloid lesions

Prevalence. Although the relationship between skin colour, pigment and keloid formation is not entirely delineated, it has been shown that people with darker skin have a higher incidence of keloids¹³. The prevalence of keloid lesions among people of African, African American and Hispanic origin is between 5% and 16%¹⁴, in Asian people it is ~0.1–1%¹⁵ and in European and North-American people prevalence is <0.1%¹⁶. Genetic components are thought to be involved in this difference, linking gene polymorphism, gene mutation and DNA methylation to keloid lesion formation¹³. Although no single gene has been shown to be responsible for keloid lesion formation, there have been multiple genes and genetic loci linked to keloid formation in a Japanese population as well as in a Chinese Han population^{13,17,18}. Immunoregulatory genes were differentially expressed in patients with keloid compared with healthy controls, and these genes were linked to cell cycle, ultraviolet (UV) response and drug resistance^{19,20}.

Patients with keloid lesions have been reported to suffer from a higher risk of developing skin cancers²¹: the overall risk of developing cancer was 1.49 times greater than for a control group without keloid lesions. Specifically, the risk of skin cancer was higher (relative risk factor 1.73 overall and 2.16 for men), and for women with keloids, a higher risk of pancreatic cancer was reported (relative risk 2.19)²¹.

Hormone involvement. Other systemic factors that are thought to be important for the formation of keloid lesions and keloid growth are hormone levels, with children and young adults 10–30 years of age having higher risks^{15,22}. The changes in sex hormones that occur in this age group and in other circumstances such as during pregnancy are thought to be instrumental in developing more pathological scars²³. Specifically, oestrogen levels have been linked to worsened scar condition, although evidence remains anecdotal²⁴.

The literature on sex differences is inconclusive. Women and girls are reported to have a higher incidence of keloids, specifically in the group with keloid onset at <15 years of age (ratio 2.7:1 cases)²⁵; however, other reports suggest that men and boys have a slightly higher risk than women and girls of developing more severe keloids¹⁴. Specifically for

acne keloidalis, a male to female ratio of 20:1 was reported²² associated with beard hair follicles.

Location of keloid lesion. Areas that experience an increased level of stretch, pulling or mechanical stress are at higher risk of development of keloids^{15,26}. In a Japanese population the highest numbers of keloids were found on anterior chest (48.9%), scapular region (26.9%) and lower jaw and/or anterior neck region (12.1%), areas²⁶ that experience relatively high levels of stretch when compared with lower leg or scalp areas, where keloids are found more seldom. Approximately 70% of keloid lesions in the head and neck area are found on the earlobes, indicating that earlobes are particularly sensitive to keloid formation²⁷. An explanation may be the increased number of piercings in earlobes. Keloid lesions in other parts of the head and neck area might result from small injuries related to beard growth and/or shaving, which could provide an onset of inflammation ultimately leading to keloid formation²⁷.

Other risk factors. Several other medical conditions have been associated with excessive keloid formation, including acne, infection of the skin, rheumatism¹⁴, as well as high IgE levels²⁸. In a Korean population, patients with atopic dermatitis were reported to suffer from keloids more often than patients without this condition²⁹. A recent study of UK Biobank data confirmed the association of atopic dermatitis with severe scarring, not only in participants of Asian origin, but also in participants with dark- or light-coloured skin³⁰. The link between systemic chronic inflammatory conditions and predisposition to poor scarring requires further exploration using strategies such as data linkage in cohort studies.

External factors such as low income (odds ratio (OR) 13.44) and severe rubbing (OR 8.65) of the keloids have been associated with the development of more severe keloids¹⁴.

Hypertrophic scars

Hypertrophy is a common scar pathology, defined as scar tissue with a thickness elevated above the surrounding skin³¹. Prevalence of hypertrophy is variable in all skin wounds; for example, it is reported to be ~35% in linear surgical wounds³² and up to 72% in burn wounds^{28,33,34}. This is hypothesized to be associated with the high and persistent level of inflammatory mediators present during the burn wound healing process³⁵.

Scars post burn. Burns are an important global public health problem, with most burns occurring in low- and middle-income countries³⁶. To highlight the extent of the problem, WHO data state that in India, more than 1 million people annually suffer moderate to severe burns³⁷. Consequently, burn scars contribute greatly to disability-adjusted life-years (DALYs) lost and morbidity³⁸.

Burn incidence shows worldwide variation; it is estimated that hospitalized burn injuries in Europe vary between 2 and 29 per 100,000 inhabitants³⁹. Globally, data from 2004 suggest that 172 per 100,000 inhabitants required medical treatment for burn injuries³⁷. Estimates of burn scar prevalence are even more difficult to extract. This is due not only to lack of registered data but also to differences in definitions and diagnosis of scars. Many aspects can be involved in defining scar pathology, from changes in appearance and texture compared with normal skin, functional problems and psychological consequences that affect social functioning and QoL. In the literature, focus is frequently on hypertrophic scars. Consequently, reports on prevalence of hypertrophic scars after burns vary from 32% to 72%^{28,33,34}.

Hypertrophy is not a static characteristic. Generally, burn scars can develop into hypertrophic scars, mainly visible as red, elevated and often itching tissue, between 3 and 6 months after injury¹¹. During the subsequent process of scar maturation, which can take up to 2 years or even longer, the hypertrophic aspects of the scar usually decline. Therefore, in reporting outcomes it is necessary to include a definition and time of assessment of hypertrophy^{11,40}.

Risk factors for burn scar development are very complex and not very well defined. General risk factors for burn scar formation include wound characteristics such as anatomical location of the wound, wound depth, time to healing and total wound area^{11,41}, as well as patient-related factors such as (young) age, skin type and potentially genetic predisposition³². Darker skin colours (IV–VI, as defined in the Fitzpatrick scale, which categorizes skin colour from I, very pale, to VI, very dark⁴²) are associated with more severe burn scar formation, but also skin type I is reported to lead to more severe burn scar formation⁴⁰. In a group of patients who underwent cardiothoracic surgery scars were evaluated using the [Patient and Observer Scar Assessment Scale](#) (POSAS) and overall opinion was that scores were significantly higher, thus worse, in patients with Fitzpatrick skin types I and IV–VI than in patients with skin type II or III⁴⁰. Next to specific skin properties and genetic factors associated with darker skin, the incidence of burn accidents is reportedly higher in African Americans (122 non-fatal burns per 100,000 inhabitants) versus white non-Hispanics (91 per 100,000)⁴³. This may be related to cultural, educational and socioeconomic factors, leading to higher prevalence of scar-related problems in skin of populations of colour. Inequalities in health have been shown to be related to factors of socioeconomic status such as income, education level and occupation⁴⁴. Not only does this seem to be the case between high- and low-income countries, but this disparity in health status and relationship to socioeconomic status is also noticed within high-income countries⁴⁵. Living in a rural area with limited access to health care is one of the risk factors of poorer health status, affordability of care is another. Specifically, for burn scar problems in a low-income country, timely access to adequate burn care was reported as a key important factor⁴⁶.

Besides scar hypertrophy, scar contracture is an important pathology in burn scars. In one cohort, reported prevalence varied between 38% and 54% at discharge from hospital care⁴⁷. In low- and middle-income countries, 60–80% of children with contractures live in rural or impoverished areas⁴⁸. Next to wound characteristics such as

wound area and depth, socioeconomic status, infrastructure and access to health care were identified as strong risk factors for late complications and contractures⁴⁸. Especially in low- and middle-income countries, contractures may have a strong impact on QoL as contractures can occur in close proximity to joints, impacting functional capacities, and in children, inhibiting adequate growth.

Surgical scars. Even though the prevalence of hypertrophy is lower in surgical scars than in burn wounds, with 310 million surgical procedures performed annually⁸, the patient population involved in surgical procedures is much larger than for burns; thus, this represents a substantial health-care problem. As with keloid lesions areas of high mechanical stress such as abdomen and chest, as demonstrated by biomechanical analyses⁴⁹, are at higher risk of developing hypertrophic scarring than areas of lower tension and lower risk such as the eyelids.

