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REVIEW

Evidence-based management of keloids and hypertrophic scars in dermatology

Emily Y. Kim[1] · Aamir Hussain[2] · Amor Khachemoune[3,4]

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Abstract

While normal, controlled wound-healing results in scars that are nearly imperceptible, hypertrophic scars (HTS) and keloids are the result of an abnormal wound-healing process that can leave unsightly, difficult-to-treat lesions. While such scars are classically associated with surgical incisions, they may also result from burns or accidental trauma to the skin. Several different measures can be taken to prevent the formation of scars or treat those that have already formed. Prevention focuses on reducing inflammation during the wound-healing process, and minimizing tension in the lesion when appropriate. Treatments range from non-invasive modalities such as pressure therapy, topicals, and symptom management, to invasive methods such as injections, lasers, and even surgery. While some treatments, such as corticosteroid injections, have been used in the treatment of HTS and keloids for decades, other newer therapies have only been described in case reports or are still in early phases of clinical trials. Because optimal scar management will not be the same for every patient, further investigation of newer agents and methods is warranted and may benefit a great number of patients. This paper will review the evidence-based management of scars, including current widely used treatment options and promising newly emerging therapies.

Keywords Hypertrophic scar · Keloid · Cutaneous scarring · Wound healing

Abbreviations

IL	Interleukin
EGF	Epidermal growth factor
PDGF	Platelet-derived growth factor
TGF-β	Transforming growth factor beta
CTCF	Connective tissue growth factor
HTS	Hypertrophic scar
FST	Fitzpatrick skin type
VSS	Vancouver Scar Scale
TAC	Triamcinolone
Th	T helper
TAC	Triamcinolone
RAS	Renin-angiotensin system
ACE	Angiotensin-converting enzyme
5-FU	5-Fluorouracil

✉ Amor Khachemoune
amorkh@gmail.com

[1] Georgetown University School of Medicine, Washington, DC, USA

[2] MedStar Washington Hospital Center/Georgetown University Dermatology Residency Program, Washington, DC, USA

[3] Department of Dermatology, Veterans Affairs Medical Center, SUNY Downstate, 800 Poly Place, Brooklyn, NY 11209, USA

[4] Department of Dermatology, Veterans Affairs New York Harbor Healthcare System, Brooklyn, NY, USA

Introduction

Scarring is the result of an essential wound-healing process. Normal healing results in scars that are nearly imperceptible, while abnormal healing may result in unsightly or even debilitating scars. The mechanism of wound healing has been well-described and broadly occurs in three phases, as outlined in Fig. 1: the inflammatory phase, the proliferative phase, and remodeling phase [1, 2]. When tissue injury occurs, platelets entering the site of injury come into contact with exposed collagen and elements of the extracellular matrix, which triggers the release of cytokines such as interleukins (IL)-6 and 8, clotting factors and growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β), inducing angiogenesis and the proliferation of fibroblasts, respectively [3]. The inflammatory phase occurs over days 1–3 after injury and involves hemostasis via activation of the extrinsic clotting pathway and formation of a platelet

