Current Advances in Hypertrophic Scar and Keloid Management

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Abstract

Hypertrophic scars and keloids are caused by excessive tissue response to dermal injury due to local fibroblast proliferation and collagen overproduction. This response occurs because of pathologic wound healing due to dysregulation in the inflammatory, proliferative, and/or remodeling phase. Patients with hypertrophic scars or keloids report reduced quality of life, physical status, and psychological health. Hypertrophic scars or keloids will develop in 30 to 90% of individuals, and despite their prevalence, treatment remains a challenge. Of the treatments currently available for hypertrophic scars and keloids few have been adequately supported by studies with appropriate experimental design. Here, we aim to review the available literature to provide up-to-date information on the etiology, epidemiology, histology, pathophysiology, prevention, and management options available for the treatment of hypertrophic scars and keloids and highlight areas where further research is required.

Keywords
- scarring
- fibrosis
- keloid
- hypertrophic scar

Hypertrophic scars (HTSs) and keloids are benign fibroproliferative disorders that arise following cutaneous injury or irritation of the skin involving the dermal layer.[1] Both are cosmetically disfiguring and are commonly associated with reduced quality of life, physical status, and psychological health.[2,3] Following surgery, development of scars is a major source of patient dissatisfaction.[4,5] In the United States alone, the cost of managing HTSs has been estimated at 4 billion dollars annually.[6] Due to the high costs associated with management and large impact on patient-reported outcomes, this article aims to inform the reader about the most up-to-date understanding of the etiology, epidemiology, histology, pathophysiology, prevention, as well as available and emerging treatment options for HTSs and keloids.

Overview of Keloids and Hypertrophic Scars

HTSs and keloids are diagnosed clinically. HTSs generally appear within 1 month of injury and grow over a 6-month period but then can regress within 1 year or stabilize.[7] HTSs are distinguished from keloids in that they are contained within the boundaries of the original injury.[8] Although they do not have a predominant anatomical site, HTS typically occur in areas of high tension. Clinically, they present as red, raised, and pruritic.[9,10]

Keloids typically arise within 3 to 12 months following cutaneous trauma in predisposed individuals.[7] They occur most commonly on the ear lobes, chest, shoulders, upper back, posterior neck, cheeks, and knees.[7,11] Patients presenting with keloids may present with burning, pruritus, pain, and hyperesthesia.[12,13]

Epidemiology

The precise incidence and prevalence of HTSs and keloids varies greatly in the literature.[12,14,15] Keloids occur equally in men and women, but are more common in younger individuals of African, Asian, and Hispanic descent.[12,16–18] In black

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and Hispanic populations, the incidence of developing keloids ranges between 4 and 16%, while in Caucasian populations incidences are below 1%.[18–24]

The incidence of keloids has also been reported to be increased in individuals with rare genetic disorders such as Rubinstein–Taybi syndrome, Dubowitz syndrome, Bethlem myopathy, Noonan syndrome, and Goeminne syndrome and in people with blood type A, hyper-immunoglobulin E, and during puberty and pregnancy due to hormonal peaks.[12,18] In Rubinstein–Taybi syndrome, keloids have most often been observed in patients with autosomal dominant mutations in CREBBP or EP300.[25] In one study, a predominance of patients presenting with keloids had blood type A.[26] Other studies have reported no association between keloid formation and blood groups, therefore future investigations are necessary to determine if there is an association between blood groups and keloids.[27]

Family heritability and prevalence in twins also suggests a genetic predisposition to keloids.[26,28] A study looking at 14 pedigrees of familial keloids suggested that the pattern of inheritance is autosomal dominant with incomplete clinical penetrance and variable expression.[28] However, studies have also reported autosomal recessive and X-linked inheritance.[29,30] Many genes are likely to play a role in keloid formation; however, current attempts in identifying these genes have been unsuccessful.[15]

Less is known pertaining to the incidence of HTSs. In contrast to keloids, there is no evidence to support genetic factors' influence on the development of HTSs.[11] Like keloids, the incidence is higher in persons 10 to 30 years old.[31] Studies have reported higher incidences of HTSs in adolescents and pregnant women and a low incidence among patients with albinism.[32] They can occur up to 91% of the time following burns.[31] Moreover, in patients with full thickness burns, the prevalence of HTSs is up to 70%.[33]

