Pruritus in Keloid Scars: Mechanisms and Treatments

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Keloids are scars that extend beyond the margins of an insulting cutaneous injury. Keloids are often thought to be primarily a cosmetic issue, as they are typically quite raised and pigmented. However, these scars also present with functional symptoms of pruritus and pain that significantly impact quality of life. The symptom of pruritus is frequently overlooked by dermatologists, and treatments are often primarily focused on the gross appearance of the scar. This review describes the prevalence and importance of pruritus in keloids. In addition, the putative mechanisms underlying the development of keloid pruritus, which include neuronal and immunological mechanisms, are discussed. Furthermore, this review describes keloid treatments that have been shown to reduce pruritus, treatments that specifically target the itch, and emerging therapies.

Key words: keloid; pruritus; therapeutics; neuropathy.

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In addition to their obvious cosmetic concerns, keloid scars often present with lesional and perilesional pain and pruritus. We showed previously that the sensation of pruritus was noted in 86% of patients with keloids (1). In a recent case-control study of 102 African patients with keloids, 67% experienced keloid-associated pruritus (2). One study of 120 African patients with keloids found that 95% of subjects experienced keloid-associated pruritus, causing a significant impact on their quality of life (3) Another study of 106 keloid patients in the Netherlands found that 71% of patients experienced at least moderate keloid-associated pruritus that negatively impacted their health-related quality of life (4). These symptoms are often overlooked by practitioners with treatment end-goals and management of keloids focusing on gross scar appearance. However, the lesional and perilesional pruritus associated with keloids is often a primary concern for patients. Clearly, keloid-associated pruritus is a major concern that warrants more attention and further exploration.

The underlying mechanism of keloid-associated pruritus remains unclear, although potential mechanisms have been proposed. There is currently no consensus on the treatment and management of keloidal pruritus. This review provides an overview of keloid-associated pruritus and the putative mechanisms by which available treatments act.

SIGNIFICANCE

Keloids are a specific type of scar that develop following injury to the skin. Keloid scars tend to overgrow and extend beyond the margins of the original injury. Usually, they are approached primarily as a cosmetic issue. However, these scars also present with functional symptoms of itch and pain that significantly impact quality of life. The symptom of pruritus is frequently overlooked by dermatologists, and treatments are often primarily focused on the gross appearance of the scar. This review describes the rates of itch in keloid scars and the potential mechanisms underlying the development of the itch. In addition, this review also discusses the available keloid treatments and how effective they are at controlling itch.

MECHANISMS RESPONSIBLE FOR KELOID-ASSOCIATED ITCH

Keloids are benign fibrous growths that extend beyond the initial boundaries of cutaneous injury, most commonly found in African American and Asian populations (5). Although there have been proliferative and inflammatory cells, cytokines, and growth factors implicated in the development of keloids, the exact mechanism underlying the formation of these scars remains poorly understood. It is thought that the dynamic process of wound healing is aberrant, resulting in the excessive production and accumulation of disorganized collagen.

Recent studies have focused on the potential contribution of the immune system to the inflammatory phase of the wound healing process, leading to keloid formation. Experimental studies in keloids have demonstrated a prolonged inflammatory period with sustained release of cytokines and growth factors from immune cells. Histological studies of keloid tissue have demonstrated high concentrations of inflammatory cells, including mast cells, macrophages, lymphocytes, and neutrophils, and Th2 cytokines, including interleukin (IL)-4 and IL-13, which are also involved in itch (6–8).

Specifically, pruritic keloids have both an increased number and density of dermal mast cells and their stored granules compared with non-pruritic keloids (1). These cells produce histamine, nerve growth factor (NGF), and serine proteases from preformed granules that can stimulate fibroblast activity and collagen formation (9–11).

Compared with normal skin macrophages, macrophages in keloids have shown significantly increased M2 polarization, which is tightly associated with the Th2-immune chronic response (12–14). Immediately after skin

injury, macrophages secrete transforming growth factor beta (TGF-b), which is signficantly elevated in keloidal skin and causes fibroblasts to proliferate and synthesize collagen (15). Moreover, TGF-b and histamine stimulate dermal fibroblasts to produce periostin, a matricellular protein that contributes to tissue remodelling and is upregulated in pathological scar tissue compared with healthy skin (16). Periostin has recently been found to be a pruritogen, which activates itch directly via integrin receptors in nerve fibres and induces itch via the Th2 cytokine cascade (17).

