Scarring and wound healing

ABSTRACT

Following injury, the skin undergoes a wound healing process culminating in the formation of a mature scar. Millions of patients worldwide are left with scars every year as a result of trauma or surgery. Scars can be painful, disfiguring and disabling, yet patients report that clinicians are often dismissive of their concerns, unable to identify pathological scars and unaware of treatment options. The normal wound healing process comprises three overlapping stages: inflammation, proliferation and remodelling. In some patients this process is deranged, resulting in the formation of hypertrophic or keloid scars. Clinicians can minimize the risk of these pathological scars developing with good surgical technique and wound aftercare. If pathological scars do form, they should be identified early and patients referred for treatment, most often topical or intralesional corticosteroids. In resistant cases, pathological scars may be treated with phototherapy, radiotherapy or surgical resection.

Every year, in hospitals across the world, millions of patients are left with scars (Sund, 2000). Every surgeon preparing a patient for theatre or emergency physician suturing a traumatic wound will, at some point, have been asked 'will I have a scar?'. Scarring is often thought of as a trivial aesthetic concern and many clinicians are unaware of the associated psychosocial, functional and physical morbidity. Patients with scars are more likely to suffer from mental health problems, such as anxiety and depression. These patients may also be the victims of stigmatization and develop avoidant coping mechanisms, harming relationships and employment prospects.

Scars can also be a source of physical discomfort with patients reporting an array of unpleasant physical sensations, most often pain and itchiness. In cases where scars form contractures, patients can be left with reduced mobility and functional impairment. Despite the morbidity associated with scarring, patients report that clinicians are often unable to diagnose pathological scars and are unaware of treatment options (Brown et al, 2008). This article provides an overview of the physiology of wound healing, the pathophysiology of hypertrophic and keloid scars, and the treatment options currently available.

Dr Daniel A Potter, Academic Foundation Trainee and Honorary Research Fellow, Department of Dermatology, Leicester Royal Infirmary, Leicester LE1 5WW

Dr David Veitch, Mohs Surgery Post-CCT Fellow, Department of Dermatology, Nottingham University Hospitals, Nottingham

Dr Graham A Johnston, Consultant Dermatologist and Honorary Associate Professor, Department of Dermatology, Leicester Royal Infirmary, Leicester

Correspondence to: Dr DA Potter (Danielpotter@leicester.ac.uk)

Physiology of wound healing

Physiological scar formation

The wound healing process is a continuum usually described as consisting of three overlapping phases: inflammation, proliferation and remodelling. The inflammatory phase begins immediately following injury, with haemostasis being achieved by the formation of platelet-fibrin clots (*Figure 1a*). Simultaneously, damaged tissues release cytokines which cause capillaries surrounding the site of injury to vasodilate and, in the days following injury, cellular components of the immune system to migrate into the wound. These cellular components use the platelet–fibrin clot as a scaffolding with which to navigate the wound.

Initially, neutrophils predominate: they act to remove bacteria, foreign bodies and cellular debris by phagocytosis as well as releasing proteases which debride dead and devitalised tissue (*Figure 1b*). These neutrophils are then expelled into the wound eschar or are themselves phagocytosed by macrophages. As the wound matures macrophages replace neutrophils as the predominant cellular component; similarly to neutrophils they act to clear the wound site as well as contributing to the coordination of the next phase of wound healing – proliferation (*Figure 1c*) (Hart, 2002; Profyris et al, 2012; Marshall et al, 2018).

The proliferation phase of wound healing occurs in the days to weeks following an injury and restores the skin defect with the formation of an immature scar. The cellular component of this phase consists predominantly of fibroblasts, endothelial cells and keratinocytes. Fibroblasts migrate into the wound and lay down collagen while also secreting matrix metalloproteases which allow them to carve paths through the extracellular matrix.

Once an adequate amount of collagen has been deposited these fibroblasts differentiate into myofibroblasts, which act to contract the wound and minimize the size of the surface defect. Concurrently, angiogenesis occurs as endothelial cells from capillaries adjacent to the wound migrate down paths in the extracellular matrix to re-vascularise the area.