Histology and Pathophysiology

Wound healing is a complex dynamic process that is subdivided into three distinct phases: inflammatory phase, proliferative phase, and remodeling phase which often overlap. The pathogenesis of HTSs or keloids is incompletely understood. However, dysregulation in any of these phases can predispose their development. While HTSs and keloids are distinct entities they lie within a spectrum of the same pathophysiologic process. Classically, proinflammatory cytokines interleukin (IL)-6, IL-8, and anti-inflammatory cytokines IL-10 are involved in wound healing.[12] It is suggested that dysregulation of these cytokines can promote the development of HTSs and keloids. Transforming growth factor (TGF)-β, a factor which regulates fibroblast proliferation, collagen synthesis, and promotes differentiation of fibroblasts into myofibroblasts is present at the site of injury.[34] TGF-β has multiple isoforms of which 1 to 3 are implicated in this aberrant process. TGF-β1 and 2 activate fibroblasts and TGF-β3 is a receptor antagonist which reduces fibroblast activity. It is proposed that upregulation of TGF-β1 and 2 and downregulation of TGF-β3 promotes increased collagen production and, therefore, increases extracellular matrix (ECM).[35] Compared with normal skin, HTSs and keloids have a 3- and 20-fold increase in collagen production.[36] Other factors that are differentially regulated include matrix metalloproteinases, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1), epidermal growth factor, vascular endothelial growth factor (VEGF), tumor necrosis factor-α, and connective tissue growth factor.[3] Altogether, these factors promote an environment where there is increased proliferation fibroblasts and overproduction of collagen and ECM and a reduction in fibroblast apoptosis.

Histologically, the epidermal layer of HTSs and keloids tend to be normal.[10] The pathological changes occur in the reticular dermal layer where there is excessive deposition of collagen fibers and increased vascularization and cellularity. In HTSs there is flattening of the epidermis and replacement of dermis by fine collagen fibers organized in a wavy, parallel-oriented regular pattern relative to the epidermis and the vessels are oriented vertically.[10] HTSs have a larger abundance of type I and III collagen compared with normal tissue but there is an increased ratio of type III to I collagen and increased levels of low-density dermatan sulfate proteoglycans.[35]

Butler et al described four characteristic features of keloids which include (1) haphazard hyalinized collagen fibers and bundles, (2) presence of a tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis, (3) a horizontal cellular fibrosis band in the upper reticular dermis, and (4) a prominent fascia-like band.[37] Based on these characteristic features, the collagen in keloids has often been referred to as "keloid collagen."[38] Keloids contain larger amounts of mature collagen (type I) than immature collagen (type III).[32] In addition to collagen, there is increased deposition of fibronectin, glycosaminoglycans, chondroitin sulfate, and proteoglycans but reduced elastic and decorin.[39] The expression of α-smooth muscle actin is variable in keloids.[40]

Prevention

Current prevention strategies are predominantly focused on reducing inflammation. One prevention method which cannot be overstated is tension-free wound closure.[41] Minimizing tension during closure is the single most important modifiable factor in the prevention of scar formation.[42] This is because when greater tension is applied at the edges of a wound, excessive scarring is more likely to occur.[43] While the complete mechanism is still unclear, by reducing mechanotransduction there is likely a reduction in the associated activation of the inflammatory response.[44]

Pressure therapy can also be used as a part of a prevention strategy. The use of pressure garments, bandages, adhesive plaster molds, or specialized devices have been previously found to minimize scarring. Pressure therapy is theorized to reduce perfusion to the wound resulting in attenuated release of inflammatory cytokines and a reduction in collagen synthesis and scar formation.[3] Moreover, the application of pressure is thought to increase apoptosis, decrease

angiogenesis also contributing to reduction in pathologic scar formation.[3]

Silicone sheeting can be used to provide passive mechanical stabilization and thereby help mitigate the growth potential of the scar and encourage normal healing. Silicone gel sheeting is a soft, self-adhesive, and semiocclusive sheet which contains medical grade silicone reinforced on a silicone membrane backing.[45] Scar reduction is felt to occur via occlusion and hydration of the outer layer of epidermis, generation of static electricity, and a reduction in mast cells.[45–47] Silicone sheeting should be started approximately 2 weeks after the primary wound treatment, and they should be left on as much as possible per day for a minimum of 2 months.[3] In areas of the body where it is difficult to apply sheets, silicone gel can be used instead which employs a similar mechanism.[3]

Similar to silicone sheeting, the use of paper tapes has been shown to reduce HTSs in animal and human models.[48–50] They can be placed over incision lines and they aid by reducing tension on wound edges and minimizing shearing.[51] More recently, a randomized controlled trial used paper tape for 12 weeks postoperatively following cesarean section and they observed decreased scar volume and HTS development.[52] Despite the positive results associated with the use of paper tapes, there is still a paucity in the literature regarding their effectiveness. Further investigation is necessary and would be valuable to the field given they are more cost effective and are easy to apply.