Mechanisms/pathophysiology

Skin healing is an evolutionarily conserved process in all mammals, with repair by scar rather than regeneration in all but trivial injuries⁵⁰. In humans, cutaneous healing after superficial epidermal trauma to the skin in disease-free, healthy individuals should result in complete repair and restoration of a fully functional epidermal barrier; however, injury beyond the basement membrane into the deeper layers of the dermis in humans (fetal regeneration is limited to skin injury sustained in approximately the first 24 weeks of gestation) results in dermal fibrosis and can potentially lead to pathological scar formation with total loss of original tissue function and structure⁵⁰. The regenerative process in skin healing observed during early fetal development produces new skin cells from stem cell reservoirs, resulting in regeneration and restoration of the cutaneous wound to the pre-injury state⁵¹. However, this regenerative capacity is deficient and absent in adult human skin⁵¹. Even though the process of healing in adult human skin is still regarded as a highly complex, coordinated set of events that involves distinct overlapping stages, comprising haemostasis, inflammation, proliferation and scar maturation and remodelling (Fig. 2). This process involves several different cells and cellular pathways⁵², primarily, keratinocytes, fibroblasts (in highly discordant states depending on tissue site)⁵³ and endothelial and immune cells (distinct stromal–immune linkages)⁵³, as well as signalling molecules and the associated extracellular matrix (ECM) components. Nevertheless, there is a dichotomy of outcome, in as much as inflammation is an important necessary step in the repair process, its presence has been linked with development of fibrosis and scar formation⁵⁴. Notwithstanding intrinsic genetic influences⁵⁵, an incessant continued inflammatory response (enabled by a pro-fibrotic extrinsic mechanosensitive microenvironment)⁵⁶ leading to hyperproliferation and deposition of excess scar tissue will ultimately lead to the development of abnormal pathological scars such as hypertrophic or keloid lesions⁴.

Phases of wound healing

Haemostasis. At the time of injury, there is an urgent immediate need for haemostasis, which is initiated by vasoconstriction followed by the aggregation and direct interaction of platelets with degranulation, initiating the clotting cascade to form a blood clot (fibrinogen crosslinked with fibrin)⁵⁷. This action of clotting not only prevents excessive blood loss, but also serves as a temporary scaffold that provides a chemotactic gradient to facilitate the process of repair and forms a temporary eschar as a barrier to reduce the entry of microorganism⁵⁸.

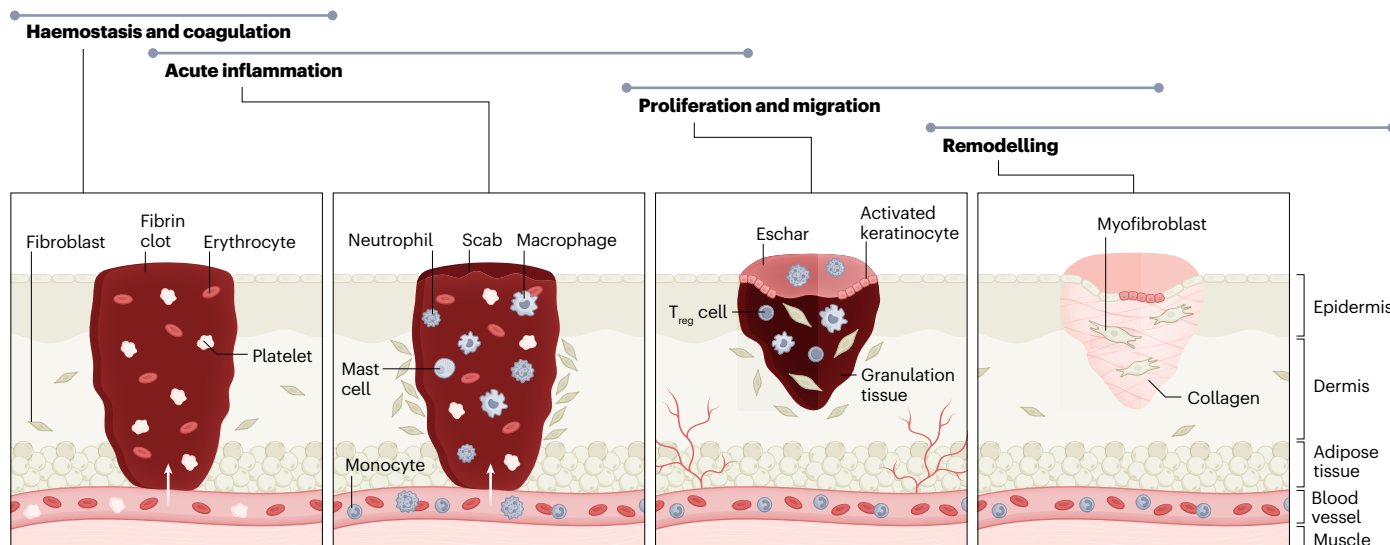


Fig. 2 | Phases of wound healing. Phases of wound healing follow a specific time sequence and include haemostasis and coagulation, inflammation, proliferation and remodelling. Platelet degranulation induces release and activation of various cytokines, which serve as chemotactic agents for the recruitment of, for example, mast cells, macrophages and neutrophils. During the proliferative phase, wound

granulation tissue is formed by new extracellular matrix (ECM). In physiological wound healing, a balance is achieved between new tissue biosynthesis and active reorganization of the ECM mediated by apoptosis (remodelling phase) that ultimately leads to scar maturation. T_{reg} cell, regulatory T cell.

Inflammation. The function and contribution of innate immune cells^{59,60} have become better understood in skin wound healing although the role of certain immune cells (adaptive) remains unclear. Immune cells are crucial to help orchestrate the inflammatory process after injury⁶¹. Immune cells migrate to the wound site, and the activation and recruitment of immune cells are initiated by and depend on signals generated by damage- and pathogen-associated molecular patterns as well as several key chemokines (such as CXCL7, CXCL4 (PF4), CXCL1 (GROα), CXCL5, CCL5 (RANTES), CCL3 (MIP1a)) and cytokines (such as platelet-derived growth factor (PDGF) receptors, and transforming growth factor-β (TGFβ)) released by degranulating platelets⁶². Neutrophils are recruited early to the wound site and are responsible for clearing invasive microorganisms through phagocytosis. Natural killer T cells (NK T cells) infiltrate soon after neutrophils, during the early inflammatory phase and produce chemokines that promote proliferation during healing such as by releasing macrophage inflammatory protein 2 (MIP2; also known as CXCL2) (ref. 63). Fibrocytes⁶⁴ are a unique subpopulation of leukocytes that proliferate at wound site after injury and become fibroblast-like cells (they have been associated with hypertrophic and keloid scar development). Mast cells respond to any form of cutaneous injury by arriving early to degranulate and release their molecular cargo (histamine and chemokines) near nerve endings and blood vessels, which act as pro-inflammatory molecules and increase proliferation and vascular permeability⁶⁵.

Proliferation. In the proliferative phase, wound granulation tissue⁵⁷ is formed by neo-matrix (new ECM) developed by signalling cues and with initially collagen III deposition – later replaced by collagen I – by the wound edge fibroblasts (locally resident or site-specific and blood-borne circulating fibroblasts) that become activated by exposure to various growth factors and are triggered to further proliferate, migrate and provide structure to form the wound granulation tissue⁵⁷.

As the granulation tissue forms, the fibroblasts continue to produce collagen to increase the tensile strength of the wound ECM⁶⁶. Indeed, during this process, increased inflammation-triggered signals upregulate biomarkers of fibrosis and can result in increased matrix deposition and formation of abnormal scarring⁶⁷. Fibroblasts also harbour site-specific inflammatory priming, which is shown to coordinate local immune cell function during the healing process in animal studies⁵³.

Re-epithelialization (formation of new epidermis)⁶⁸ starts from the stumps of skin appendages (sweat and sebaceous glands plus hair follicles) and from the cut wound edge epithelium (basal layers of the epidermis). Upregulated gene induction at the wound edge supported by several key growth factors (EGF and FGF) and proteases (matrix metalloproteinases (MMPs)) enable cell-to-matrix loss of adhesion (loosening of desmosomal junctions), cellular proliferation (new keratinocytes sourced by stem cells from the skin appendages and basal epidermis), epidermal migration to neo-matrix (fibrin-rich) and formation of migrating epidermal tongue leading to the formation and advancement of the neo-epidermis⁶⁸.