Throughout these processes, keratinocytes from the wound edge and from nearby hair follicles migrate across the surface of the wound. These cells act both to phagocytose unwanted material and to re-epithelialise the wound surface. The end point of the proliferation phase is the restoration of the initial skin defect with an immature scar mostly composed of disorganized type III collagen fibres, capillaries and a surface layer of epithelium (*Figure 1d* and *e*) (Stephens and Thomas, 2002; Profyris et al, 2012; Marshall et al, 2018).

Up to a year following the proliferation phase the scar matures, undergoing a process of remodelling. During this period fibroblasts alter the extracellular matrix, replacing type III collagen with type I

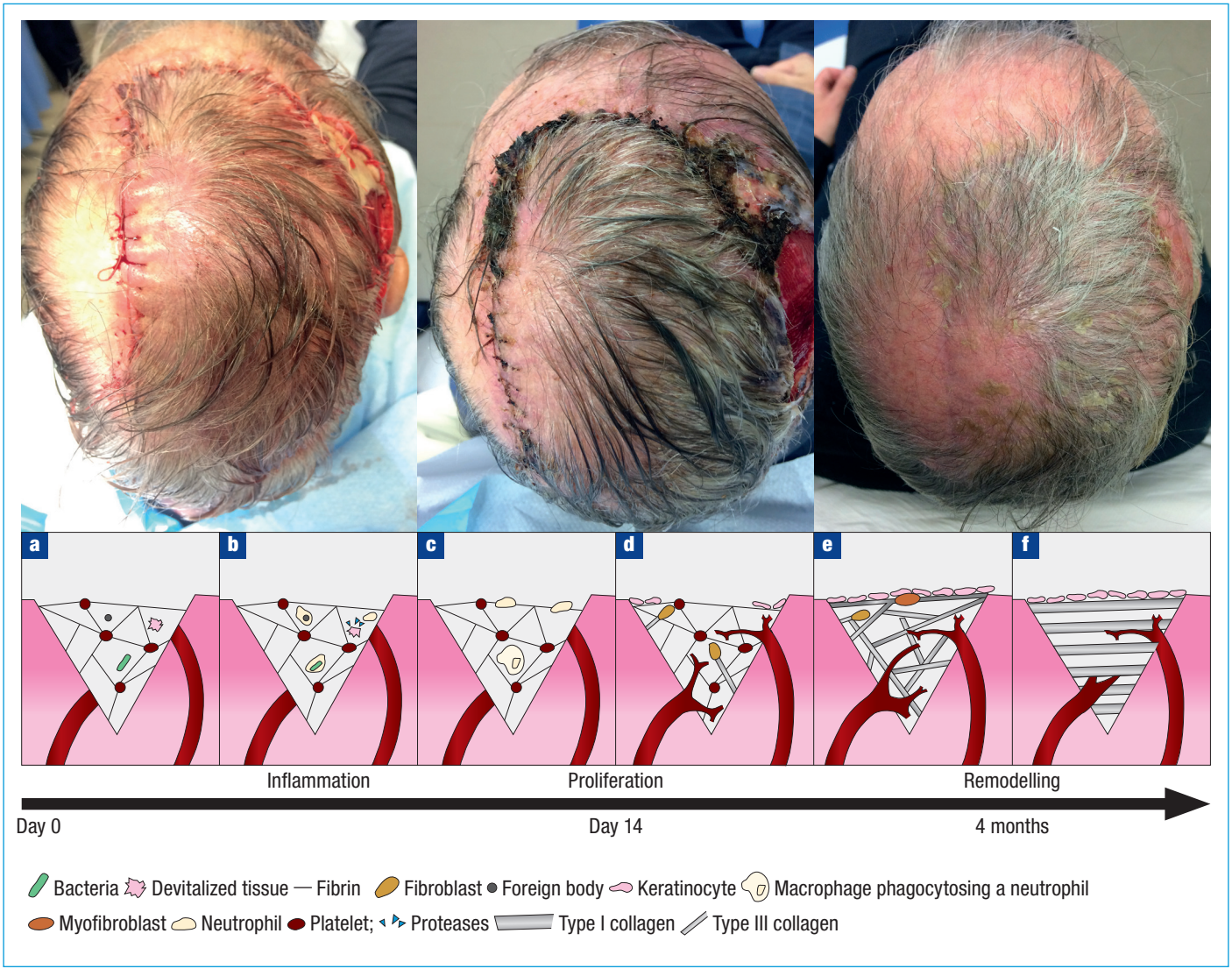

Figure 1. Normal wound healing. a. Haemostasis is achieved by the formation of a platelet-fibrin clot. **b.** Capillaries vasodilate and cellular components of the immune system (predominantly neutrophils) migrate into the wound. Bacteria and foreign bodies are phagocytosed. Dead and devitalised tissues are broken down by proteases. **c.** Neutrophils are expelled into the wound eschar or are phagocytosed by macrophages. **d.** Fibroblasts migrate into the wound, carving paths in the extracellular matrix and laying down type III collagen. Angiogenesis occurs as endothelial cells from adjacent capillaries migrate into the wound. Keratinocytes migrate across the surface of the wound, phagocytosing unwanted material and re-epithelialising the wound surface. **e.** Fibroblasts differentiate into myofibroblasts, which act to contract the wound. Fibroblasts replace type III collagen with type I collagen. Excess capillaries begin to regress. **f.** Final scar composed of parallel strands of type I collagen, covered by a surface layer of epithelium.