Flavonoids are compounds obtained from plants that have garnered some research interest in management of scars due to their anti-inflammatory properties. *Allium cepa*, a derivative of the flavonoid quercetin found in natural products such as onion extract, has been suggested to play a role in the prevention of scar formation due to its anti-inflammatory properties; however, efficacy has yet to be demonstrated clinically.[53] Quercetin (found in plants, vegetables, and fruits like onions, apples, and berries) has been shown to inhibit fibroblast proliferation, collagen production, and contraction of keloid and HTS-derived fibroblasts.[54] Gels containing flavonoids (e.g., Mederma Skin Care Gel, Contractubex) have also been used; however, their efficacy has not been born out in the literature.[55–57] Due to the heterogeneity in the evidence further studies are necessary to determine the efficacy of flavonoids as a modality for severe scar formation.

Hydration with emollients such as petrolatum and the application of sunscreen are two other methods used for prevention.[58] Avoiding the sun or using sunscreens with a high protection factor helps protect from ultraviolet radiation exposure which has been shown to increase scar pigmentation and as such can worsen the clinical appearance of the scar.[59,60]

Scar massage has also been shown to decrease scar-related pain and itchiness; however, no studies have successfully demonstrated its effectiveness of HTS prevention.[7] Randomized clinical trials assessing the effectiveness of scar massage as a means of prevention is warranted. Compression garments also do not have clinical studies; however, compression therapy has been shown to reduce collagen synthesis and is a first-line treatment in burn scars.[7]

Treatments: Current Practice and Emerging Therapies

There are numerous treatment options available for the management of HTSs and keloids. Available treatments include noninvasive, injectable, and surgical options and they vary in efficacy. However, despite the many modalities that exist, it is important to note that HTSs can regress over time without treatment.[7,11]

Noninvasive Therapies

Silicone sheeting and pressure therapy which were previously described above as a method of prevention/prophylaxis are commonly used as noninvasive topical therapy options. Silicone sheeting is one of the first-line therapies for HTSs and keloids, with modest, yet inconsistent efficacy.[61]

Several topical agents have been investigated for sure in management of HTS and keloids. Imiquimod, a Toll-like receptor immune response modifier, has previously been reported to help when the cream was applied daily or on alternate days; however, other studies show conflicting results.[62–66] Verapamil has also been investigated as a potential agent for management of HTS and keloids. Verapamil is a calcium channel blocker that stimulates the enzyme collagenase which increases degradation and prevents production of collagen. Two randomized controlled trials have shown its efficacy; however, like imiquimod, conflicting results have been reported.[67–69] More specifically, one study showed that verapamil may be as effective as intralesional triamcinolone acetonide but results in fewer adverse events.[67,69] Similarly, in the study by Danielsen et al, verapamil was shown to be safe but was associated with a higher rate of recurrence.[68] They also noted that further studies are necessary as their cohort only consisted of 14 subjects.[68]

Injectable Therapies

There are several types of injectables which can be used for treatment. One of the first-line treatments for HTSs and keloids are intralesional corticosteroid injections, they are often also done in combination with silicone sheeting.[61] Steroids have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive properties which can help reduce pain and pruritus.[70,71] Steroids reduce collagen and glycosaminoglycan synthesis, inhibit fibroblast proliferation, and cause degeneration of collagen and fibroblasts.[3,72,73] Using intralesional corticosteroids allows for attainment of higher concentrations of steroid at the scar site with minimal systemic absorption.[74] Intralesional corticosteroid injections are usually done with triamcinolone at a dose of 10 to 40 mg/mL every 4 to 6 weeks.[75] Typically, systemic side effects are not seen since low doses are used; however, it has been reported that repeated dosing with steroid injection can be associated with hypertension, heart failure, uncontrolled diabetes, and bacterial and fungal infections.[71] Intralesional injections have also been associated with early effects such as bleeding, bruising, infection, impaired wound healing, sterile abscesses, and delayed effects such as cutaneous and

subcutaneous lipoatrophy, leukoderma, telangiectasia, and localized or distant steroid acne.[71,76]

5-Fluorouracil (5FU) is a pyrimidine analog that inhibits thymidylate synthase enzyme. Its use as a therapy option in HTSs and keloids is based on the fact that it inhibits fibroblast proliferation, induces fibroblast apoptosis without necrosis, delays cell cycle progression, and inhibits TGF-β-induced collagen type I synthesis.[3,77] The preferred method of administration is intralesional.[78] When using corticosteroids or 5FU, combination with other treatment modalities is common.