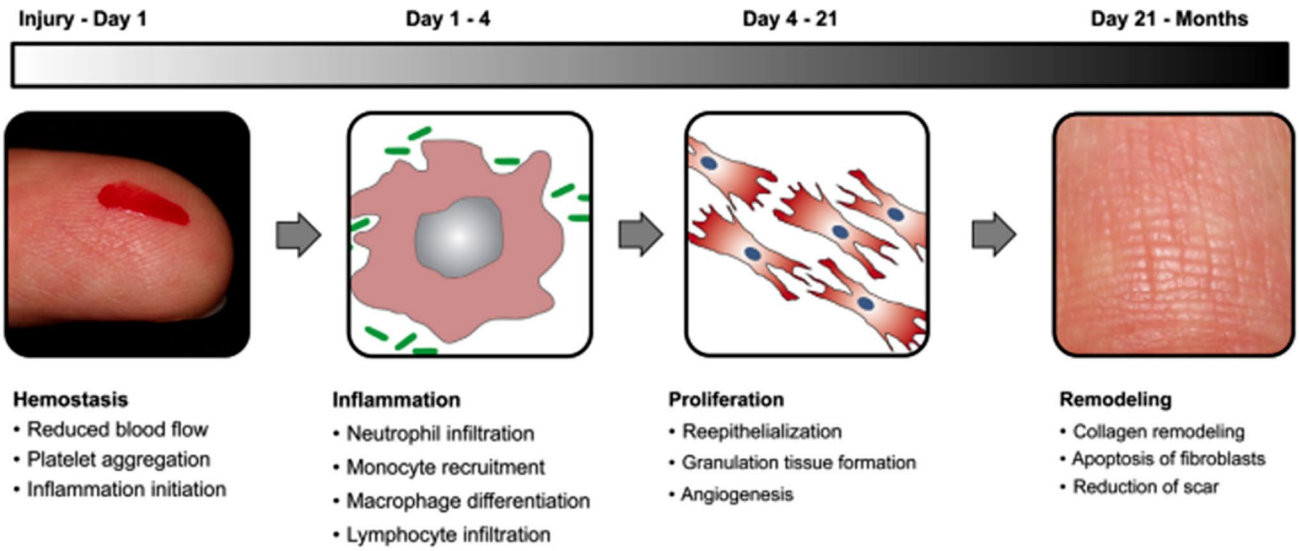

Fig. 1 Phases of wound healing. Reproduced with permission from Das S, and Baker AB (2016) Biomaterials and Nanotherapeutics for Enhancing Skin Wound Healing. Front Bioeng Biotechnol. 2016;4:82

plug, followed by a fibrin plug. Next, there is an influx of inflammatory cells and neutrophils to phagocytose pathogens and tissue debris, release growth factors, cytokines, and chemokines. Interleukin (IL)-8 is an inflammatory cytokine that is expressed on day 1 after injury and serves as a strong chemoattractant for neutrophils; connective tissue growth factor (CTGF) expression also increases at the same time, inducing fibroblast proliferation and matrix deposition as well as endothelial proliferation, migration, survival, and adhesion, before decreasing back to baseline by day 5 [4]. Additionally, there is coordinated upregulation of other proinflammatory cytokines such as IL-1a, IL-1b, IL-6, and tumor necrosis factor alpha (TNF-a) during the inflammatory phase that is important for normal wound healing [4]. For example, it was shown that knockout of the mitogenic IL-6 in animals caused dramatic delay in reepitheliazation and granulation tissue formation compared to wild-type controls; conversely, excessive levels are associated with scarring [5].

The inflammatory phase is followed by the proliferative phase from days 4 to 21, in which the key cells are macrophages, endothelial cells, and fibroblasts that deposit type III collagen to form granulation tissue, replacing the fibrin plug initially formed during the inflammatory phase. Fibroblasts proliferate and secrete extracellular matrix proteins that facilitate tissue remodeling and angiogenesis, while platelets and macrophages continue to secrete PDGF and TGF-β1 [2, 6, 7]. Keratinocytes around the wound edge undergo dedifferentiation and reorganize adhesion molecules to loosen connections between each other and to the basement membrane, thus allowing them to migrate across the wound surface and close the skin defect. This re-epithelialization is important to reestablishing tissue integrity. At this stage, the scar may be called "immature," and is characterized by a pink color with a "healing ridge" of edema plus collagen synthesis which peaks at about 3 weeks post-injury [8].

Finally, the remodeling phase occurs from day 21 to 1 year after injury. This phase involves reorganization of the extracellular matrix, apoptosis of the cells that had formed granulation tissue, and degradation and replacement of the type III collagen with stronger type I collagen. Later, actin-rich myofibroblasts with attachment points to collagen contract to reduce the surface area of the scar. When the wound healing process results in abnormal architecture of collagen during the remodeling phase, it leaves a visible scar [9]. While maximal strength of a scar is reached by 6 months, it may take a year or longer to become a mature scar, as characterized by resolution of erythema [8].