A recent RNA sequencing study found a significant increase in Th2-related cellular infiltrates within keloidal skin, including tryptase-positive mast cells, IL-4 receptor alpha-positive cells, and periositin-positive cells (18). Moreover, the Th2-associated cytokines IL-4 and IL-13 that have a major role in itch have been reported to be elevated in keloidal tissue and play a major role in skin fibrosis and pathologic scarring (19, 20). In human fibroblasts, it has been found that IL-4 and IL-13 cause increased TGF-b signaling and enhanced fibrosis via periostin (20).

Other proposed mechanisms underlying keloid-associated pruritus focus more on neuronal dysfunction. One study used quantitative thermosensory testing to evaluate the function of small nerve fibres in keloid lesions and found increased thermosensory thresholds to warmth, cold, and heat pain and allokinesis and allodynia suggestive of neuropathy (1). This suggests an impaired function of small C-nerve fibres in keloids with the severity of neural damage correlating with itch severity.

Another proposed mechanism suggests that the keloid lesion itself induces a compressive neuropathy-like phenomenon. With excessive proliferation of fibroblasts and subsequent deposition of excess and disorganized collagen, afferent nociceptive neurones are physically compressed. This compression can then cause damage to the afferent nociceptive neurones, as is seen in compression neuropathies (1). Consequently, regenerating, uninhibited C-fibres transmit the itch sensation within the keloid. Another study reported longer and thinner nerve fibres in keloidal skin compared with non-lesional skin, potentially secondary to compression from excessive collagen deposition (21).

The presence of small-fibre neuropathy was further supported in a study that showed reduced epidermal nerve density in itchy keloids (22). These observations may be due to itch-transmitting nerve fibre hypoplasia from chronic pruritus. However, there was no correlation noted between itch intensity and nerve fibre density of keloidal skin.

Another potential mechanism is the sensitization of cutaneous nerve fibres within the keloid to inflammatory mediators. Significantly increased expression of NGF has been observed in keloidal skin, probably in response to the decreased nerve fibre density found in keloidal skin (23). NGF has been reported to induce release of histamine from mast cells (24). Histamine potentiates further production and secretion of NGF by keratinocytes (25). This may result in a cyclical relationship between histamine and NGF, causing a histamine-driven pruritus.

Modulation of peripheral nociception probably contributes to chronic neurogenic itch within keloids. Injured peripheral nerve fibres release neuropeptides, such as substance P (SP), and there are an increased amount of SP-positive nerve fibres within pathological scars (26). SP causes prolonged fibroblast survival, M2 polarization of macrophages, and degranulation of mast cells, which all contribute to the development of a positive feedback cycle of neurogenic inflammation (27). In addition, cutaneous nerve fibres within hypertrophic scars display increased expression of the opioid receptors mu (MOR), kappa (KOR), and delta (DOR) (28). There are also markedly higher levels of beta-endorphin, the endogenous ligand for the MOR, known to cause itch within hypertrophic scars, and interaction with MOR may alter the function of all 3 opioid receptors (29).

The Th2-related profibrotic cytokines IL-4 and IL-13 are also able to directly stimulate nerve fibres and induce pruritus via the IL-4 receptor, which is significantly increased in keloidal skin (30). Interestingly, a recent experimental mouse model of wound healing found TGF-b induces dermal dendritic cells to produce IL-31, a Th2-related cytokine that is elevated in skin wound tissue and significantly associated with itch intensity (31).

TREATMENT OF ITCH IN KELOIDS AND THEIR PUTATIVE MECHANISMS

Treatments that have been reported for keloid-associated pruritus are described here. A recent review article provided a comprehensive summary of the therapeutic management of keloid scars (32). Many of these treatments are recognized as primary treatment options for stopping progression and inducing the eventual regression of the scar. A majority of these studies failed to measure and report pruritus as a study endpoint. However, some of the listed treatments do not treat the driving process underlying keloid development and proliferation, but rather focus on symptomatic treatment of the associated pruritus. A schematic of the underlying processes driving keloidal pruritus and how listed treatments probably decrease/eliminate this symptom is shown in **Fig. 1**.