Bleomycin has also been investigated as a treatment modality for HTS and keloids. Bleomycin is a cytotoxic antibiotic that has antiviral, antineoplastic, and antibacterial properties. Its mechanism of action is still unclear, but studies have shown that it can decrease collagen synthesis, reduce lysl-oxidase levels, and can induce apoptosis.[79] Like bleomycin, mitomycin C (MMC) has antineoplastic and antiproliferative properties. Studies thus far support the use of MMC topically; however, higher-powered studies are required.[80] Generally, the intralesional MMC is less tolerated by patients.[80,81]

Surgical Therapies

Cryotherapy is a modality which has shown effectiveness for small keloids and HTSs.[31] Liquid nitrogen can be delivered externally (spray or contact) or via an intralesional needle cryoprobe.[31] The intralesional needle cryoprobe has been shown to be the most efficacious form of cryotherapy.[82] This technique consists of an intralesional cryosurgical needle connected to a canister of liquid nitrogen that causes the cryoprobe to freeze then it is used to freeze HTSs from the inside out.[83] Following just one session, patients saw a 51.4% reduction in scar volume and required less treatment cycles overall.[82] Following a second session 30 to 75% of keloids improved, and higher rates were seen in HTSs.[7,31] A recently published review assessing intralesional cryotherapy concluded that the technique is safe, requires few treatments, and is associated with depigmentation, recurrence, and pain.[84] Notably, the pain and recurrence are uncommon and depigmentation was often temporary.[84] External methods have been associated with hypopigmentation, blistering, pain, delayed healing, and infection.[85,86] Freeze-thaw cycles between 10 and 20 seconds are delivered at the site; larger scars require repeated sessions.[31] Cryotherapy works by inducing cell injury and necrosis in the treatment area (i.e., the scar). It is often performed in combination with other treatment modalities.[3]

Surgical excision to reduce/remove the scar can be indicated. Generally, surgery is not recommended unless conservative therapies are not successful or do not provide significant improvement. While recurrence rates are usually low in HTSs, the rates vary between 45 and 100% for keloids.[13,32,87] Combination with other therapies such as intralesional corticosteroids, intralesional fluorouracil, cryotherapy, and radiation therapy can lower the recurrence rates.[88–91]

Other

Laser therapy is another modality used for treatment. Generally, laser therapy is considered a second- or third-line option for treatment of both HTSs and keloids following failure of silicone sheeting or intralesional steroids.[61] Recently, a systematic review assessing laser treatments for specific characteristics of HTSs and keloids was published.[92] Lasers being used as treatment modalities included pulsed dye lasers (PDLs) 585 and 595 nm, fractional CO_2 lasers, ER:YAG 2940 nm lasers, and Er-doped laser 1550 nm.[92] The most commonly used laser therapy in practice is the 585 nm PDL.[93] Overall, improvement in scar erythema, height, and pliability was seen with the fractional ablative CO_2 lasers and ER:YAG 2940 nm lasers followed by the PDL 585 nm laser.[92] Regarding scar erythema, improvements of 56, 53, 26, and 11% were seen using the CO_2 laser 10,600 nm, ER:YAG 2940 nm, the PDL 585 nm, and the PDL 595 nm, respectively, with an overall mean of 37%.[92] The scar mean height was reduced by 46% using the CO_2 laser 10,600 nm and ER:YAG 2940 nm and by 37% using the 585 nm PDL and 19% using the 595 nm PDL and an overall reduction of 37%.[92] Lastly, a 59, 42, and 40% improvement in scar pliability was observed for the CO_2 laser 10,600 nm, ER:YAG 2940 nm, and the 585 nm PDL, the overall mean scar pliability was 47%.[92] The Er-doped based laser 1550 nm showed little improvement in scar erythema (1.20) and pigmentation (0.93) (scale: 0 = no improvement or worsened, 3 = marked improvement).[92]