In addition to these locally present fibroblasts at the wound edge, a pool of circulating bone marrow-derived mesenchymal stem cells (MSCs)⁶⁹ also contribute to the overall sum of fibroblasts present in a wound bed. After exposure to TGFβ1 (refs. 70,71), some fibroblasts will transform into myofibroblasts⁷² (an intermediate cell between a fibroblast and a smooth muscle cell), with a uniquely specialized contractile ability that responds to mechano-stimulatory signals such as the focal adhesion kinase/extracellular signal-regulated kinase⁷³. During normal healing, the presence of myofibroblasts is limited both temporally and spatially. However, in fibroproliferative scarring such as in hypertrophic scars, there is persistence of the myofibroblast population of cells. Proto-myofibroblasts (α-smooth muscle actin (α-SMA)-negative fibroblast-containing stress fibres) appear in early granulation tissue and lay down first collagen bundles to be deposited in

the wound bed⁷². They differentiate to α -SMA-positive myofibroblast in response to exposure to growth factors such as TGF β 1 and increased stress in the ECM⁷².

Monocytes and macrophages arrive later and start to release cytokines and recruit fibroblasts into the wound site, initiate signals for angiogenesis and are responsible for removing dead leukocytes. Both tissue-resident macrophages^{54,74} (arise from different lineages, dependent and independent of haematopoietic stem cells) and circulating bone marrow-derived monocytes have an important diverse function (anti-fibrotic (M1) or pro-fibrotic function (M2)) in generating and resolving the inflammatory response⁷⁵. In addition, fibrocytes are considered to be hybrid mesenchymal–haematopoietic cells, having been identified in various fibrotic disorders such as keloid scars as the precursors of abnormal fibroblasts⁶⁴. $\gamma\delta$ T cells are thought to release certain growth factors responsible for epidermal migration. Naive T helper (T_H) cells (CD4⁺) can present as T_H1 (exposed to IL-12) or T_H2 (exposed to IL-4) phenotype in response to certain antigens and/or cytokines. In hypertrophic scars, it has been shown that there is a shift towards T_H2 cell phenotype with increased IL-4 production^{76,77}. The role of innervation in cutaneous healing and scar formation needs further exploration even though developmental studies suggest a reciprocal positive association⁷⁸.

Remodelling. The remodelling phase is characterized by the active reorganization (increase in total number of crosslinks between collagen fibres) of the ECM that leads to scar maturation⁷⁹. This is the inevitable final step in healing of cutaneous wounds, which typically results in dermal fibrosis when injured tissue is replaced with collagen type I-rich connective tissue (immature type III collagen during the early stages of repair is replaced by mature type I collagen)⁸⁰, which is spatially characterized by densely bundled oriented collagen fibrils. Ultimately, scar tissue is made up primarily of collagen type I fibres arranged in a parallel bundle⁸¹. The degree of fibrosis varies between anatomical sites (certain sites under increased mechanical tension such as the pre-sternum are more prone) and individuals (genetic predisposition)⁵⁵.

The fate of scar formation seems to be determined by the degree and severity of the inflammatory response (influenced by the mechanosensitive wound environment), impacting and resulting in aberrant keratinocyte–fibroblast crosstalk, abnormal fibroblast–myofibroblast

transformation, non-apoptosis of fibroblasts and excessive hyperproliferative ECM deposition⁸². Abnormal wound healing can result in the formation of the following types of scar: stretched, contracture, atrophic and raised scars in the form of hypertrophic and keloid scars.

In normal skin healing, completion of re-epithelialization is followed by a substantial decrease in cellularity of the granulation tissue and disappearance of myofibroblasts through apoptosis⁵⁷. Overall, a delicate fine balance exists between ECM synthesis and its degradation by MMPs. In addition, the expression of ECM components by dermal fibroblasts is thought to be influenced by epidermal–mesenchymal interaction during cutaneous healing³. For example, a delay in re-epithelialization after injury is a potential risk factor for hypertrophic scar development. The re-establishment of the blood supply to the wound granulation tissue is by ongoing angiogenesis influenced by angiogenic factors to enable endothelial cells to complete neo-vasculogenesis^{57,83}.

Clear understanding of the cellular mechanisms during healing and scarring is essential to develop therapeutic strategies; for example, in view of the role of inflammatory cells in cutaneous healing, we should aim to target these cells specifically and at specific time points to control the degree and extent of the inflammatory process and by association reduce fibrosis and aid in improvement of skin scarring outcome. Furthermore, the knowledge of scar turnover and collagen bonding has identified lysyl oxidase inhibition as a therapeutic target, due to its involvement in collagen stabilization⁸⁴.

Diagnosis, screening and prevention

Diagnostic criteria, classifications, staging systems

Scars can often be diagnosed according to their appearance and/or origin. This distinction leads to different categories of scar^{50,85}. Scars are dynamic, beginning in the immature phase with an obvious vascular component that is red and warm, then maturing over time with a reduction in the vascular component⁸⁶. Scars may be hyper- or hypopigmented on the surface, or have a flat or raised surface, be contracted or expanded or widened. Scars can be described as hypertrophic or atrophic depending on the thickness of the scar above the surrounding skin or depressed relative to the surrounding skin.

Differential diagnosis of keloid lesions and hypertrophic scars.

Classification of scars is mostly based on visual diagnosis, using scar scales, measurement of scar tensile properties and scar activity such as measurement of vascularity, but it can also include imaging techniques such as ultrasonography, CT scans, optical coherence tomography, thermal imaging and optical fringe projection^{87–90}.

Hypertrophic scars and keloid lesions can be differentiated histologically from normal skin by assessment of several features: flattened epidermis with reduction in the layers of keratinocytes, loss of rete ridges between the epidermis and dermis, papillary or reticular structural boundary and excess disordered collagen deposition within the expanded dermis (Table 1).

These histological differences may be used to diagnose hypertrophic scars and/or keloid lesions and differentiate them. However, for the routine clinical diagnosis, the differentiation of hypertrophic scars and keloid lesions is mostly based on clinical characteristics and patient history, as, specifically in keloids, any unnecessary trauma or surgical biopsy should be avoided to prevent worsening of the keloid lesions.

As aforementioned, although keloids and hypertrophic scars have been well defined histologically there has been a lack of classification and scoring of these scars based on visible inspection. Therefore,

Table 1 | Histological features of hypertrophic scars and keloid lesions

Normal skin	Hypertrophic scar	Keloid lesion
Normal epidermis	Flattened epidermis	Flattened epidermis
Normal number of rete ridges	Loss of rete ridges	Loss of rete ridges
No scar tissue	Excess scar tissue	Excess scar tissue
Collagen orientation basket weave-like fibrils	Thick parallel oriented bundles	Whorls of collagen and hypercellular nodules
Low contraction or presence of α -smooth muscle actin-positive myofibroblasts	Substantial presence of normal α -smooth muscle actin-positive myofibroblasts	Substantial presence of normal α -smooth muscle actin-positive myofibroblasts
Normal blood vessels	Increased angiogenic intensity	Occluded blood vessels

implementation of classification was needed and was developed. The visual classification was developed and added greatly to the diagnostic objectivity, consecutively to therapeutic interventions and the introduction of valid, objective, comparable multicentre trials. The first classification was proposed as an international consensus in 2002 (ref. 91) (Box 1 and Fig. 1), and includes the most important symptoms.

Grading. The main signs and symptoms include pruritus and pain, erythema and thickness, pigmentation disorders and scar contractures⁹¹. To quantify and compare scars, several assessment scales have been developed. In general, the assessed variables can be classified into four groups: colour (vascularization, pigmentation), metric variables (extent of area affected by scar tissue, height and volume), biomechanical properties (for example, elasticity, stiffness) and physiological changes (for example, hydration)⁹¹.

All scales assess multiple variables, of which the visual aspect (colour, thickness and roughness) is initially considered the most important. Progressively, the impact of the scar on the patient, such as psychological burden, pain, itching and contractures will become more important.

The Vancouver Scar Scale (VSS), was initially validated for burns scars in 1990 (ref. 92). Scar characteristics such as pigmentation, vascularization, pliability and scar height were rated, and higher scores (out of 13 points) indicate increased scar severity, and subsequently, it was used for a range of scars as a mean of assessment to report and track progress.

