Keloids: Prevention and Management

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KEYWORDS

• Keloid • Scar management • Hypertrophic scars
• Wound healing • Keloid pathophysiology

Key Points

- Keloids can be difficult to differentiate clinically from hypertrophic scars; however, there are distinguishing characteristics of each
- The pathophysiology of keloids continues to require ongoing research
- Surgical excision followed by intralesional steroid injection is considered a first line treatment
- Silastic gel sheeting can improve keloid appearance when used appropriately
- Radiation can be a safe and effective means of keloid treatment with the appropriate precautions
- Topical application of chemotherapy medication is a reasonable alternative in patients with keloid recurrence after surgical excision and steroid treatment

PATHOPHYSIOLOGY AND HISTOLOGY

Wound healing is tightly regulated, and errors in the process can manifest anywhere along the pathologic spectrum from chronic wounds to the aggressive scar formation seen in keloids, the latter being the topic of interest here. On the subject of keloids, hypertrophic scars must also be mentioned because the two are often, incorrectly, used interchangeably. This distinction must be made, as the appropriate application of current and future interventions mandates understanding the clinical, histologic, and biochemical pathology of keloids.

Keloids can occur immediately after trauma, or grow months after a mature, stable scar has formed. This trauma can range from vaccination needle sticks, lacerations, bug bites, and burns, to dermatologic conditions such as acne or folliculitis. In all cases, the end result is skin inflammation. Hypertrophic scars follow the pattern of evolution, stabilization, and involution within the boundaries of the original wound. By contrast, keloids continue to proliferate, resulting in a raised, erythematous scar with a wide variability of height progression and scar distribution. As such, keloids will grow outside the boundaries of the original scar. Although keloids can reach a quiescent phase, very rarely do they regress. Lee and colleagues[1] found that symptomatically, 46% of patients noted keloid-associated pain and 86% noted pruritis.[2]

Keloids affect darker-skinned individuals approximately 15 times more than Caucasians, suggesting a genetic factor. Keloids affect roughly 15% to 20% of the African American and Hispanic populations.[3,4] Keloids typically occur during and after puberty, between the ages of 10 and 30 years. Although there is no gender predilection, keloids can regress during menopause or worsen during pregnancy.

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The pathogenesis of keloids continues to undergo investigation, and understanding this process requires knowledge of the normal wound-healing process. Normal wound healing occurs in 3 stages[3]: the inflammatory phase,[4] the proliferative/granulation phase, and[5] the maturation/remodeling phase. The inflammatory phase begins immediately after the injury. Hemostatic mechanisms of platelet degranulation and activation of complement and clotting cascades occur quickly. Cytokines and growth factors such as transforming growth factor β (TGF-β), platelet derived growth factor (PDGF), and epidermal growth factor (EGF) are released through platelet degranulation and from the surrounding tissue.[6,7] These cytokines and growth factors induce the influx of neutrophils, macrophages, mast cells, and epithelial cells.[6] After the first 24 to 48 hours, the inflammation is perpetuated by mast cells and neutrophils and can last for anywhere from 3 to 8 days.[3,8] Macrophages aid in wound debridement as fibroblasts and smooth muscle cells migrate into the wound. Prolongation of this phase occurs in cases of large wounds or in the presence of infection, and results in greater exposure to fibrogenic cytokines.[6]

During the proliferative phase, at approximately 3 to 6 weeks, fibroblasts deposit type III collagen and synthesize granulation tissue, composed of procollagen, elastin, proteoglycans, and hyaluronic acid.[8] This scaffold allows the ingrowth of vasculature, and with wound contracture and closure facilitated by myofibroblasts, allows the wound to undergo continued remodeling in the final phase of wound healing.

The maturation/remodeling phase can take from several months to more than a year. During this phase, the type III collagen is replaced by stronger type I collagen fibers. Proteoglycans are synthesized, and fibrin and fibronectin are degraded. In addition, the extracellular matrix produced by fibroblasts undergoes simultaneous degradation by mostly serine proteases (ie, tissue plasminogen activator and urokinase plasminogen activator) and matrix metalloproteinases (MMPs). Collagen fibers are rearranged, cross-linked, and aligned along tension lines. The tensile strength of the scar improves, but at best achieves only 80% the tensile strength of normal skin.[3]

Histologically, keloids invade the normal surrounding dermis, a distinct difference from hypertrophic scars, which stay within the confines of the wound borders. In keloids, collagen fibers are larger, thicker, wavier, and oriented haphazardly. Collagen fibers in hypertrophic scars and normal scars are oriented parallel to the epidermal surface.[9] The collagen fibers in keloids are arranged into thick collagen bundles that are packed tightly together within the dermis, where there is a lack of sebaceous glands and rete ridges.[10,11] These collagen bundles are also found to lack the presence of myofibroblasts. Hypertrophic scars form fibrous nodules composed of fibroblasts, mostly type III collagen fibers, and vessels.[8,12] By contrast, keloid scars form nodules with reduced vascularity and a hypocellular appearance (**Fig. 1**).[4,8,12,13] This acellular core within keloids is characterized by thick bundles of type I and type III collagen fibers interspersed with fibroblasts (see **Fig. 1**B).[8,12,13]

Summarizing the overall histologic findings of keloids, Butler and colleagues[4] classified 4 distinct pathognomonic findings on histology:

1. Keloidal hyalinized collagen
2. Tongue-like advancing edge underneath normal-appearing epidermis and papillary dermis
3. Horizontal cellular fibrous bands in upper reticular dermis
4. Prominent fascia-like fibrous bands.

Despite advances in histologic knowledge of keloids, their exact pathogenesis and etiology remain unclear. Accordingly, the number of possible treatment options reflects multiple hypotheses on how the normal wound-healing process goes awry in keloids. The authors review here the most common theories that are based on accepted observations and proposed contributing factors.

Growth Factors

Elevated levels of TGF-β and PDGF have been found in keloid tissue along with aberrant levels of their activity. The heightened growth-factor activity is likely a result of increased expression of their respective receptors.[3,14,15] TGF-β stimulates fibroblasts to produce and deposit collagen and extracellular matrix (ECM) factors. Of interest, keloid fibroblasts exhibit a heightened sensitivity to this growth factor. TGF-β also induces production of PDGF, which controls the rate of granulation tissue formation and stimulates collagen production during the later stages of wound healing.[3] Furthermore, the enzymes that remodel and break down scar ECM are regulated by TGF-β, and decreased levels of collagenase, plasminogen activator, and MMPs could further explain the failure of scar regression evidenced in keloids.

Genetics

Keloids occur more commonly in those of African, Asian, and Hispanic descent, suggesting a genetic susceptibility in darker-skinned individuals. Familial cases of an autosomal dominant pattern of keloids have been reported, and further genetic