One method of classifying scars categorizes them as widespread, atrophic, contracture, hypertrophic, or keloidal [10]. Hypertrophic scars (HTS) and keloids are formed when the equilibrium of collagen synthesis and breakdown that occurs during scar maturation is lost, and collagen continues to accumulate, leaving a scar that is elevated above normal skin. Keloids and HTS differ in that HTS remain within the boundaries of the original lesion and tend to regress spontaneously after the initial injury, while keloids spread beyond the boundaries of the original wound, often grow over time, and have a high frequency of recurrence [10, 11]. Hypertrophic scars can further be subclassified as either linear, or widespread, the latter of which tend to form after burns [8]. Both HTS and keloids tend to be inflamed and can be pruritic and/or painful, though keloids tend to

be more severe [11]. Hypertrophic scars tend to form on the extensor surfaces of joints or at skin creases, while keloids usually form on earlobes, chest, shoulders, upper back, and posterior neck [11]. There may be a genetic predisposition to the formation of keloids, as they tend to occur frequently in individuals with Fitzpatrick skin types (FST) IV–VI [10, 12, 13]. The growth pattern of keloids tends to vary based on location [10]. Keloids tend to form between the ages of 10–30, especially during puberty or during pregnancy [10].

Superficial injuries that spare the reticular dermis never cause keloid and hypertrophic scarring; thus, the mechanism of their formation likely involves persistent inflammation and aberrant wound healing caused by injury to the reticular dermis [14]. The reticular layer of keloids and hypertrophic scars contains many inflammatory cells, fibroblasts, and newly formed blood vessels.

Prevention

A simple way to prevent formation of keloids or HTS is to avoid non-essential trauma to the skin (e.g., ear piercing, cosmetic surgery). Before surgery, scarring can be reduced with careful planning; incisions made parallel to Langer lines, which correspond to the natural orientation of collagen fibers in the dermis, heal with better cosmetic outcomes compared to incisions that cut across these lines [15]. Additionally, wounds along the sternum or that span joints are subject to increased mechanical force and heal more poorly. Since keloids and HTS likely result from chronic inflammation in the reticular dermis, surgical techniques such as hiding sutures in natural skin folds, and limiting the wound to a single cosmetic subunit may prevent scarring by reducing tension on the edges of the wound [16, 17]. Additionally, closing surgical wounds with subcutaneous tensile reduction sutures may result in superior cosmetic outcome compared to octyl cyanoacrylate tissue adhesive (Dermabond) [18].

Avoidance of UV exposure

UV exposure may aggravate the clinical appearance of scars [8, 19]. In the first randomized control study in humans to examine the effects of UV exposure on scars after dermatological surgery, punch biopsy wounds were randomized to post-op solar UV irradiation or no UV exposure. In wounds healed by secondary intention, UV-irradiated scars were more disfiguring, had significantly higher scores of color, infiltration, and surface area, and showed significantly higher skin-reflectance measurements of skin pigmentation compared to non-irradiated scars at 12 weeks post-op [19]. While UV radiation did not result in more disfiguring scars in wounds healed by primary closure, there were higher scores of scar infiltration at week 5 and color at week 12 for UV-irradiated scars. These outcomes may be skewed by the general irregularity of wounds due to stitching in primary closure, making it difficult to compare to wounds healed by secondary intention.

Silicone products

Though the exact mechanism is not fully understood, studies have shown that silicone gel sheeting likely potentiates healing through occlusion and hydration of the stratum corneum [20]. Sheeting provides mechanical stabilization to the lesion, which may reduce growth potential and encourage normal healing [21]. Several controlled comparative studies have shown that postsurgical treatment with silicone gel may both prevent formation of keloids or HTS, as well as improve the appearance of scars that do form compared to placebo [20, 22–24]. Despite the apparent benefits of silicone products, practicality and patient adherence is a potential barrier to treatment. Silicone gel or sheeting should be applied after the incision or wound has been epithelialized, around 2 weeks after primary wound closure, and worn for a minimum of 12 h daily for two months, though continuous 24-h coverage with washing twice daily is preferable [21, 25]. In areas where it is difficult to apply a sheet, gel may be used.