The more recent POSAS (Supplementary Figs. 1 and 2) includes two item scores, one to be completed based on the observer's assessment and the other one based on the patient's perspective⁹³. Although observer-rated scar characteristics are similar to those of the VSS, patients are asked to rate subjective measures that include pruritus, pain and scar stiffness. The POSAS represents a valuable tool to produce reliable documentation for all different scar types, at initial diagnosis and during treatment.

The Visual Analogue Scale (VAS) introduced in 2006 provides a very basic tool that enables the scar to be scored based on photographs along a 10 cm scale in which 0 cm represents normal skin and 10 cm represents a severe scar. Owing to its basic nature the VAS represents a very simple assessment tool and should potentially be combined with more comprehensive scales⁹⁴.

The Japan Scar Workshop Scar Scale (JSS) is the first specific keloid and hypertrophic scar scale⁹⁵. The first version of JSS was reported in 2011 (ref. 96) and was revised in 2015 (ref. 97). The JSS differentiates between physiologically mature scars, hypertrophic scars and keloids. It also helps to indicate the most promising treatment for the respective scar type and is used to monitor response to therapy and changes over time.

Innovative diagnostic approaches. A cutometer, a hand-held spring pressure sensor, may be used when diagnosing scars⁹⁸ for scar elasticity characteristics or colorimetric measurements for redness and pigmentation. Currently, these instruments are still predominantly used in the context of clinical studies; however, as smartphone applications become more feasible and reliable, application will become easier. The use of the touchscreen of a smartphone can be used to measure skin hydration via electromagnetic field assessment, colour measurement of skin or scar by converting the red-, green- and blue-based colours registered by the smartphones into CIElab values⁹⁹ and elastography measurements¹⁰⁰.

Scar prevention

Preventive measures should start at the time of the injury or before surgery, for example, in determining the position of the incision line before elective surgery (respect of Langer lines¹⁰¹). Understanding differential skin tension allows the placement of incisions parallel instead of perpendicular to the lines of tension within the skin, reducing tension in the sutured repair. Mechanical stress is known to stimulate scar formation and should be avoided as much as possible¹⁰². This can be accomplished during surgical interventions by using suture techniques that can reduce tension on the wound edges and underlying tissue¹⁰³. There are also other methods of reduction of mechanical stress such as use of compression, tension reducers over the suture edges or aspiration to reduce volume and pressure on the wound.

Also important are preventive measures to reduce the risk of infection; these can include rinsing, disinfection with antiseptics, systemic antibiotics and, if necessary, surgery to obtain rapid wound closure¹⁰⁴.

Every patient with keloid lesions and/or hypertrophic scars should individually conduct ongoing prevention and risk reduction. One of the central measures is application of sunblock¹⁰⁵ as exposure to sun has been demonstrated to be pro-inflammatory¹⁰⁶, can induce pruritus¹⁰⁷ and can have a negative effect on scar formation.

Another important aspect is education and knowledge. It is important for a patient to know their skin type and their risk of pathological scar formation based on family history and accompanying factors. This should be a red flag for care providers, and prevention in these cases is more focused on education than preventing a potential scar or keloid.

Scar prevention after burn injury. Burn injuries represent a substantial proportion of hospitalizations each year, and burns are reported as the second greatest cause of accidental mortality in children¹⁰⁸. Burn injury is known to be associated with a prolonged and substantially increased inflammatory response, which could be the underlying cause of poor scar outcomes. Efficient wound healing is followed by the introduction of compression garments, splinting, topical silicone therapies, scar tape to reduce tension and massage with a range of topical preparations¹⁰⁹. The evidence base for these therapies is often limited and sits within the space of clinical experience instead of being proved by randomized trial. However, the use of pressure therapy is widely practised with increasing evidence presented in meta-analysis but in trials with relatively low numbers and heterogeneity in the scars treated^{110,111}.

Although recovery and survival rates after burn injury are good, specific needs must be addressed, one of which is scarring control. The ongoing pain and itch also have to be addressed to reduce the ongoing stimulus for scar activity¹¹². An appropriate scar team approach is mandatory, combining all possible treatments, including pressure therapies, sophisticated techniques of massage and skin manipulation, adapted and regularly re-adapted psychological management including pain relief, psychological support, carried out by a comprehensive support team of nurses and physiotherapists¹¹³.

Management

Management of excessive scars should take into consideration age, activity (itchiness, redness, growth) and location of the scar¹⁹. Specific and individualized management is imperative for success. Suggested treatment algorithms for hypertrophic scars (Fig. 3) and keloid lesions (Fig. 4) have been developed and provide guidance in the complex care cascade.

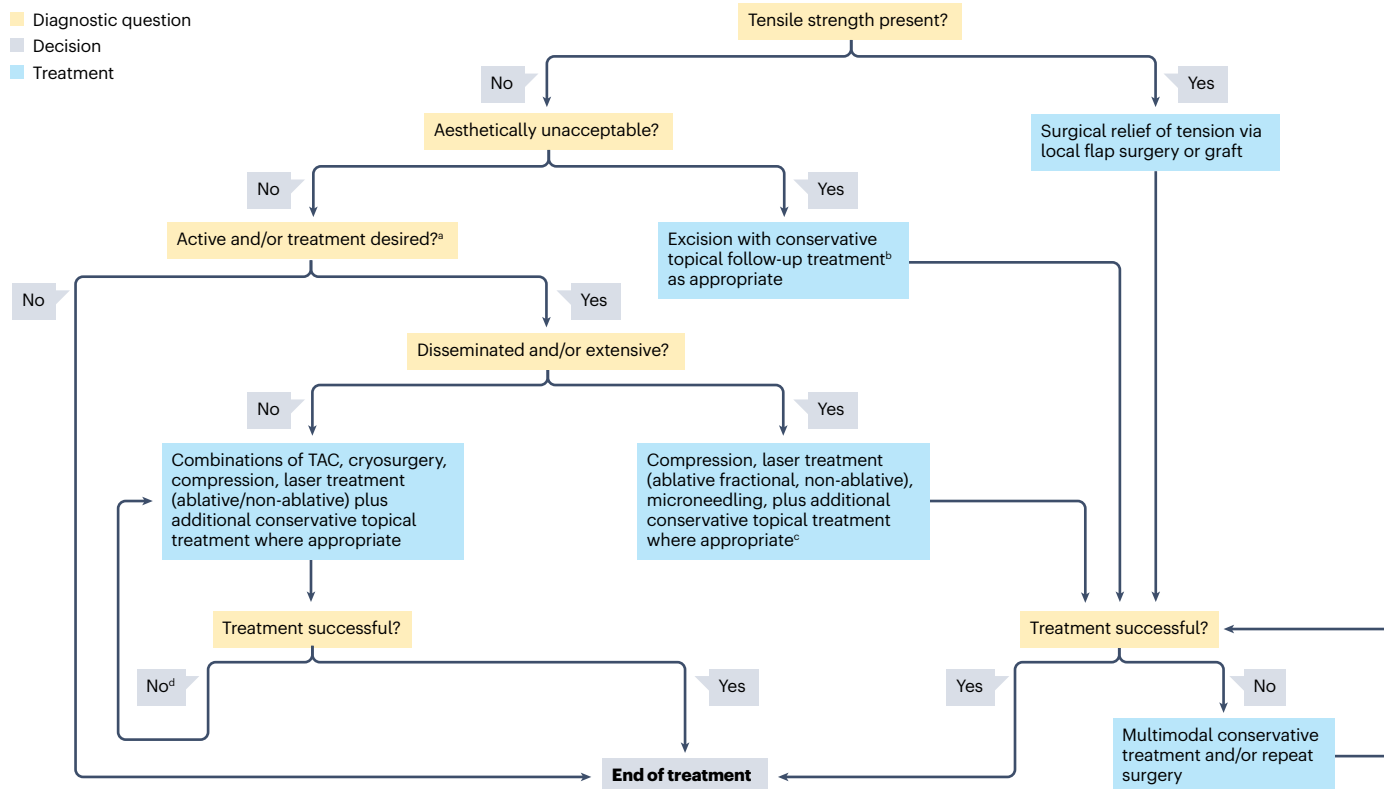


Fig. 3 | Proposed treatment algorithm for hypertrophic scars. Treatment algorithm based on recommendations of the German Dermatologic Society 2021. Treatment modalities include a wide range of treatment interventions from conservative intralesional cortisone injections, cryosurgery, laser,

microneedling to surgical interventions. TAC, triamcinolone (injection).