and re-aligning collagen fibres into denser bundles which run parallel to one another, as opposed to the basket-weave arrangement of collagen in uninjured skin. Throughout this phase cells which entered the wound during the inflammatory phase leave or undergo apoptosis. Similarly, excess capillaries regress. These processes result in a mature scar with approximately 80% of the tensile strength of uninjured skin, which is softer to the touch and less erythematous than the initial scar formed following the proliferation phase (*Figure 1f*) (O'Kane, 2002; Profyris et al, 2012; Marshall et al, 2018).

Pathological scar formation

In some patients the normal wound healing process is deranged resulting in the formation of a pathological scar. Pathological scars can be classified as either hypertrophic or keloid. Hypertrophic scars are abnormally large scars which remain within the boundaries of the original injury (*Figure 2*), whereas keloid scars are abnormally large scars which grow beyond the margins of the original wound site (*Figure 3*).

The underlying pathophysiology for the formation of these scars is not completely understood. However, in both keloid and hypertrophic scars the cytokines which coordinate wound healing are disordered. Compared to physiological scars, there are relatively greater numbers of cytokines stimulating fibroblasts to proliferate and lay down extracellular matrix and fewer promoting apoptosis. Concurrently, the receptors on fibroblasts corresponding to these cytokines may be up- or downregulated to exaggerate the effect of this cytokine imbalance. This results in excess extracellular matrix deposition, manifesting as an abnormally large scar (Andrews et al, 2016; Berman et al, 2017; Ghazawi et al, 2018).

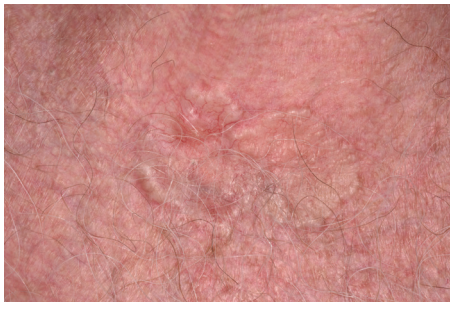

Figure 2. Hypertrophic scarring after surgical excisions.

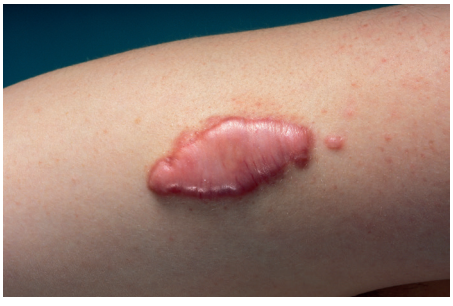

Figure 3. Keloid scar.