Paper tape

The use of paper tape may be arising as an option for scar prevention; a randomized controlled trial to determine the efficacy of paper tape in preventing hypertrophic scar formation are surgical incisions that crossed Langer lines found that treatment with paper tape for 12 weeks significantly reduced the development of hypertrophic scars, as well as decreased scar volume in those that did form [26]. Another study by Lin et al. found similar improvements in the Vancouver Scar Scale (VSS) with paper tape compared to silicone gel sheeting [27]. However, there is still a paucity of evidence in the literature regarding the effectiveness of paper tape; if shown to be efficacious, paper tape would be ideal from a cost-effectiveness and patient accessibility standpoint.

Management

A wide variety of invasive and non-invasive management options exist for scars and range from watchful waiting to topicals, injections, and surgery. These are summarized in Table 1. The management of HTS and keloids differs from that of atrophic scars, and the decision of whether to treat is based on four factors: the site, symptoms, severity of functional impairment, and amount of distress the lesion

Table 1 Summary of management options and non-invasive adjunctive treatments for hypertrophic scars and keloids

Treatment	Dose	Level of evidence
Intralesional corticosteroids	10 to 40 mg/mL	1
Laser + 5-FU ± Triamcinolone*	50 mg/mL 5-FU alone or 4:45 mg/ml TAC:5-FU	2
Bleomycin	1.5 IU/mL	2
Pentoxifylline	400 mg TID PO 1 mg/mL intralesional	2
ACE inhibitors/ARBs*	0.2–5% topical	2
Cryotherapy	1–10 sessions	2
Pressure therapy and splinting	12–23 h/day	3
Onion extract	Application 2–3 × daily	3
Dupilumab*	300 mg (600 mg loading dose)	4
Surgical excision		

Key to evidence-based support: (1) RCT or meta-analysis; (2) large series; (3) lesser quality large series; (4) small series ($n < 5$) or individual cases

*Clinical trial ongoing

causes the patient [10]. The "leave-alone" option may be suitable for scars < 1 year old, and HTS that may become much less noticeable on their own over time [10]. Success with non-invasive treatment is largely individualized; patients may choose to try these modalities as monotherapy or as adjunctive therapy, though they may not provide significant improvement. It is especially important to note that widespread hypertrophic scars often result from burns, and should be managed in a specialty burn unit. Therapy should be initiated only once the epithelium is intact and stable [25].

While already discussed for prevention, silicone-based products are considered a first-line non-invasive treatment option that reduces scar thickness, erythema and scar elasticity [26–35]. While they may be effective, regimens used in trials are intense and required application of gel sheeting for a minimum of 12 h/day for 6–12 months. If a trial of silicone products is not effective, or if the scar is severe and/or pruritic, intralesional steroid injections may be added [25].

Intralesional corticosteroids such as triamcinolone have long been considered a first-line treatment for HTS and keloids. Corticosteroids modulate intracellular gene expression to reduce synthesis of inflammatory mediators. Downstream effects include inhibition of collagen and glycosaminoglycan synthesis and fibroblast proliferation, while causing degradation of existing collagen and fibroblasts [21]. Further, triamcinolone increases collagenase production and reduces levels of collagenase inhibitors and induces ultrastructural changes in collagen synthesis via fibroblast glucocorticoid receptors to enhance organization of collagen bundles and degenerate the collagen nodules that are characteristic in keloids [30, 31]. Adverse effects of corticosteroid injection include fat atrophy, dermal thinning, and pigment changes, and responses to treatment may vary; thus, a multimodal approach may be necessary [32].