^aGenerally, after >1 year. ^bConsider risk–benefit ratio and additional risk factors.

^cIndividual prominent lesions: intralesional triamcinolone and/or cryosurgery.

^dTreatment modification. Reprinted with permission from ref. 137, Wiley.

When setting therapeutic goals, it is important to understand that, although keloid lesions usually never improve with time, some hypertrophic scars frequently mature over a 1- to 2-year period and may show significant flattening and softening without any additional treatment⁹¹. The goal of scar therapy is to demonstrate improvements that are independent of spontaneous resolution.

Conservative treatment

Conservative treatments, including scar massage, scar tissue moisturization and compression, are fundamental principles for scar treatment¹¹⁴. Massage^{110,115} and compression^{111,116,117} are central treatment approaches in burn injuries and have been shown in large trials to be very effective, and these treatment options should also be used in hypertrophic scars and keloid lesions.

Corticosteroid injection. In both hypertrophic and keloid scars, corticosteroids (triamcinolone acetonide, TAC) are used to reduce scar thickness by suppressing inflammation, collagen biosynthesis and proliferation of fibroblasts¹¹⁸. Systemic adverse effects are rare if injection is directly into the scar tissue¹¹⁸; however, local adverse effects can occur, such as atrophy of the subcutis (if injected too deeply) and the formation of telangiectasia¹¹⁸. Although newer studies on its efficacy are widely missing, the use of injected TAC remains first-line therapy for active, excessive scars^{119,120} (Fig. 5), and in instances where steroids

alone are ineffective in scar control, combined therapies may be used, for example, with cryotherapy^{121,122}.

Corticosteroid tape/plaster. Corticosteroid tape or plaster is the first-line therapy for keloid lesions and hypertrophic scars in Japan⁹⁵. The advantages of tape or plaster are that it is easy to use and is less invasive. Tape or plaster should be used as early as possible, before abnormal scar development, ideally at the point of epidermal restoration. Several months after treatment via tape or plaster, stiffness of scars may be decreased such that, if injections are undertaken, the tissue is softer and the pain of intervention is alleviated⁹⁵. Globally, several corticosteroid tapes and plasters are available, but recent analysis reported deprodone propionate to be the most effective in adults at improving scar appearance when other tapes would not^{123,124}.

Cryotherapy. Intralesional cryotherapy is used to non-specifically destroy abundant tissue within the keloid lesion or hypertrophic scar. Cryotherapy induces alterations in the microcirculation and causes apoptosis or necrosis of fibroblasts and myofibroblasts¹²⁵. It also results in localized dermal oedema, which often eases injections into stiff scar tissue if cryotherapy is performed before the injection¹²⁶. Adverse effects include pain, prolonged healing owing to blistering, hypo- or hyperpigmentation and potential reactivation of keloids¹²⁷.

Chemotherapeutic agents including 5-fluorouracil and bleomycin.

5-Fluorouracil (5-FU) and bleomycin are both used as antimetabolites in cancer chemotherapy and have been shown to effectively inhibit cellular proliferation¹¹⁸. Both agents have been used for the reduction of keloid tissue even though clinical trial evidence is scant¹²⁸.

Protocols vary between studies with regard to concentration, absolute doses and intervals between treatments; however, in all studies repetitive treatments are needed^{129,130}.

There is an increasing body of literature to support the combination of corticosteroid injections (TAC) and 5-FU, which are mixed in various ratios (9:1 or 3:1, 5-FU:TAC). This combination is associated with a reduction in recurrence of the lesion without increasing the side effect profile if injected directly into the scar tissue^{131–133}. Combination therapies may be best used if steroid alone fails to control the scar.

Other therapies. Calcium antagonists such as verapamil have been used for injection to control redness and pruritus and have shown some success as a third-line intervention¹³⁴. However, in a randomized trial that compared verapamil with steroid injection it was shown to have no consistent benefit¹³⁵.

Invasive treatment

Laser therapy. Lasers were initially used in scar therapy to facilitate resurfacing. This approach was inconsistent, with delays in secondary healing influencing the outcome¹²⁵. Lasers can be tuned to obliterate the vascular elements within the scar, and the use of the fractional laser has been associated with consistent positive results in scar treatment. The laser creates microthermal zones that trigger local healing responses and increased turnover in the dermal collagen. The mode of action is dependent on the wavelength used; the ultimate result is the induction of scar remodelling and scar maturation^{119,136,137}.

Several types of laser have been used in the treatment of keloids and hypertrophic scars, for example, ablative (fractional) CO₂ or erbium–YAG lasers, non-ablative fractional erbium–glass lasers, vascular lasers such as pulsed-dye laser (PDL) and Nd–YAG as well as pigment lasers such as q-switched ruby or picosecond lasers^{136,138}. Consensus papers indicate an increasingly important role for several wavelengths for various scar types, such as burns and traumatic and acne scars¹³⁹.

The Nd–YAG laser follows a comparable mode of action; however, owing to higher penetration depths, it may be superior for thicker scars¹³⁷. Usually, several treatment sessions are needed; some studies suggest treatments early after wounding whereas others use