Corticosteroids

Corticosteroids are commonly used in the treatment of keloids, typically introduced intralesionally. The methods by which corticosteroids cause scar regression include interruption of the inflammatory process by inhibition of inflammatory cell migration and phagocytosis, vasoconstriction resulting in disruption of oxygen and nutrient

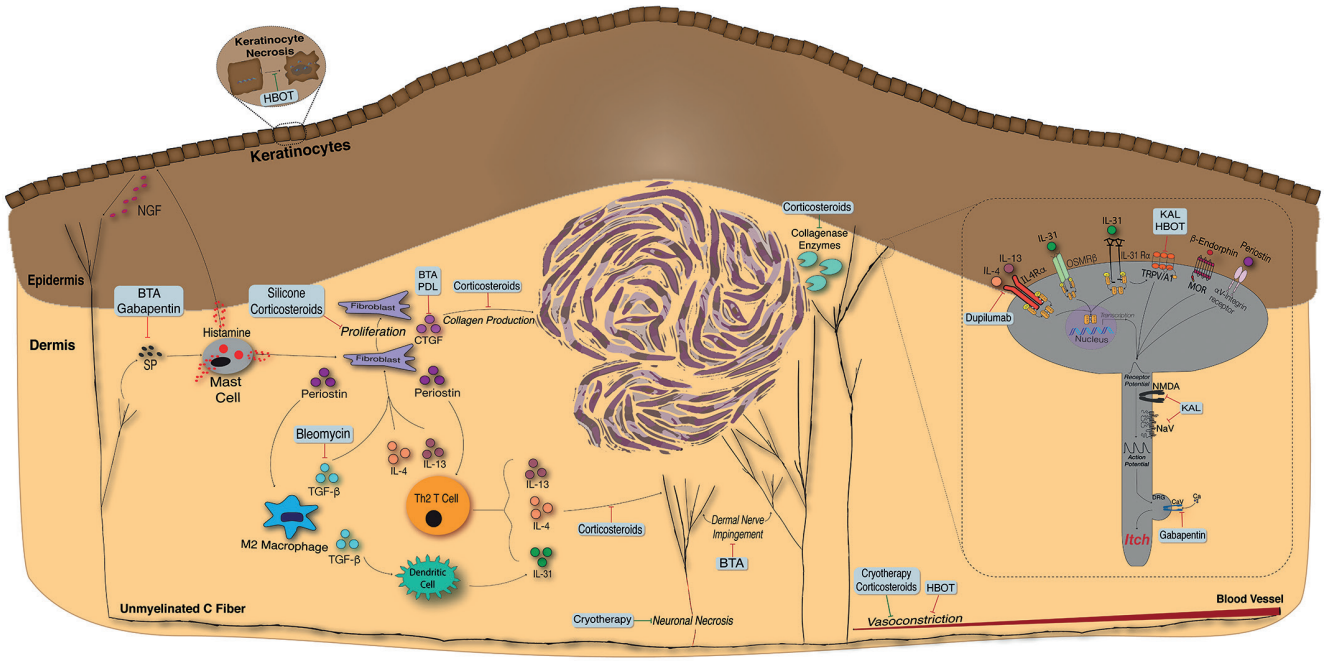

Fig. 1. A putative mechanism of the mediators of pruritus in keloids and the effect of different treatment modalities. *Green line*: activation; *red line*: inhibition; 5-FU: 5- fluorouracil; BTA: botulinum toxin A; CaV: voltage gated calcium channel; CTGF: connective tissue growth factor; TGF-b: GABA: gamma aminobutyric acid; HBOT: hyperbaric oxygen therapy; IL: interleukin; Ra: receptor alpha; KAL: ketamine amitriptyline lidocaine; M2: type 2 macrophage; MOR: mu opioid receptor; NaV: voltage gated sodium channel; NGF: nerve growth factor; NMDA: N-methyl-D-aspartate; OSMRb: oncostatin M receptor beta; PDL: pulse dye laser; SP: substance P; TGF-b: transforming growth factor beta; Th2: type 2 helper T cell; TRP: transient receptor potential; TRPV: transient receptor potential vanilloid.

supply to the wound, antimitotic activity on fibroblasts, and enhancement of collagenase activity, thus achieving collagen degradation within scars (33). Corticosteroids have also been shown to exert their anti-pruritic effect by acting to reduce expression of IL-31, the "itchy cytokine", as shown in other chronic pruritic conditions, such as cutaneous T-cell lymphoma (CTCL), prurigo nodularis, and scleroderma patients (34–36). Another study showed that even low-potency topical steroid use reduced the expression of many inflammatory cytokines, including the Th2-associated cytokine IL-13 (37).