ACE inhibitors and angiotensin receptor blockers

Activation of the renin-angiotensin system (RAS) is associated with fibrosis in several organs such as the heart, liver, lung, and kidney [33–37]. RAS components including angiotensin II, angiotensin AT_1 and AT_2 receptors, and angiotensin-converting enzyme (ACE) are also expressed in the skin and act independently from the plasma RAS. Expression of AT_1 and AT_2 is increased in wounded skin. Stimulation of the AT_1 receptor, which is expressed by keratinocytes, activates cell proliferation and migration, collagen production, and angiogenesis by stimulation of angiogenic and fibrogenic factors such as TGF-β. Blockage of the AT_1 receptor with angiotensin receptor II blockers (ARBs) inhibits collagen production and has antifibrotic effects [38]. In a pilot placebo-controlled single blind study of 30 adults with HTS or keloids, VSS scores dropped significantly in the patients receiving losartan 5% ointment compared to the placebo group [39]. In another study, scars treated with 0.2% losartan-urea cream had significantly smaller scars compared to untreated controls, with decreased fibroblast proliferation and more regular collagen fibers [40]. Similar benefits can be seen with ACE inhibitors which ACE inhibitors exert anti-fibrotic effects through suppression of TGF-β1/SMAD and TGF-β1/TAK1 pathways both in vitro and in vivo [41]. In a double-blinded clinical trial including patients with second- or third-degree burn hypertrophic scars, the mean size and itching scores of scars topically treated with enalapril 1% ointment twice daily were significantly decreased compared to scars that received placebo [42]. Ramipril and captopril have also been reported to reduce scar size via inhibition of TGF-β and PDGF expression, and the use of captopril 5% cream for 6 weeks was reported to reduce the height, redness, and itching in a keloid from burn injury in a case report [40, 41, 43]. Several other molecules are involved in the mechanism by which RAS components are involved in scar formation and reduction, and more in-depth studies are needed to elucidate the clinical benefit of RAS inhibitors. A randomized control trial of intralesional ACE inhibitor in combination with triamcinolone for the treatment of keloids is currently underway (NCT05259137).

Pentoxifylline

There is increasing evidence for use of oral pentoxifylline—a methylxanthine derivative and a nonspecific phosphodiesterase inhibitor used for intermittent claudication—in keloid

treatment. In vitro studies have shown that pentoxifylline doubles the collagenase activity of fibroblasts, inhibits lattice contraction and slows wound contraction, while decreasing amounts of collagen, glycosaminoglycans, fibronectin, and fibroblast proliferation [44–47]. In one pilot study, patients who took pentoxifylline 400 mg by mouth 3 times daily for 6 months after surgical excision of their keloid(s) saw a recurrence rate of 10.5% compared to 66.7% in the control group that did not take pentoxifylline post-surgery [48]. A recent study comparing intralesional injection of pentoxifylline and TAC reported that pentoxifylline is safe and well-tolerated in the treatment of keloid but has lower efficacy than TAC when used alone; however, the combination of pentoxifylline and TAC significantly improved treatment results and lowered the risk of side effects from steroids [49].

5-fluorouracil (5-FU) and laser therapy

5-FU is a fluorinated pyrimidine analog that inhibits the synthesis of the nucleoside thymidine, halting DNA replication. While traditionally used as a chemotherapeutic agent, the mechanism of 5-FU in scar treatments seems to be via inhibition of fibroblast proliferation and induction of apoptosis without necrosis, as well as inhibition of TGF-β-induced type I collagen synthesis [50]. While injections of 5-FU alone may provide significant improvement of keloids, one systematic review found that TAC combined with 5-FU resulted in the greatest reduction in scar size, compared to lasers, topicals, and physical treatments [31, 37].

5-FU may be effective as an adjunct to laser therapy. A prospective, double-blinded, single-subject study comparing fractional laser-assisted corticosteroid versus laser-assisted 5-FU delivery in the treatment of HTS found that both methods resulted in similar reduction in overall scar area, but treatment with steroids resulted in additional side effects such as dermal atrophy and telangiectasia formation that were not associated with 5-FU [52]. Another study that investigated the efficacy of laser-assisted 5-FU delivery to 44 keloid lesions in 24 patients found significant improvement after three treatment sessions, as measured by a reduction in mean VSS of 65%, from 8.45 ± SD 0.93 at the baseline to 3 ± SD 1.8 one month after the end of treatment [53]. The greatest improvement was seen in scar height and pliability. Reported adverse effects included post-inflammatory hyperpigmentation and skin erosion, and recurrences occurred in 21% of patients at 1-year follow-up; however, this recurrence rate is much lower than those reported in other studies that used either FCO_2 laser (95% recurrence) or 5-FU (35% recurrence) monotherapy for keloids [53]. Intralesional 5-FU seems to be less effective as monotherapy, only showing utility for management of small keloids of shorter duration, and should be combined with other treatment modalities to improve outcomes and reduce duration of treatment and recurrence [54, 55].