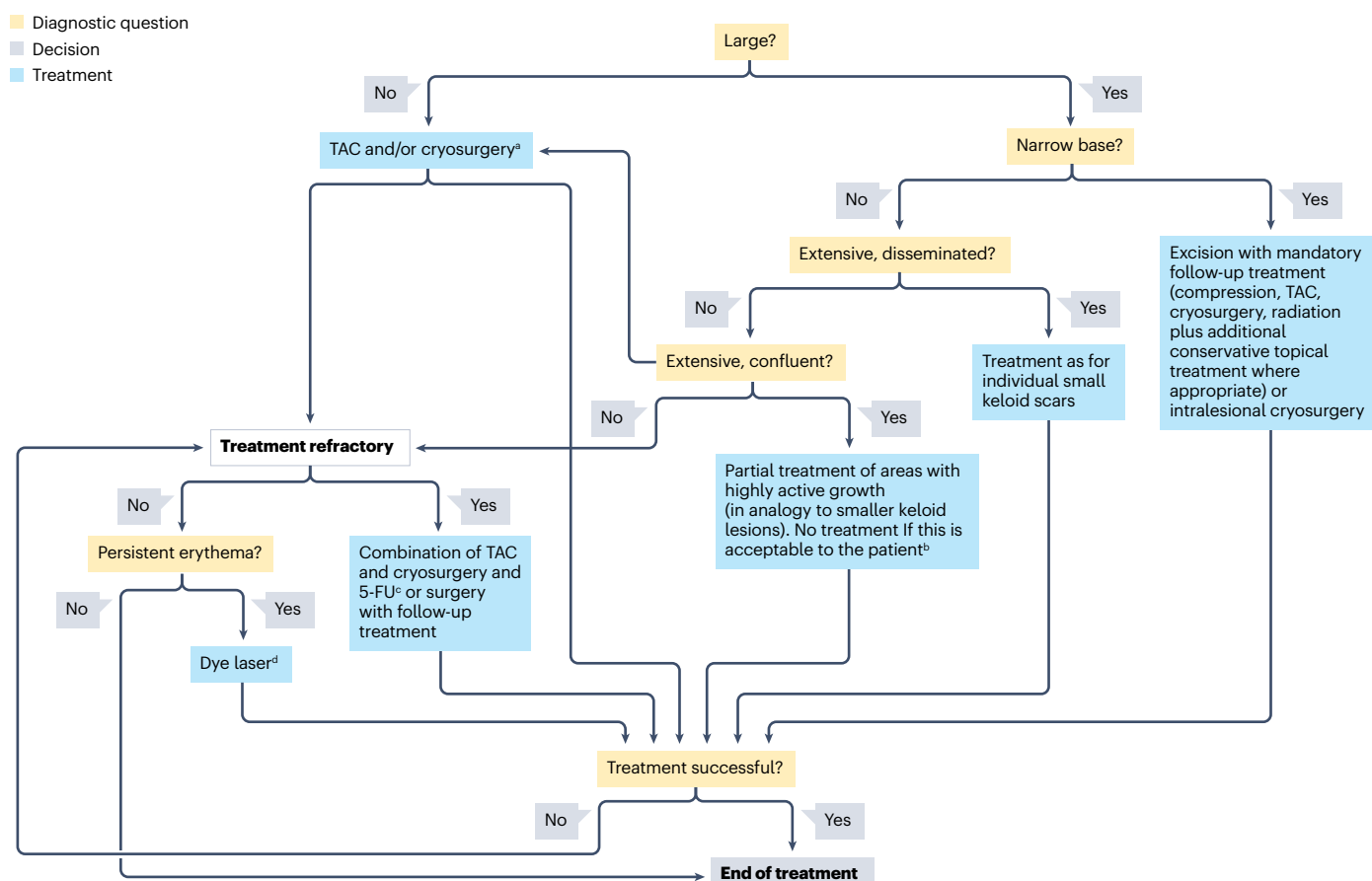


Fig. 4 | Proposed treatment algorithm for small and large keloids. Treatment algorithm based on recommendations of the German Dermatologic Society 2021. Treatment modalities include a wide range of treatment interventions from conservative intralesional cortisone injections, cryosurgery, laser, microneedling to surgical interventions. 5-FU, 5-fluorouracil; TAC, triamcinolone (injection).

^aAblative fractional laser therapy may be considered for non-active flat keloid lesions.

^bWhere appropriate: additional antiseptic or antibiotic treatment.

^cOff-label use. ^dIntense pulsed light (IPL) therapy for treating blood vessels or Nd–YAG laser (for deeper penetration and darker skin types) may be considered as alternatives. Reprinted with permission from ref. 137, Wiley.

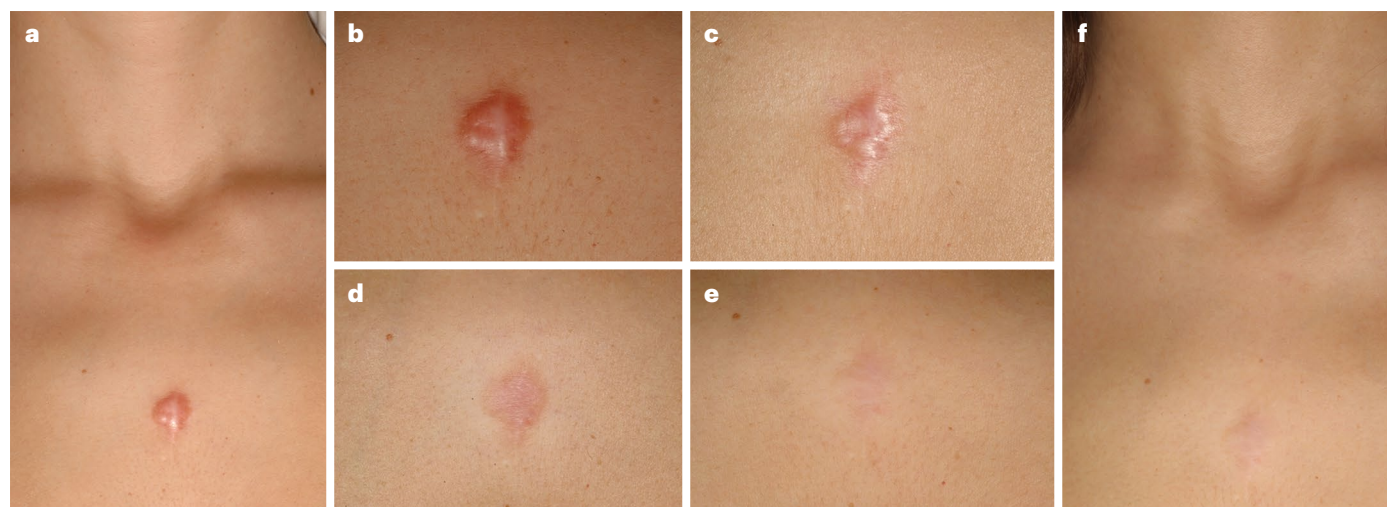


Fig. 5 | Keloid lesions on the chest of a patient during treatment course. **a,b**, Baseline photograph at initial presentation before initiation of combination therapy with cryotherapy directly followed by intralesional injection of triamcinolone (TAC). **c**, Result after three cycles of combined cryotherapy or intralesional TAC therapy before initiation of four pulsed-dye laser (PDL).

d, Result after PDL applications and continuous administration of silicone gel, demonstrating marked improvement of height and colour. **e,f**, No signs of recurrence or reactivation at follow-up 6 months after the last laser treatment. Reprinted with permission from ref. 126, © 2013 The Author.

the vascular lasers mostly for reduction of persistent erythema of pretreated scars for more cosmetic purposes.

Short-pulsed lasers with pulse durations in the nano- and pico-second range, for example, 694 nm (ruby) or 1,064 nm (Nd-YAG), may help to treat hyperpigmentation, particularly that resulting from traumatic tattoos or the inflammation itself in patients with darker skin (post-inflammatory hyperpigmentation)¹³⁸.

Erbium-glass lasers with a wavelength of 1,540–1,565 nm have also been shown to be able to improve shallow hypertrophic or atrophic scars such as linear scars or striae distansae; however, owing to their limited penetration depth, these wavelengths are not suitable for thicker scars¹⁴⁰.

Additional ideas include the use of laser-generated microscopic microthermal ablation zones to increase penetration through the skin's barrier for specific agents in scar therapy. Known as laser-assisted drug delivery (LADD) or transdermal drug delivery, this approach has already been widely used for treating some conditions, including non-melanoma skin cancer and photodamage¹⁴¹. Laser parameters need to be adapted to skin type, condition and drug; however, low densities of microthermal ablation zones are sufficient. LADD thus provides a promising technique that enhances the absorption of topical molecules (for example, TAC, 5-FU or platelet-rich plasma) while adding the synergic effect of the laser. However, study data remain partially contradictory, with some randomized controlled trials showing the efficacy of LADD, whereas other data did not reveal any significant differences in outcomes but demonstrated reduced adverse effects¹⁴². As adverse effects are rarely standardized in scar studies and in general well-designed representative studies comparing different protocols for comparable indications are missing, it currently remains difficult to generate clear recommendations on LADD scar treatments. In clinical routine, however, LADD using fractional CO₂ lasers for widespread hypertrophic scars is gaining more and more popularity among scar experts, simply owing to its ease of application.

Newer findings confirm the importance of early fractional CO₂ laser treatments^{143,144}, which may be initiated directly after suture removal or even directly before elective surgery in the area of wounding to prevent any unphysiological scarring. Treatment series of at least three to six sessions at 4-week intervals are being recommended^{143,145}. However, owing to the lack of large multicentre studies, protocols vary and are mostly based on the experience of the treating physician; further studies are needed for general recommendations. Other trends include the combination of different wavelengths in the same treatment sessions to treat more targets at the same time to have a more comprehensive approach. However, as with all treatments of excessive scars, lower settings and rather low densities may result in more sustainable progress.

Microneedling. Microneedling is a relatively novel solution for acne and hypertrophic scars that was first reported in the 1980s^{146,147}. The technique is based on mechanical disruption of the skin by small needles. This causes a local wound healing reaction, promoting the skin to produce new ECM. The depth of needle penetration can vary, thereby provoking reactions in the more superficial or deeper layers of the skin. The technique is also used for drug delivery. The effect of microneedling on keloid lesions is controversially discussed, and there are no guidelines about the use of microneedling in keloid lesions.

Radiotherapy. Compared with surgery or radiation therapy alone, the combination of surgical excision followed by immediate postoperative radiation has been shown to decrease the recurrence rate of scarring to ~20%¹⁴⁴. In general, radiation can be considered for recurrent keloids, patients with a high-risk of recurrence, including those with marginal resections, wider spread and unfavourable locations⁹⁵.