While there are some similarities in pathogenesis between hypertrophic and keloid scars, they differ in terms of epidemiology, aetiology and histological composition (*Table 1*). Keloid scars occur more often in people with darker skin, whereas the incidence of hypertrophic scars does not vary by Fitzpatrick skin type. Hypertrophic scars tend to be caused by either wound breakdown or excessive tension across the wound. This type of scar does not usually re-occur if excised and, over time, will often reduce in size. Conversely, keloid scars can occur spontaneously, re-occur if excised and do not spontaneously involute. Keloid scars have also been found to run in families, with an autosomal dominant inheritance pattern (Andrews et al, 2016; Berman et al, 2017; Ghazawi et al, 2018). This suggests that keloid scars occur secondary to a genetic predisposition whereas hypertrophic scars are the result of an exogenous stimuli causing an exaggerated wound healing response.

There are also differences in the cellular and extracellular matrix composition of hypertrophic and keloid scars. While both have higher numbers of inflammatory cells than normal scars, in hypertrophic scars this inflammatory infiltrate falls with time while in keloid scars it persists. Hypertrophic scars, unlike keloid scars, also have larger numbers of myofibroblasts which persist in the wound for longer than in physiological scars, possibly explaining why some hypertrophic scars form contractures (Ghazawi et al, 2018). In hypertrophic scars there is also a relatively greater amount of type III collagen arranged in thin fibrils running parallel to the skin, whereas keloid scars are mostly composed of type I collagen in thick bundles with a chaotic arrangement which projects under normal epidermis (Andrews et al, 2016; Berman et al, 2017; Ghazawi et al, 2018). The differences between hypertrophic and keloid scars have implications for the way in which patients with these scars should be managed.

Table 1. Differences between keloid and hypertrophic scars

	Hypertrophic	Keloid
Macroscopic	■ Remains within the boundaries of the original injury ■ May spontaneously involute ■ Tend not to re-occur if excised ■ Most often affect the skin overlying joints	■ Tend to re-occur if excised ■ Affect a variety of sites including the ear lobes, shoulders, anterior chest wall, upper back and the skin overlying joints
Microscopic	■ Inflammatory infiltrate falls with time ■ Larger number of myofibroblasts ■ Extracellular matrix composed of type III collagen in linear fibrils running parallel with the skin ■ Highly vascular	■ Inflammatory infiltrate persists ■ Fewer myofibroblasts ■ Extracellular matrix composed of type I collagen arranged chaotically in thick bundles that project under normal epidermis ■ Less vascular
Epidemiology	■ No predisposition to a particular Fitzpatrick skin type ■ Non-inheritable	■ More common in people with darker Fitzpatrick skin types ■ Inheritable
Aetiology	■ Only occur following injury	■ May occur without injury
Symptoms	■ Mild pruritis, tend not to be painful	■ Pruritic and painful

Adapted from Ghazawi et al (2018)

Management

There is a variety of interventions that can be made from the point of injury until after a mature scar has formed to optimize a scar's appearance and minimize the associated psychosocial, functional and physical morbidity (*Table 2*).

Before creating a surgical wound or closing a traumatic wound, obtaining a personal and family history of scarring and being aware of the factors which may adversely affect wound healing (*Table 3*) can allow the clinician to counsel the patient appropriately and manage expectations. It also allows the clinician to plan interventions to minimize the risk of pathological scar formation. When planning a procedure, making incisions parallel to the direction of tension in a patient's skin will produce wound edges which are more easily opposed. Equally, avoiding sites of high natural skin tension, such as across the sternum, will produce wounds which are easier to close.

In some patients, either because of trauma or the nature of the surgical procedure, creation of highly tensile wounds is unavoidable. In these patients, surgical techniques, such as skin flap or full thickness skin graft repairs, can be used to reduce wound tension and improve cosmetic outcome. Another useful technique to improve cosmetically poor or malorientated scars is a Z-plasty. This uses a double triangular transposition flap to alter the vector of wound tension and thereby improve scar quality. Other surgical techniques to reduce wound tension include undermining, in order to mobilize skin adjacent to the wound, and subcuticular sutures, to minimize tension across the surface of the wound (Monstrey et al, 2014).