Several studies have shown the efficacy of intralesional corticosteroid use (as monotherapy or adjunct therapy) for keloid treatment, with concomitant reductions in associated pruritus (38, 39). Use of intralesional corticosteroid injections for the treatment of keloid scars is an official recommendation from the International Advisory Panel on Scar Management (40). The adjunctive use of intralesional corticosteroids in the treatment of hypertrophic scars also significantly reduced associated pruritus (41).

Silicone-based products

Silicone-based products have been used in the management of scars. Although the mechanism of action has not been made very clear, it has been suggested that the occlusion and hydration of the stratum corneum by the silicone products is essential (42). The hydration of epidermal layers suppresses the metabolism of underlying fibroblasts and leads to reduced collagen deposition (43).

Silicone gel sheets have been shown to reduce pruritus and pain in hypertrophic scars and keloids. One study of 6 patients with keloid scars showed reduction of lesional pruritus and pain after 4 weeks of silicone gel sheet use and complete resolution after 12 weeks (44). Interestingly, this resolution of the pruritus and pain preceded the reduction in scar redness and elevation. The study also recognized a reduction in the number of mast cells with treatment (44). This would, in turn, decrease the itch mediators released in the tissue and is thought to be the mechanism by which pruritus is reduced with this treatment.

Another report studied the effects of silicone gel sheet treatment on post-operative scar treatment following total knee arthroplasty (45). This report showed a modest reduction in visual analogue score (VAS) pruritus scores, although it was not found to be statistically significant. This was despite significant improvement in the height and colour of the scar.

Botulinum toxin A

Botulinum toxin A (BTA) is a potent neurotoxin derived from *Clostridium botulinum*. BTA is thought to prevent further scar proliferation by inhibiting expression of connective tissue growth factor (CTGF) (46, 47). BTA

alleviates the small fibre neuropathy within hypertrophic scars by immobilizing the local muscles and reducing skin tension (48). Subcutaneous injection of BTA reduces local levels of substance P, which is an important neural mediator in itch, probably alleviating neurogenic inflammation in hypertrophic scars (49).

Although not studied specifically in keloids, a prospective study of 19 patients with hypertrophic scars treated with monthly intralesional injections of BTA for 3 months resulted in a mean decrease in Itching Sensation Score from 3.50 to 0.83 (50).

5-Fluorouracil

5-Fluorouracil (5-FU) is an antineoplastic agent that inhibits rapidly proliferating cells and causes fibroblast apoptosis. In a prospective study of 24 patients with keloids treated with weekly 50–150 mg/ml intralesional injections of 5-FU, 70% of patients reported resolution of all accompanying symptoms including pruritus and pain (51). Another case report showed the successful use of 5-FU (300 mg spanning 3 months) with resolution of pain and itch in a patient with refractory keloids and hypertrophic scars (52).

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is an established treatment method for a variety of skin disease and infections. In HBOT, patients are treated with oxygen in a compression chamber under a pressure greater than 1 atmosphere absolute of 100% oxygen. This form of therapy is believed to help wound healing by increasing local blood circulation and blood oxygen capacity and consequently reducing inflammatory reactions.

Improvement in keloid-associated pruritus was reported recently with the use of hyperbaric oxygen therapy (53). In this study, 88.7% of patients reported alleviated keloidal pruritus. Interestingly, compared with non-HBO treated keloids, keloidal skin after HBO therapy also showed significantly decreased expression of known itch-related mediators, including tryptophan hydroxylase-1 (TPH1) and transient receptor potential vanilloid type-1 (TRPV1).

Cryotherapy

Cryotherapy is a treatment in which low temperatures are used to cause vascular damage and tissue necrosis. There are a variety of delivery methods, including spray, contract probes, and intralesional injections. Compared with contact and spray methods, intralesional injections were found to be the most effective method in treating keloid scars (54). Intralesional cryotherapy is a novel treatment in which liquid nitrogen is used to freeze scar tissue from the inside out. Cryotherapy is thought to achieve scar destruction by the formation of intracellular ice crystals that cause cell anoxia. In addition, the cold temperature damages cells and ultimately results in tissue necrosis (55).

In a study of 10 patients with hypertrophic scars and keloids, use of intralesional cryotherapy achieved reduction in size of scar as well as significant decrease in itch and discomfort (56). In another study of 12 patients with large recalcitrant keloids, all patients reported the disappearance of all associated symptoms, including pruritus (57).