The most common adverse effects of radiation are erythema, hypopigmentation, hyperpigmentation, oedema, desquamation, ulceration; however, these are rarely observed. Late complications that

can occur weeks to months after treatment include hypopigmentation or hyperpigmentation, alopecia, atrophy and telangiectasis. To minimize the risk of secondary carcinogenesis, radiation therapy should generally be avoided around glandular tissue such as the mammary glands and the thyroid, even in adults, and particularly in children¹⁴⁸. Furthermore, radiation should be conducted by experienced providers only¹⁴⁴.

Surgery and surgical scar revision. The goal of surgery in scar management is to restore range of motion. At the same time release of scar contractures improves joint function and accelerates the maturation of surrounding scars¹⁴⁹. Small and/or linear scars can be treated by complete surgical resection. Commonly used surgical approaches are z-plasty, w-plasty and local transpositional flaps¹⁵⁰.

Removal of keloids with no additional therapy is not recommended as the rate of recurrence is high. Surgery in combination with radiation, or after treatment with intralesional corticoid injection or 5-FU when activity of the scar has profoundly decreased is an option, but the consent of the patient has to clearly delineate the risk of recurrence. Combining surgery with postoperative radiotherapy has been suggested to treat keloids more effectively and less invasively than radiation monotherapy⁹⁵. This combined approach yields high success and low recurrence rates¹⁵¹. This approach should only be conducted in collaboration between surgeon and an experienced provider of radiation owing to increased risk of adverse effects.

The traditional plastic surgery reconstructive ladder will guide the appropriate decision in conjunction with the on-site local availability of tissue that can serve as a donor site¹⁵². Patient history should be consulted when planning surgical removal, to reduce the risk of further scarring. The use of laser may be included either in resurfacing, or as fractional laser with the development of microthermal zones to facilitate scar remodelling¹⁵³ at the time or early after surgery. Scar resurfacing may be used to improve the quality of a scar by reducing the bulk of the scar and controlling the secondary healing process by introduction of an epithelial layer, known to influence the underlying dermis. The use of autologous cells harvested from the dermal–epidermal junction can improve the pigment load of the skin repair¹⁵⁴.

Many skin replacement products that can help in reaching the best possible result in surgical scar revision have been developed over the years and are now commercially available. Release of a scar contracture and treatment with a split thickness skin graft will in many cases result in recurrence of poor scar quality and contraction, possibly leading to new contractures¹⁰⁸. The use of dermal substitutes¹¹³ can help to improve this result, without the need for a more complicated surgical procedure such as flap reconstruction. Dermal substitutes provide a new dermal structure to the wound, preventing adherence to the underlying tissue and serving as a biological matrix for cell and vascular ingrowth. Many of these materials are based on biological skin proteins such as collagen, elastin components, glycosaminoglycans or are even composed of whole dermal tissue. These materials are gradually remodelled by the body and ultimately replaced by the patient's own tissue. Nevertheless, synthetic material is also now used as a dermal replacement¹⁵⁵.

Scarring after burn

It has been well established that the key to limiting long-term scarring is in reducing the time to healing¹⁵⁶. The initial first aid, resuscitation, infection control, oedema management, dressing strategies and surgical

interventions are all focused on tissue salvage to facilitate healing conservatively when possible. In situations in which the extent of injury overwhelms the capacity to heal, then timely surgical intervention aims to restore skin integrity to limit scarring¹⁵⁷.

Surgical repair of a burn wound involves a complex decision-making matrix; factors known to influence the outcome require consideration when making the surgical plan. The use of parameters such as blood flow has led to the development and clinical use of the laser Doppler scanner. In addition, the body site involved, donor site availability, associated injuries and comorbidities influence the surgical plan¹⁵⁸.

Excision of the necrotic burn tissue removes the toxic load and is the essential first step in controlling the burn wound, reducing the main driver of poor scar outcome¹⁵⁹. Early debridement assists in reducing the overall time to healing but requires skin repair. Early excision of major full thickness wounds is considered to be within the first 24–72 h (ref. 113). When considering partial thickness skin wounds the healing potential is related to the amount of dermis uninjured as well as the capacity of the individual to heal. The aim is to diagnose those who would heal in a timely fashion, for example, within 14 days, such that a conservative path is followed. Those who would take more than 14 days will have an increasing risk of poor scar outcome, and early identification will facilitate early surgery within 7 days¹¹⁶.

Traditional skin repair is split thickness skin grafts from a non-injured donor site. The skin will retain the characteristics of the site of origin and will result in a scar¹⁶⁰. The survival of major burn injuries, with limited donor sites, has driven exploration of tissue engineering solutions for skin repair¹⁶¹. The development of a range of solutions including dermal scaffolds, cell-based therapies and tissue-engineered skin composites are used to restore skin integrity. The availability of off-the-shelf products, point-of-care devices to harvest cells and laboratory-based tissue expansion culture techniques has enabled flexibility in achieving expedient skin repair¹⁶².

In situations in which the dermis can be salvaged, cells alone can be used; when seeking to restore the dermis then the introduction of a dermal matrix will enable in situ tissue guided regeneration in a staged skin repair. The aim of tissue regeneration requires cell delivery into a prepared wound bed to facilitate cell phenotypic expression for skin regeneration¹⁶³. Surgical repair needs to consider the integration of the repaired skin segment to blend with the surrounding tissue needing attention to scar control¹⁶⁴.

After healing, the wound will mature with the scar developing over time as the ECM proteins, specifically collagens, are being laid down, peaking between 6 and 12 weeks after injury in most cases. In the early post-healing phase attention to detail with respect to hygiene and protection will reduce the risk of secondary breakdown and the associated increased scarring. Pressure therapy will assist in oedema control and is a frequently used modality for scar treatment after burn injury. Topical hydrocolloid dressings can assist in maintaining moisture and protecting the newly healed skin¹⁶⁵.

Post-burn scars to the face remain a major challenge in terms of reconstruction, as there is no available flap in the human anatomy capable of covering the entire area. A possible approach is to prefabricate a large surface of adapted tissue using a vascular carrier branched over the facial vessel applied subcutaneously over a large skin expander located on the shoulder¹⁶⁶. Other authors proposed allogenic face transplantation, which has been successful but it comes with the risk of immunomodulatory treatment that will last lifelong¹⁶⁷.

Quality of life

Scars can have a devastating effect on a person's QoL, both from an individual and a social perspective. Having visible scars and/or scars that impact the capacity for a full range of movement may damage self-perception and body image and have a negative effect on social interactions. How others look at a person with scars (or how the person perceives that others look at them) is part of the social perspective of QoL. To measure these effects, health-related quality of life (HRQoL) instruments can be helpful. The Medical Outcome Study Short Form (SF-36) and EuroQol five dimensions questionnaire (EQ-5D) are both generic instruments, whereas the Burn Specific Health Scale-Brief (BSHS-B) was specifically designed to measure QoL of patients after burn injuries¹⁶⁸.

BSHS-B data for post-burn patients showed that within the first 12 months, most problems were experienced within the domains 'work', 'simple abilities', 'hand function', 'affect', 'body image', 'treatment regimens' and 'heat sensitivity'. Scores of most of these domains improved with time; however, 'body image' and 'heat sensitivity' remained below the maximum score (scores improved to 3–4 and 2.5–4, respectively). The higher scores refer to a good perceived health status³⁸ up to 9–10 years after injury^{38,169,170}.

Data from SF-36 is generally divided into a physical component summary (PCS) and a mental component summary (MCS)¹⁷¹. For patients with post-burn scars, mainly the PCS scores were lower (indicating a lower physical HRQoL as perceived by the individual) shortly after the injury and recovered somewhat at later time points. Domains 'bodily pain' and 'physical role limitations' were low in the short term, whereas both 'physical role limitations' and 'emotional role limitations' were low at later time points, indicating lower perceived health status.

The general conclusion concerning QoL from patients with burn injuries based on data from EQ-5D analysis is somewhat similar: domains 'anxiety/depression' and 'pain/discomfort' remained below norm scores derived from healthy populations³⁸ during follow-up periods of up to 5 years, indicating long-term problems for these subjects.

For patients with keloid lesions, SF-36 data are available: these patients were found to score lower than a matched reference group on domains 'bodily pain', 'vitality' and 'social functioning' as well as on the MCS, indicating that patients with keloid lesions reported a worse mental HRQoL (Fig. 6). Pain and itch complaints were strong indicators of impaired QoL¹⁷².

