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Keloids and Hypertrophic Scars: A Review of Risk Factors, Pathophysiology, Prevention, Management, and Treatments in Dermatology and Surgical Practice

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Introduction: Hypertrophic scars and keloids are the results of a fibroproliferative disorder involving an aberrant wound healing response to dermal injuries that lead to the development of these benign lesions. Careful consideration of the patient populations that are most prone to developing keloids and hypertrophic scars has revealed that genetics may play a role in developing these pathological scars. The clinical distinction between these two lesions has classically relied on the characteristics of the scars borders with hypertrophic scars remaining within the borders of the original wound and keloids extending beyond the original wound borders.
Conclusion: The most important factor in hypertrophic scar and keloid formation is prevention. A key strategy for prevention of hypertrophic scarring and keloid development is to identify those

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patients predisposed to this wound healing response and to control the Inflammation that can trigger these scars. Primary goals of treatment include reducing the cosmetic appearance of these lesions and preventing their recurrence once treated.

Keywords: Keloids; hypertrophic scars; polypropylene; prolene; scars.

1. FORMATION

Hypertrophic scars and keloids are the result of a fibroproliferative disorder involving an aberrant wound healing response to dermal injuries that leads to the development of these benign lesions. Physical or physiological trauma that occurs in dermal tissue activates the normal wound healing process found in the reticular dermis of these scars [1]. The normal sequence of tissue repair occurs in three phases – inflammation, followed by proliferation, and ending with remodeling. Fibroblast activity maintains the inflammatory and proliferative phases of wound healing and is a key component in the development of these exuberant lesions during the proliferative phase [2]. In hypertrophic scars and keloids, the dysregulation of fibroblast activity during the proliferative phase of wound healing leads to an imbalance between collagen deposition and degradation and creates an environment amenable to abnormal scarring [3].

Although the pathogenesis of hypertrophic scars and keloids has not been fully elucidated, per se, current research suggests these lesions form as a result of localized inflammation and continues to grow as this inflammation remains constant [1]. The stimulus for the inflammatory response is based on the interplay between internal and external factors related to dermal trauma and the unique nature of how the trauma occurred. Additionally, one study notes that it is necessary for cutaneous injuries to penetrate down to the reticular dermis in order to activate the inflammatory cascade that eventually leads to the formation of these particular scars [4]. In keloidal skin, there is an increase in pro-inflammatory markers to include interleukins IL-1α, IL-β, IL-6, TNF-α indicating an increased response to dermal injuries in these patients skin. This can predispose patients to develop a chronically inflamed environment that allows for the development of these fibroproliferative scars [1].

Careful consideration of the patient populations that are most prone to developing keloids and hypertrophic scars has revealed that genetics may play a role in developing these pathological scars. These fibroproliferative lesions may be seen in patients with specific chromosomal changes and single nucleotide polymorphisms (SNPs). Clinically, dermatologists see keloids most often in African-American, Han Chinese and Japanese patients. Researchers have identified that this may result from changes in keloid-associated loci in the following chromosomes for each respective group: 7p11 [5], 10q23.31 [6] and 2q23 [5]. One SNP identified in the literature on chromosome 15, rs8032158 in intron 5 of the Neuronal precursor cell-Exposed Developmentally Downregulated 4 (NEDD4), is associated with the clinical severity of keloids and may contribute to their dysregulated fibroblast proliferation [7].

The clinical distinction between these two lesions has classically relied on the characteristics of the scar's borders with hypertrophic scars remaining within the borders of the original wound and keloids extending beyond the original wound borders. Keloids overgrow their boundaries and invade surrounding tissue while hypertrophic scars push out the margins of the scar to increase its size. The aesthetic differences between keloids and hypertrophic scars rely on the intensity, duration and frequency of reticular dermal inflammation [1]. Additionally, the timing from dermal injury to scar appearance can distinguish hypertrophic scars, which generally appears soon after injury, from keloids that appear much later after dermal insults. Moreover, hypertrophic scars may regress over time, but keloids are known to exhibit a malignant nature, per se, as they can grow without restrictions into normal, non-injured dermal tissue [3,8].

When examining the histological differences among these lesions, keloids exhibit thick, eosinophilic, hyalinized collagen bundles along with an increased number of blood vessels when compared to hypertrophic scars. However, these findings are not exclusive to keloids and may be displayed interchangeably in both scars, which may point to these lesions representing a spectrum of the same disorder.

2. PREVENTION

The most important factor in hypertrophic scar and keloid formation is prevention. An atraumatic operation technique should be used, followed by efficient hemostasis. Wound closure should include eversion of the wound edges, avoiding suture marks and maintaining uniform tensile strength along the skin edges, and precise approximation of the skin edges. The authors preferred suturing technique for obtaining good cosmetic results includes using Polypropylene (Prolene). In order to avoid scarring and poor wound healing, the suture material must be strong, handle easily, and form secure knots. Polypropylene has as an extremely smooth surface, which decreases knot security and therefore must be accounted for. However, it causes minimal tissue inflammation and does not promote infection. The low tissue reactivity and high tensile strength are significant advantages of Prolene. It has high plasticity, can accommodate wound edema, and it is not subject to degradation. As a synthetic, nonabsorbable, monofilament suture, polypropylene is easy to remove and is therefore an ideal suture for a running, subcuticular stitch.

Given the relationship between ongoing dermal inflammation and development of these pathological scars, reducing the likelihood of extended inflammation and increasing rapid wound healing can help mitigate the presentation of these scars following procedures [9].