Interestingly, the type of suture material used, absorbable or non-absorbable, does not appear to affect the appearance of the scar produced (Gillanders et al, 2018). Tension can also be offloaded following procedures by using tape or 'stress shielding' dressings. In any wound the risk of pathological scar

Table 2. Scar management

Time point	Management	
Before injury	Personal and family history of scarring to identify high-risk patients	
	Optimize factors adversely affecting wound healing (*Table 3*)	
	Counsel patient regarding likely outcome and manage expectations	
Time of injury	Optimize surgical technique to reduce wound tension	■ Avoid sites of high natural skin tension ■ Make incisions parallel to the direction of skin tension ■ Z-plasty or W-plasty ■ Undermining ■ Subcuticular sutures ■ Skin grafts, flaps or tissue expansion
	Stress shielding dressings or taping	
Mature scar	First line (1 month post injury)*	■ Emollients ■ Silicon dressings or gels ■ Compression dressings ■ Counsel patient to avoid exposing the scar to sunlight and to use sunscreen
	Second line (2 months post injury)	■ Topical super-potent steroids (e.g. clobetasol proprionate 0.05% cream) under occlusion dressings ■ Steroid-impregnated tapes (e.g. fludroxycortide tape)
	Third line (6 months post injury)	■ Intralesional steroids injections (e.g. triamcinolone acetonide)
	Fourth line (1 year post injury)†	■ Topical imiquimod ■ Alternative intralesional therapies (e.g. bleomycin, 5-fluorouracil and verapamil) ■ Autologous fat grafting ■ Radiotherapy ■ Laser therapy ■ Photodynamic therapy ■ Scar revision surgery or cryotherapy
	Fifth line (at any point following injury)	■ Psychological therapy ■ Skin camouflage

**Timings and the order in which therapies are listed are provided for guidance only; interventions may be used in combination or in an alternative order at differing time points depending on local policy and expertise.*
†The evidence base for these therapies is less well established and many are not widely available within the NHS.
Adapted from Monstrey et al (2014)

Table 3. Factors adversely affecting wound healing

Local	Micro-organisms
	Foreign bodies
	Necrotic tissue
	Excessive pressure
	Trauma
	Excessively dry or wet wound environments
Systemic	Older age
	Body habitus (obesity or emaciation)
	Malnutrition
	Comorbidities (particularly: cardiovascular, metabolic, haematological, oncological, renal, hepatic and endocrine diseases)
	Psychological stress
	Immunosuppression
	Radiotherapy
	High ratio of androgens to oestrogens
	Medications (particularly corticosteroids and chemotherapy agents)
	Smoking
	Alcoholism

Adapted from Guo and DiPietro (2010), Thomas Hess (2011)

formation can be minimized by taking precautions to reduce the risk of infection (Monstrey et al, 2014).

There are several interventions which can be made following wound closure to optimize the appearance of the scar formed. Scar tissue does not retain moisture as well as undamaged skin. Treatments to help newly formed scars retain water include emollients and silicon dressings or gels. These reduce both the size of and unpleasant physical sensations associated with scars. In larger scars pressure dressings may also be applied and have been shown to independently reduce scar size and symptoms, and to augment the effects of silicon dressings when used concurrently. It is thought that compression dressings may exert their positive effects by influencing the wound healing process via the stimulation of mechanoreceptors. Patients should also be advised to avoid exposing their scar to sunlight and to use a high factor sunscreen in order to minimize pigmentation (Bayat et al, 2003; Monstrey et al, 2014).

The interventions outlined above can be used in the management of most wounds. Ideally, every patient's scar should be reviewed 1–2 months following closure. When assessing a scar, the size, texture, pliability, colour and associated symptoms should be considered (Bayat et al, 2003). This may be done using standardized assessment tools, such as the Patient and Observer Scar Assessment Scale. If possible objective measures, for example scar height, should also be recorded (Draaijers et al, 2004; Verhaegen et al, 2011). Where scars are healing well, treatments such as silicon and pressure dressings can be stopped, but in cases where pathological scars are developing these dressings should be continued and patients referred for further treatment.