The Dermatologic Life Quality Index (DLQI) is another tool to study the impact of skin and scar disorders on QoL of patients^{173–175}. However, the DLQI does not directly rate the scar; thus, its use as a single tool for scar assessment may be limited. Its main value is that it provides insight into the various aspects of daily life that can be hampered by a scar condition.

Patients with acne suffer strong reduction in QoL¹⁷⁶. Like patients with post-burn scars, risks of development of anxiety and depression are high. In this pathology, effective treatment of the physical symptoms was shown to improve not only these, but also QoL parameters¹⁷⁷. This is in contrast to patients with burn injuries, in which treatment is mainly directed at psychological factors such as depression, post-traumatic stress disorder (PTSD) or social problems¹⁷⁸. This is related to the fact that currently no treatment exists that can fully remove the scars.

In paediatric scar populations the QoL subjects 'parental concern' and 'appearance' required prolonged attention in aftercare for burned children¹⁷⁹. Parental concern could be met by including parents specifically in aftercare programmes. Change in appearance caused concern



Fig. 6 | Clinical image demonstrating major keloid lesions formed in a patient with a positive family history for keloids, indicating genetic predisposition. Major keloid lesions developed over 1–2 years after dermatological treatment for acne. No scar management has been effective and consequently quality of life of the patient and their family has been substantially negatively affected.

for burned children over a wide range of ages. Other aspects of HRQoL improved over time; however, special attention is required for children with more extensive burns and hand and face burns in aftercare.

Despite the fact that QoL can be measured, reports on changes in QoL after therapies are scarce⁹¹. Studies on intralesional 5-FU¹³³ and fractional CO₂ laser treatment¹⁸⁰ for the improvement of keloids and hypertrophic burn scars, could, however, demonstrate improved QoL based on DLQI measurements during the course of the respective treatment. The presence of PTSD was found to be related to long-term reduction in HRQoL¹⁸¹. Improvements can take a long time before they can be measured, which explains why these outcomes are scarcely reported in studies.

Outlook

The goal of scar treatment is the restoration of the skin to its original morphology, specific for that body site of the patient, requiring repair by regeneration rather than fibrosis. Despite the advances made in understanding and clinical strategies over the past few decades the restoration of fully functional skin remains elusive.

There are significant challenges ahead; for example, understanding the basic biology is complex with many factors involved from the time of injury to the full maturation of the skin repair. To restore skin integrity, cells capable of differentiation into the appropriate phenotype facilitated by interaction with the ECM are essential. The direction of cell phenotype by manipulation of the matrix may provide an opportunity for scar reduction in the future¹¹³. Currently, interventions – both locally and systemically – can influence the outcome with little insight into the underlying mechanisms. There is a need to address the mechanistic gaps in knowledge such that therapeutic targets can be identified.

Examples that follow this line are cell-seeded skin substitutes that are currently in trials, such as Denovoskin (CUTISS)¹⁸², self-assembled skin substitute (SASS)¹⁸³, cell therapies using directly isolated cells such

as Recell (RECELL)¹⁸⁴ and autologous fat used as an anti-fibrotic agent in lipofilling protocols. All of these have demonstrated beneficial effects in various areas of scar revision and scar management. Denovoskin is an autologous full-skin substitute that is currently in clinical trials for burns and reconstructive wounds¹⁸². SASS is an autologous bilayered skin substitute to provide skin for patients who lack donor sites (unwounded skin) to cover their burn wounds. SASS shows skin-like attributes, such as an autologous dermal and epidermal layer. An ongoing cross-Canada study is further assessing the product's safety and efficacy¹⁸³. Recell has a long history in acute burn treatment, but is also frequently used to manage pigmentation disorders in skin¹⁸⁴ and scars¹⁸⁵. Lipofilling is a technique that uses fat harvested from the patient to inject this under adherent and fibrotic scars. It was shown that this leads to improved scar quality, as measured by objective and subjective scar assessment tools, from POSAS to optical coherence tomography. Understanding the capacity to self-organize to a regenerative pattern is an opportunity to develop novel therapeutic approaches; for example, what is the role of innervation in modulating skin restoration and secondary scar treatments?

The interventions to date in scar management are predominantly at the scar site. There is clear evidence that the systemic condition of the individual and their response to injury are fundamental in driving scar outcome. In addition, individualized treatment aspects of the scar such as activity, acuity and timing of the scar are often not considered in a treatment approach. These are opportunities for the future for new diagnostic approaches and the development of new therapies. One being currently tested is the use of pirfenidone as a systemic treatment for keloid lesions and hypertrophic scars¹⁸⁶.

Clinical trials to date are challenged by the complexity of making the correct diagnosis of the scar, based on clinical criteria. The heterogeneity of the scars within an individual at differing body sites, with further differences by injury type, as well as the significant differences between populations, is further complicated by the collection of data that are hard to compare across the trials. The diagnosis is key as it is well known that the natural history of most scars is improvement over the subsequent months to years. Keloid scars do not improve but continue to grow at varying rates. The changes over time require that the clinical trial has adequate long-term follow-up, itself challenging. In the future, to improve the voracity of clinical trials the development of a diagnostic strategy and a series of validated outcome measures are essential.

Recent work looking at the epigenetics, methylation pattern and single-cell sequencing of the cells within scars has demonstrated consistent and clear differences between hypertrophic (expected to improve over time) and keloid (expected to grow over time) scars, providing a potential starting point to augment the clinical diagnosis. Scar assessment as an outcome measure has been discussed and remains a challenge with varying subjectivity. Assessment of the changes in cell phenotype as demonstrated by epigenetics may also be a valuable adjunct to the outcome measures. Skin metabolomics and single-cell nuclear polymorphism are new diagnostic approaches that will characterize each scar individually and lead to personalized treatment interventions. These new interventions will include delivery of agents or cell products that will 'normalize' either metabolic, signal pathways and/or intracellular activity profiles, leading to normal healing without scar formation¹⁸⁷. The behaviour of fibroblasts in culture and the characteristics of collagen formation may also bring basic science to assist diagnosis and outcomes. These strategies require access to the tissue to extract cells by biopsy. Exploration into the use of skin surface chemistry as a predictor of cell activity in the scar is worthy

of further investigation to negate the need to further injure the tissue by biopsy. Skin surface chemistry as a predictive tool to assist in scar risk assessment could also be used to initiate earlier intervention to prevent scarring.

There is increasing clarity that susceptibility to poor scar outcome is not strictly related to local skin characteristics of the scar site¹⁸⁸, but that there are also systemic factors at play. This provides an opportunity for the investigation of predictive biomarkers for both diagnosis and monitoring clinical outcome. Furthermore, it provides an opportunity to explore systemic therapies, particularly in extensive debilitating keloid lesions based on the increasing understanding of the role of the immune response. The high turnover of collagen and cell proliferation within the scar ECM represents an opportunity for intervention with manipulation, for example, with lysyl oxidase inhibition⁸⁴.

The treatment of scarring, particularly keloid lesions, remains vexed with high recurrence rates and the development of extensive scarring affecting the individual's capacity to function¹⁴². With objective measurement of the scar locally, systemically and clinically along with scar assessments over time, we will be able to undertake clinical trials of new interventions, for example, exploring the role of monoclonal antibodies, manipulation of the microbiome, immune response and inflammation. To determine the efficacy of new interventions, care providers need to be rigorous in the development of high-quality clinical trials that have common definitions and the same data dictionary, thus enabling comparison across the globe.

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Introduction (M.G.J., F.M.W. and G.G.G.); Epidemiology (M.G.J., E.M., F.M.W. and G.G.G.); Mechanisms/pathophysiology (M.G.J., A.B. and G.G.G.); Diagnosis, screening and prevention (M.G.J., E.M., L.T., R.O. and G.G.G.); Management (M.G.J., E.M., L.T., R.O. and G.G.G.); Quality of life (M.G.J., E.M. and G.G.G.); Outlook (M.G.J., F.M.W. and G.G.G.); Overview of the Primer (M.G.J. and G.G.G.).

Competing interests

The authors declare no competing interests.

Informed consent

The authors affirm that human research participants provided informed consent for publication of the images in Fig. 6.

Additional information

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