Remembering that the epidermis of surgical wounds regenerates within 14 days of injuries, the reticular dermis continues through the wound healing process of inflammation while the dermal matrix matures. It is at this point that limiting inflammatory stimuli is critical to prevent the chronic inflammatory environment that yields the initial appearance of hypertrophic scars and keloids 3 months post-injury [1].

A key strategy for prevention of hypertrophic scarring and keloid development is to identify those patients predisposed to this wound healing response and to control the inflammation that can trigger these scars. Patients with darker skin are fifteen times more likely to develop keloids and hypertrophic scars compared to their lighter complexioned counterparts [10]. As part of a comprehensive dermatological history, physicians should ask all their patients if they have a history of developing keloids or hypertrophic scarring in the past from minor trauma or procedures with a particular focus given to Fitzpatrick skin type IV through VI patients. Additionally, examination of previous scars may help better inform clinicians of their patient's wound healing capacity. Hypertrophic scars and keloids have characteristic shapes and locations on the body based on tension lines within these wounds, thus, relieving mechanical tension on wounds is an important factor in reducing the development of these scars. With regard to sutures, while the epidermis regenerates in 10 days, the dermis takes 3 months to resume 90% of its tensile strength; thus, controlling the mechanical forces within these wounds can reduce the risk of scarring [11].

Keloids have a preference for highly tense areas of the body, to include the anterior chest, shoulders and upper arms but rarely form on the relaxed skin of the upper eyelids [12]. As dermatologists perform procedures in these high-risk areas prone to hypertrophic scarring and keloid scarring, maintaining a heightened awareness for their development may help reduce the extent of scarring with early interventions.

3. TREATMENT

Primary goals of treatment include reducing the cosmetic appearance of these lesions and preventing their recurrence once treated. Several treatment options exist and the best results are achieved when a combination of therapies are used synergistically. Treatments can be divided into three main categories: noninvasive medical, invasive and investigative therapies. Noninvasive techniques work to minimize the physiology of the wound healing process, while invasive techniques are used to remove the lesions entirely.

Noninvasive techniques include the following: intralesional corticosteroid injections, pressure garments, silicone gel sheets, Fluorouracil (5-FU), Bleomycin, onion extract. Intralesional corticosteroid injections are the most common treatment used for keloids and hypertrophic scars. Triamcinolone acetonide (10-40 mg/ml) is used based on the size and location of the lesion. Injections are aimed at the mid-dermis and repeated every 3-4 weeks based on the density of the lesion and response the therapy [13]. Pressure garments are commonly used, but their mechanism of action in reducing hypertrophic scars and keloids are unknown and

studies support their use in preventing hypertrophic scarring in burn patients [14]. Silicone sheets are commonly recommended, though their use has conflicting support in the literature. Again, their exact mechanism of scar reduction is unknown but is believed to result from maintaining wound hydration and occlusion of the stratum corneum resulting in cytokine-mediated signaling from keratinocytes to dermal fibroblasts. Fluorouracil (5-FU) is effective when used with Triamcinolone to prevent recurrence of surgically excised lesions [15].

Bleomycin has similar results to steroids and 5-FU but is less cost effective [16]. Finally, onion extract has been noted in the literature to have conflicting efficacy in the few studies that tested its use on keloids [17,18].

Invasive techniques for scar removal include: surgery, cryotherapy, radiotherapy and lasers. Surgical excision is commonly associated with high recurrence rates when used as monotherapy, except when used on ear lobes. Thus, surgery is recommended along with adjuvant therapies such as steroid injections, 5-FU injections or radiation [19]. Surgical techniques to reduce wound tension are recommended such as subcutaneous sutures, zig-zag sutures and local flap transfers. Dermal sutures provide minimal tension reduction on the dermis, thus, suturing into the superficial or deep fascia elevates wound edges for smooth closure while reducing dermal tension [9]. Zig-zag sutures and z-plasties relieve linear scar contractures and tensions and z-plasties provide the additional benefit of creating segmented scars that heal faster in comparison to continuous ones. Local flaps can expand naturally and reduce scar tension making this an effective treatment for severe keloids that cover a large area of skin. Cryotherapy is successful when used for at least 3 sessions [20-22]. When used prior to intralesional injections, this may help with medication dispersal. Alternatively, intralesional cryotherapy helps improve aesthetic outcomes with less hypopigmentation [19]. Radiotherapy has its best results when utilized within 24 hours of a surgical procedure [23]. The types of radiation used include high dose rate-superficial brachytherapy (HDR-SB) and electron beam irradiation [24-28]. Current research suggests, postoperative radiation for keloids in 10-20 applications of Gy with daily fractions of 5 Gy [29]. Finally, different lasers have different success rates with keloids – carbon monoxide (CO) lasers have high recurrence rates compared to pulsed dye lasers that help with keloid regression.

Several investigative treatments may become mainstays of treatment in the future, pending their success in clinical trials. These treatments include: Verapamil, Imiquimod, growth factors, Botox, UV light therapy, ACE inhibitors, Tamoxifen and calmodulin inhibitors. Of note, Verapamil was able to reduce collagen production in keloids by increasing collagenase activity in one study, but more studies are needed prior to endorsing this as a treatment option [30].

4. CONCLUSION

More randomized clinical trials are necessary to generate strong, evidence-based recommendations for the removal and prevention of hypertrophic scars and keloids. Effective treatments are based on several factors related to the lesion along with a physician's experience with treating these scars and the patient's preferred treatment modality. These fibroproliferative aberrant lesions present treatment challenges for even the most experienced dermatologist, but success in significantly improving the appearance of these lesions is not impossible.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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