Radiotherapy is a treatment modality that can be delivered through external beam, internal radiation (brachytherapy), or with radioactive skin patches.[94] In susceptible areas such as the head, neck, and breast and in patients under 18 years old, it is recommended to proceed with caution as there is increased risk of carcinogenesis.[13] Radiotherapy is suggested to work by inducing antiangiogenic and anti-inflammatory properties. Studies have shown that postoperative radiotherapy was more effective than radiotherapy alone at lowering the recurrence of keloids.[95] It is typically performed 24 to 48 hours postoperatively, across several sessions and the total recommended dose is 40 grays.[96]

Emerging/Experimental Therapies

There are several therapies which are currently emerging that may help reshape the current management of HTSs and keloids. Intralesional injection of botulinum toxin A has been proposed as a treatment option as it would induce paralysis of the musculature that surrounds the scar and thus cause less tension.[97] In both HTSs and keloids, all treatment patients showed some level of improvement with botulinum toxin A treatment.[98,99] In one study, 12 patients presenting with keloids were administered intralesional injections of botulinum toxin A.[98] Here, a significant decrease in the size of the keloids was observed as well as no reappearance of the lesion or symptoms at 1-year follow-up and high patient satisfaction.[98] In addition, in a randomized controlled trial, when intralesional injection of botulinum toxin A was compared with intralesional corticosteroids for the treatment of keloids, it was found to be as effective and better tolerated.[100] Similarly, when botulinum toxin A was administered for HTSs, all patients showed acceptable improvement and the erythema, itching sensation, and pliability scores were all significantly reduced compared with pretreatment.[99]

Moreover, there was high patient satisfaction with the treatment.[99]

A second emerging therapy option is mesenchymal stem cell (MSC) therapy. Through the release of growth factors, MSCs can modulate inflammatory responses and have an antifibrotic effect.[12] Current studies in cell and animal models have been introducing MSCs through systemic or local injection or using an MSC-seeded tissue scaffold.[101] Recently, a systematic review evaluated the effectiveness of MSC transplantation in the treatment of HTSs and keloid scars in an in vivo model.[102] All included studies found improvements in macroscopic and histological appearances of scars and the authors concluded that the data supports a role for MSCs in the treatment of scars in in vivo models and suggest that further exploration of MSCs as a treatment modality is warranted.[102]

Fat grafting, either by fat injection or fat tissue grafting underneath or into the wound have been investigated as adjuvant therapies.[3] While the mechanism is still unclear, it is theorized that adipose-derived stem cells (ASCs) possess biological properties that improve cutaneous fibrosis, in part related to angiogenic and antiapoptotic properties.[103,104] In vitro and animal studies have demonstrated that fat grafting stimulates angiogenesis due to IGF-1, VEGF, and PDGF.[105] VEGF also plays an important role in fibrotic tissue replacement.[105] The ASCs are also able to regulate vessel density, collagen thickness, and the granulation process which altogether can lead to improved appearances of scars.[106] To our knowledge, no clinical studies have specifically assessed fat grafting for the treatment of HTSs and keloids. A review aimed at assessing the use of fat grafting to treat HTSs and keloids found that although no studies independently looked at these scars, individual cases and qualitative results using this technique were promising.[103] Based on the available literature which shows a positive effect of fat grafting in wound healing and radiation-induced cutaneous fibrosis, further investigations should be performed to determine if it would be an effective treatment modality for HTSs and keloids.[103]

Trials with interferon-α-2β are also being conducted. When administered with triamcinolone or postexcision of keloids, studies demonstrated significant decreases in volume and depth as well as reduced recurrence rates compared with controls; however, there was a significant dropout rate of patients across studies related to significant pain at injection site and flu-like symptoms associated with interferon.[107–109]

As previously mentioned, TGF-β1–3 has been elucidated to play a large role in the development of HTSs and keloids. Animal studies have shown, that neutralizing TGF-β inhibited fibrosis thereby suggesting that human recombinant TGF-β1,2,3 neutralizing antibodies may serve as an important treatment modality; however, it is currently not unavailable.[3,110,111]

Conclusion

Despite being a benign proliferative disorder, HTSs and keloids significantly reduce the quality of life, physical status, and psychological health of patients.[2,3] They also present a significant cost to health care systems. Tremendous efforts have been made to gain a comprehensive understanding of their pathophysiology, prevention, and management. Although several treatment modalities are available, there is considerable variation in the literature as to efficacy. As both scars appear due to dysregulation in the wound healing process, modalities which aim to alter the inflammatory milieu and the immune response are promising areas of continued research.

Conflict of Interest
None declared.

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