Pathological scars are likely to be treated with either topical or intralesional

KEY POINTS

- Scars are common and can cause physical and psychological symptoms, which may result in social and/or functional disability.
- The inflammatory phase begins immediately following injury and results in haemostasis and the removal of dead tissue and foreign material from the wound.
- The proliferative phase begins in the days following injury and results in the formation of an immature scar, which is highly vascularised and composed of disorganised type III collagen.
- The remodelling phase begins in the months following injury and continues for up to a year, resulting in the formation of a mature scar which is less vascular and composed of organized type I collagen.
- Hypertrophic scars are abnormally large scars that remain within the boundaries of the original injury; they can occur in any patient and usually form secondary to excess wound tension or infection.
- Keloid scars are abnormally large scars that grow beyond the boundaries of the original injury; they occur in genetically predisposed individuals either spontaneously or following injury.
- Clinicians can minimize the risk of pathological scar formation with good surgical technique and wound aftercare.
- Patients developing pathological scars despite initial interventions should be referred for further management, most often topical or intralesional corticosteroids.

corticosteroids. In most patients, topical super-potent steroids, such as clobetasol proprionate 0.05% cream, are applied under occlusion dressings. Alternatively, steroid-impregnated tapes, for example fludroxycortide tape, can be prescribed by both hospital specialists and GPs. If topical therapies are ineffective, intralesional injections of steroids, such as triamcinolone acetonide, can be used. Intralesional steroids are usually given every 4–6 weeks and, depending on response, may be continued for up to 6 months. The aims of the above treatments are to reduce both the size and symptoms associated with pathological scars.

In non-responsive cases there are a multitude of less well-evidenced therapies, which are not widely available within the NHS. These include alternative topical treatments, for example imiquimod, and intralesional therapies, including bleomycin, 5-fluorouracil and verapamil. Autologous fat grafting, where fat is removed from the patient using liposuction and injected beneath scars, is an emerging therapy that currently lacks high-quality evidence and is unlikely to be used in the UK (Riyat et al, 2017).

Radiotherapy, laser therapy and photodynamic therapy may also be used in some patients. There are several different types of laser therapy currently available, varying in type of laser, treatment duration and energy level. The choice of laser therapy is determined by the characteristics of the scar treated. However, there is currently a paucity of high quality studies to guide treatment decisions (Al-Harithy and Pon, 2012). Similarly, the use of radiotherapy is controversial because of the absence of high-quality evidence as well as the potential risks of malignancy inherent to treatments exposing patients to radiation.

If medical therapies fail, removal of the scar, via surgical resection or cryotherapy, may be considered. Scar removal is often combined with postoperative application of the interventions described above, and is most likely to be offered for hypertrophic scars, as keloids tend to re-occur (Bayat et al, 2003; Monstrey et al, 2014). In some cases, resolution of pathological scars might not be possible. These patients may benefit from being directed towards support groups, such as Changing Faces, who provide information, counselling and practical advice, for example on skin camouflage, to help people learn to live with their scars.

Conclusions

Scars are the unavoidable consequence of physiological wound healing and many patients will be left with one as a reminder of their time in hospital. In some cases, deranged wound healing will result in the formation of abnormally large, pathological scars. Both physiological and pathological scars can be a cause of distress for patients, adversely affecting quality of life via a reduction in physical, mental and social wellbeing. All hospital clinicians have the opportunity to minimize the morbidity associated with scarring by optimizing surgical technique and wound aftercare.

CURRICULUM CHECKLIST

This article addresses the following requirements from the general internal medicine training curriculum

- Managing patients in an outpatient clinic, ambulatory or community setting, including management of long term conditions
- Managing medical problems in patients in other specialties and special cases

This article addresses the following requirements from the Royal College of Surgeons curriculum

- Technical knowledge and clinical expertise and ability to apply knowledge to the investigation of problems – e.g: eliciting the necessary information from patients, identifying key issues, knowledge of appropriate options, good hand–eye coordination.

Furthermore, by reviewing wounds and differentiating between the different types of scar clinicians can correctly identify patients who may benefit from being referred for more intensive treatment. Scars are unavoidable but not untreatable – if correctly diagnosed and appropriately managed, patients' lives can be greatly improved. **BJHM**

Conflict of interest: none.