Laser therapy may be considered as second or third-line treatment of HTS and keloids, especially as it is a more expensive treatment modality [25]. A systematic review of laser treatment found the greatest improvement in scar erythema, height, and pliability after treatment with the fractional ablative CO_2 and Er: YAG 2940 nm lasers, with slightly less improvement with the PDL 585 nm laser [56]. It is important to note that studies using ablative lasers for other indications such as skin rejuvenation and ecchymosis found scarring to be an adverse effect [56, 57]. Results from laser treatment may vary by patient; one systematic review suggests that response to this treatment is greatest for FST I-III [51].

Cryotherapy

Cryotherapy may be a reasonable adjunct therapy for HTS and keloids, however large-scale comparison studies are not yet available. While results are mixed, some studies suggest that it is safe and can achieve good scar reduction with just a few treatments [58, 59]. In an 18-month trial of intralesional needle cryoprobe in the treatment of HTS and keloids, an average 51.4% reduction of scar volume was seen after one session with significant alleviation of objective measures such as hardness and color, as well as subjective symptoms such as pain, tenderness, pruritus, and discomfort [60]. Adverse effects of cryotherapy include depigmentation, recurrence, and pain, though these are uncommon and often temporary [59].

Dupilumab

There have been increasing reports of the use of dupilumab for the treatment of keloids and HTS [61–63]. Dupilumab is a monoclonal antibody that blocks T helper (Th)2-mediated IL-4 and IL-13 signaling, and has been shown to improve symptoms such as pruritus in patients with atopic dermatitis and bullous pemphigoid, among other inflammatory conditions [64–66]. These inflammatory cytokines have been shown to stimulate human dermal fibroblasts to secrete periostin and indirectly, TGF-β, which are central to abnormal scar formation [67]. Dupilumab has been shown to effectively alleviate pruritis and improve clinical appearance of HTS [61]. IL-4 and IL-13 are have been implicated as key mediators in the pathogenesis of fibroproliferative disorders; indeed, keloids show increased expression of IL-4 and IL-13, making blockade of these cytokines a target for treatment [63, 68]. Diaz et al. reported that after treatment with dupilumab, their patient had shrinkage and flattening of a large keloid, and complete disappearance of a smaller

keloid [63]. After this report, others have reported significant improvement in pain after just 4 weeks of dupilumab therapy, with near complete absence of symptoms after 3 months [62]. However, more studies are needed to elucidate the efficacy of dupilumab in the treatment of keloids, and a clinical trial (NCT04988022) is currently underway.

Bleomycin

Bleomycin is a glycopeptide antibiotic that is traditionally used as a chemotherapeutic agent but may also be effective in the intralesional treatment of HTS and keloids, though evidence is largely anecdotal. One study comparing intralesional injection of bleomycin versus 5-FU found significantly greater improvement on the VSS in the group treated with intralesional bleomycin compared with intralesional 5-FU alone or 5-FU plus TAC [69]. There was less ulceration in the group that received bleomycin alone, but more pain after injection; additionally, there was no relapse in this group whereas the 5-FU alone or 5-FU plus TAC groups had relapse rates of 40% and 46.67%, respectively [69]. The authors concluded that bleomycin injection was more effective and better in remission than intralesional 5-FU in the treatment regardless of patient's age, sex, disease duration or site of the lesion. A study of 50 patients receiving bleomycin by multiple superficial puncture technique for HTS and keloids resulted in complete flattening in 22 patients (44%), significant flattening in 11 patients (22%), adequate flattening in 7 patients (14%) and no flattening in 10 patients (20%) [70]. In another study of 13 patients receiving bleomycin injections for keloids or HTS, 6 patients had complete flattening, 6 had highly significant flattening (> 90%), and 1 had significant flattening (75–90%) [71]. Though similar studies suggest bleomycin may be a promising drug in the treatment of HTS and keloids, it should not be the initial treatment of choice until further controlled studies have been conducted.