Bleomycin

Bleomycin is an antineoplastic agent that inhibits DNA and RNA synthesis. Although the exact mechanism by which bleomycin improves scar tissue has not been fully elucidated, studies have shown that it inhibits collagen synthesis in dermal fibroblasts by suppressing the effect of TGF-β1 (58). One study of 50 patients with either hypertrophic scars or keloids reported complete resolution of lesion-associated pruritus in 89% of patients with administration of intralesional bleomycin (59). In a study of 13 patients with keloids and hypertrophic scars treated with 1.5 IU/ml bleomycin per session, all patients reported disappearance of pruritus within one week of treatment without relapse (60).

Laser therapy

Laser therapy has been introduced as a treatment option for the management of keloid scarring. Although there are some head-to-head studies comparing the efficacy of different laser types (CO_2, Er:YAG, Nd:YAG, and pulsed dye laser (PDL)) on keloid therapy, there is no clear consensus on the type of laser to be used for keloid nor the settings at which the therapy should be administered.

The PDL is the most commonly used laser for keloid treatment. The PDL is suggested to act on connective tissue growth factor (CTGF) and reduce its expression in cultured keloid fibroblasts. Reduction of CTGF attenuates the pathological scarring leading to keloid development (61). There are several studies demonstrating the reduction on keloid size and appearance following PDL use.

One study tested the long-pulsed (LP) 1064 nm Nd:YAG laser as a treatment for the pain that is commonly associated with keloids. A population of 8 patients with keloids were treated with the 1064 nm LP Nd:YAG laser, and 62.5% of these patients reported a complete resolution of pain, with all patients reporting significant reduction in pain (62).

The data demonstrating the effect of laser therapy on keloid-associated pruritus is limited. One small study reported a 75% improvement in keloid-associated pruritus after PDL treatment in combination with intralesional steroid use (63). One study demonstrated the efficacy of PDL use in the treatment of hypertrophic scars, not

keloids, showing significant relief of associated pruritus after use (64).

Ion channel manipulators

Gabapentin and pregabalin are anti-epileptic drugs that are structural analogues of the neurotransmitter gamma-aminobutyric acid (GABA) and exhibit anti-pruritic effects. Their mechanism of action involves the inhibition of voltage-gated calcium channels in the spinal cord, thereby reducing central neural hypersensitization. They are particularly effective in the treatment of neuropathic pruritus (65). A study of 58 patients with scar-associated pruritus following burn injury found a significant decrease in peak pruritus in patients treated with gabapentin compared with placebo (66).

Topical compounded ketamine, lidocaine, and amitriptyline (KAL) is used to treat keloidal itch by targeting transient receptor potential (TRP) ion channels, sodium channels, and N-methyl-D-aspartate (NMDA) receptors. In our clinic, we have successfully treated pruritic scars with this formulation (unpublished data). We have published data on the efficacy of this topical formulation for a scarring congenital naevi and neuropathic itch (67, 68)

FUTURE THERAPY CONSIDERATIONS TARGETING TH2 CYTOKINES

A recent case report described the administration of intralesional dupilumab, a monoclonal antibody against the IL-4 receptor alpha, to a patient with significant atopic dermatitis (AD). After starting this therapy, a significant reduction (over 50% shrinkage) of an untreated keloid lesion was noted, along with marked improvement in pruritus (69). Since AD is an independent risk factor for keloid formation (70), further studies may be warranted to test the efficacy of dupilumab and other IL-13 inhibitors in this patient population.

An additional consideration for a future therapy is psychotherapy for severe itchy keloids. Although there is no evidence for the management of keloid-associated pruritus with psychological intervention, there is evidence suggesting a correlation between personality traits and coping mechanisms and persistence of pruritus in post-burn injury patient who commonly have keloids (71). Degrees of post-burn injury pruritus (occasional vs persistent) were also predicted by different personality traits (71). Anecdotally, we refer specific pruritus patients with severe itch of various underlying dermatological conditions to a psychologist for assessment and potential cognitive behavioural therapy (72).

In conclusion, keloids commonly present with lesional pruritus that cause significant impairment of quality of life. This review examined the incidence of keloidal pruritus, the mechanisms underlying the pruritus, and the treatments available for management of the pruritus. We suggest that keloid-associated pruritus should be considered as a secondary endpoint of keloidal treatment, as active pruritus may be a marker of underlying fibroblast activity and neuronal dysfunction.

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