Al Harithy R, Pon K. Scar treatment with lasers: a review and update. Curr Dermatol Rep. 2012 Jun;1(2):69–75. https://doi.org/10.1007/s13671-012-0009-7

Andrews JP, Marttala J, Macarak E, Rosenbloom J, Uitto J. Keloids: the paradigm of skin fibrosis — Pathomechanisms and treatment. Matrix Biol. 2016 Apr;51:37–46. https://doi.org/10.1016/j.matbio.2016.01.013

Bayat A, McGrouther DA, Ferguson MWJ. Skin scarring. BMJ. 2003 Jan 11;326(7380):88–92. https://doi.org/10.1136/bmj.326.7380.88

Berman B, Maderal A, Raphael B. Keloids and hypertrophic scars. Dermatol Surg. 2017 Jan;43 Suppl 1:S3–S18. https://doi.org/10.1097/DSS.0000000000000819

Brown BC, McKenna SP, Siddhi K, McGrouther DA, Bayat A. The hidden cost of skin scars: quality of life after skin scarring. J Plast Reconstr Aesthet Surg. 2008 Sep;61(9):1049–1058. https://doi.org/10.1016/j.bjps.2008.03.020

Draaijers LJ, Tempelman FRH, Botman YAM, Tuinebreijer WE, Middelkoop E, Kreis RW, van Zuijlen PPM. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. Plast Reconstr Surg. 2004 Jun;113(7):1960–1965, discussion 1966–1967. https://doi.org/10.1097/01.PRS.0000122207.28773.56

Ghazawi FM, Zargham R, Gilardino MS, Sasseville D, Jafarian F. Insights into the pathophysiology of hypertrophic scars and keloids. Adv Skin Wound Care. 2018 Jan;31(1):582–595. https://doi.

org/10.1097/01.ASW.0000527576.27489.0f
Gillanders SL, Anderson S, Mellon L, Heskin L. A systematic review and meta-analysis: do absorbable or non-absorbable suture materials differ in cosmetic outcomes in patients requiring primary closure of facial wounds? J Plast Reconstr Aesthet Surg. 2018 Dec;71(12):1682–1692. https://doi.org/10.1016/j.bjps.2018.08.027
Guo S, DiPietro LA. Factors affecting wound healing. J Dent Res. 2010 Mar;89(3):219–229. https://doi.org/10.1177/0022034509359125
Hart J. Inflammation 1: its role in the healing of acute wounds. J Wound Care. 2002 Jun;11(6):205–209. https://doi.org/10.12968/jowc.2002.11.6.26411
Marshall CD, Hu MS, Leavitt T, Barnes LA, Lorenz HP, Longaker MT. Cutaneous scarring: basic science, current treatments, and future directions. Adv Wound Care. 2018 Feb;7(2):29–45. https://doi.org/10.1089/wound.2016.0696
Monstrey S, Middelkoop E, Vranckx JJ, Bassetto F, Ziegler UE, Meaume S, Téot L. Updated scar management practical guidelines: non-invasive and invasive measures. J Plast Reconstr Aesthet Surg. 2014 Aug;67(8):1017–1025. https://doi.org/10.1016/j.bjps.2014.04.011
O'Kane S. Wound remodelling and scarring. J Wound Care. 2002 Sep;11(8):296–299. https://doi.org/10.12968/jowc.2002.11.8.26426
Profyris C, Tziotzios C, Do Vale I. Cutaneous scarring: Pathophysiology, molecular mechanisms, and scar reduction therapeutics. J Am Acad Dermatol. 2012 Jan;66(1):1–10, quiz 11–12. https://doi.org/10.1016/j.jaad.2011.05.055
Riyat H, Touil LL, Briggs M, Shokrollahi K. Autologous fat grafting for scars, healing and pain: a review. Scars, Burns & Healing. 2017 Jan;3. https://doi.org/10.1177/2059513117728200
Stephens P, Thomas DW. The cellular proliferative phase of the wound repair process. J Wound Care. 2002 Jul;11(7):253–261. https://doi.org/10.12968/jowc.2002.11.7.26421
Sund B. 2000. New developments in wound care. Clinical Report CBS 836. London: PJB Publications: 1–255.
Thomas Hess C. Checklist for factors affecting wound healing. Adv Skin Wound Care. 2011 Apr;24(4):192. https://doi.org/10.1097/01.ASW.0000396300.04173.ec
Verhaegen PDHM, van der Wal MBA, Middelkoop E, van Zuijlen PPM. Objective scar assessment tools: a clinimetric appraisal. Plast Reconstr Surg. 2011 Apr;127(4):1561–1570. https://doi.org/10.1097/PRS.0b013e31820a641a