Surgical excision

Surgical excision is generally used for refractory cases of HTS or keloids. While the rate of recurrence for keloid scars treated with surgery alone ranged from 50%-80%, the use of corticosteroids after surgery lowers the recurrence rate to less than 50% [64, 65, 68, 73]. One study found that combined intralesional and topical corticosteroids following surgical excision resulted in recurrence rates of 14.3% in keloids and 16.7% in HTS [74]. The addition of radiation following surgery further reduces the recurrence rate to < 10%; the best outcomes were achieved with 30 Gray administered within 2 days of surgery [72]. Radiotherapy alone is likely insufficient, as monotherapy had a recurrence rate of 37% compared to 22% as an adjunct to excision; recurrence rates were highest for x-ray (35%) compared to brachytherapy (21%) and electron beam (17%) [75]. Radiotherapy is usually reserved for abnormal scars that are resistant to other treatments, and the overall consistency of effects across studies is low [75].

Non-invasive adjunctive treatments

Pressure therapy and splinting

There is variable evidence to support the use of pressure (compression) therapy in the treatment of scars. This is most suitable for scars in the limbs and trunk, and results may vary widely based on the amount of pressure used. One study reported significant decrease in thickness of HTS, though only in the first month of treatment, and no difference in erythema [76]. One 12-year prospective study of patients who wore pressure garments over burn scars found that scars in the normal compression zone (mean pressure 25.0 mm) saw significant decreases in thickness and hardness compared to those in the low compression zone (mean pressure 6.4 mm) [77]. Poor patient compliance detracts from study validity, as dressings should be worn at least 23 h a day at 20–40 mmHg in order to see improvement [77]. The potential morbidity and costs currently appear to outweigh its still unproven efficacy, as pressure garment therapy has not seemed to alter global scar scores compared to controls [78]. Static and dynamic splints can be tried for scars that span joints or are in areas of excessive movement to establish appropriate positioning of affected extremities during healing to prevent contractures and restore normal range of motion [79].

Onion extract

A randomized controlled trial showed that onion extract gel improved scar softness, redness, texture, and global appearance at the excision site after superficial shave removal of skin lesions; these results have been reproducible [80, 81]. However, onion extract may be ineffective in treating deeper scars [82]. In an open-label study, patients who applied a combination gel containing onion extract to their scars twice daily for 24 weeks saw significant reduction of erythema and markers of neoangiogenesis, overall improving the appearance of their scars [83]. Another study found that TAC combined with onion extract was more effective than TAC alone in improving pain, itching, and thickness [84]. However, several studies suggest onion extract does not provide more therapeutic benefit than a petrolatum emollient, and the overall strength of evidence is low [85, 86].

Scar massage therapy

Scar massage therapy may only be anecdotally effective; one meta-analysis of 144 patients across 10 different studies found weak evidence for its efficacy, as reported outcome measurements were neither standardized nor objective, and treatment regimens varied widely [87]. Benefits of scar massage seem to be only symptomatic and psychological relief, as patients have reported reduced itching, pain, and anxiety and improved mood after massage therapy sessions [88, 89].

Conclusion

Abnormal wound healing after skin trauma may result in HTS and/or keloids, which may cause significant medical and psychosocial distress to patients. There are a variety of potentially helpful prevention and treatment options, including medications, surgical procedures, and combination therapies. Further research is needed for head-to-head comparisons among these treatment modalities, as well as special considerations regarding post-inflammatory hyperpigmentation and scarring in patients with deeper skin tones (e.g., FST IV-VI).

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Declarations

Conflict of interest Emily Y. Kim, Aamir Hussain, and Amor Khachemoune declare that they have no conflict of interest.

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