Review Article

Keloids: A review

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Abstract

The management of keloids remains a difficult clinical problem. This article is a review of the current methods available for the treatment of keloids. Online search was made on review articles and other publications on keloids mainly from PubMed (search results from National Center for Biotechnology Information at the US National Library of Medicine [NLM]) and African Journals Online. A review of the selected articles was carried out. The various methods of treatment available suggest that there is still no one method that is completely satisfactory. Currently, combination therapy using surgical excision followed by intralesional steroid or other adjuvant therapy appears to yield the best results for keloidal management.

Key words: Keloids, management, review

INTRODUCTION

The term keloid is derived from the Greek word cheloides, meaning "crab's claw."[1,2] This description was as a result of the extension of the lesion into normal tissues. Keloids are elevated fibrous scars that extend beyond the borders of the original wound do not regress, and usually recur after excision.[1] They present as benign, fibrous proliferations of tissue that develop in predisposed individuals at sites of cutaneous insult or irritation.[2-4]

Keloids affect only humans, occur in all races, but the African of negroid origin is particularly susceptible.[5] Though the dermis of the skin[1,5] is commonly affected, keloids of the cornea[6-8] have been reported. The various and multiple modalities of treatment available are a pointer to the fact that there is still no perfect modality of treatment.

EPIDEMIOLOGY

Keloids are found all over the world, and there is a preponderance in Africans with darkly pigmented skin.[5,9]

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The primary risk factor for keloids is a darkly pigmented skin, perhaps because of melanocyte stimulating hormone anomalies.[1,3]

Black, Hispanic and Asian persons are far more likely to develop keloids than Caucasians.[9-11] It is rare in albinos of all races.[9,12] Familial predisposition, with both dominant and recessive modes of inheritance have been recognized.[1,9,13] The younger age group, persons <30 years, are more prone to develop keloids with risk peaking between 10 and 20 years of age[1] in patients with elevated hormone levels as occurs during puberty or pregnancy.[14] It affects both sexes equally[5,12,15] with a greater prevalence in women probably because of piercing of ears.[9] Keloid scars affect all age groups, but they are rare in the extremes of life.[5,9] Sternal skin, shoulders and upper arms, earlobes, and cheeks are most susceptible to developing keloids.[16] Keloids on the palms and soles are rare[5,9] but keloid on the sole has been reported.[17-19] Keloids on the very lax skin like the upper eyelids, penis, scrotum, and areola of the breast are very rare,[5] but the pubic area, such as the chest wall and shoulder areas, is an area of preferential occurrence due to the high concentrations of sebaceous glands in these sites.[20] A similar lesion is a hypertrophic scar. Hypertrophic scars are red and elevated scars characterized by prolonged chronic inflammation and excessive collagen deposition.[21]

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HYPERTROPHIC SCARS VERSUS KELOIDS

Clinical characteristics

Keloids and hypertrophic scars are separate clinical and histochemical entities.[15,20,22] The difference between keloids and hypertrophic scars is that while hypertrophic scars can mature and improve over time, keloids rarely improve over a natural course.[21] Hypertrophic scars usually develop within 4–8 weeks following wound infection, wound closure with excessive tension or other traumatic skin injury,[23] have a rapid growth phase for up to 6 months, and then gradually regress over a period of few years, finally resulting in flat scars with no further symptoms.[24] In contrast, keloids may develop several years after minor injuries and may even form spontaneously in the absence of any known injury.[12] Keloid formation may complicate minor skin lesions such as acne, septic spots, or insect bites.[5] Furthermore, keloids usually persist for long periods of time and do not regress spontaneously,[5,25] They appear as firm, mildly tender, bosselated tumors with a shiny surface and sometimes telangiectasia and thinned epithelium.[12] They remain raised and thick[5] and gradually proliferate indefinitely.[25,26] Keloids and hypertrophic scars are commonly pruritic, but keloids may be associated with significant pain[17] and hyperesthesia.[23,27] Keloids tend to recur after excision, whereas recurrence of the hypertrophic scar after excision of the original scar is rare.[26]

HISTOLOGY

Histologically, both hypertrophic scars and keloids contain an overabundance of dermal collagen.[12] Keloids appear as fibrotic collections of excessive thick collagen bundles, elastin, fibronectin, and proteoglycans along with atypical fibroblasts.[21] The fibroblasts in keloids have increased prolyl hydroxylase activity, which is involved in collagen synthesis, at levels much higher than that of normal skin or hypertrophic scar.[28] In normal scars, collagen forms regular cross-links, whereas in keloids the collagen is arranged irregularly, forming nodules in the dermis.[21] In normal wound healing, the immature type III collagen of the early wound can be modified into mature type I collagen.[29] Hypertrophic scars contain primarily type III collagen oriented parallel to the epidermal surface with abundant nodules containing myofibroblasts, large extracellular collagen filaments, and plentiful acidic mucopolysaccharides.[29] In contrast, keloid tissue is mostly composed of disorganized type I and III collagen, containing pale-staining hypocellular collagen bundles with no nodules or excess myofibroblasts.[29,30] Both lesions demonstrate overproduction of multiple fibroblast proteins, including fibronectin, suggesting either pathological persistence of wound healing signals, or a failure of the appropriate down-regulation of wound healing cells.[30]

GENETICS OF KELOIDS

The increased prevalence of keloids in dark-skinned races, the increased concordance among identical twins and the increased familial clustering suggest a strong genetic predisposition to the formation of keloids.[31] Patients with a keloid diathesis have been associated with group A blood type and human leucocyte antigen B14, 21, BW35, DR5, and DQW3.[9,15,32] The mode of inheritance is not definitely known, but several theories have been proposed including autosomal recessive,[13] autosomal dominant with incomplete penetrance[33,34] and variable expression. Elevated levels of serum immunoglobulin E and a disproportionately high incidence of allergic diathesis have been observed in patients who develop keloids.[35] A systemic immune state genetically predisposed to keloid formation is suggested by trends in patterns of serum complement, immunoglobulin G and immunoglobulin M levels in patients with keloids.[32,36] Some genetic connective tissue disease have been associated with keloids including Rubinstein–Taybi syndrome, Ehlers–Danlos syndrome, progeria, osteopoikilosis, scleroderma, and pachydermoperiostosis.[20,37-40] The significance of this association between congenital connective tissue diseases and keloid formation is unknown.[37] In a study[34] of some families with keloids, syndromes associated with keloids, namely Rubinstein–Taybi and Goeminne syndrome were not found.

TREATMENT

The management of keloids continues to be a challenge, and no single therapeutic modality is best for all keloids.[9,21] Prevention is important[21] as the lesion is notoriously recurrent.[5,41,42] Some modalities of treatment include occlusive dressings, compression therapy, intralesional corticosteroid injections, excision, cryosurgery, radiation therapy, laser therapy, 5-fluorouracil (5-FU), bleomycin, verapamil, retinoic acid, imiquimod 5% cream, tacrolimus, botulinum toxin, and over-the-counter treatments (e.g. onion extract, combination of hydrocortisone, silicon, and Vitamin E). Other methods of treatment are an ultrasound and heat therapy or a combination of techniques.[43] A combination of silicone gel sheeting and intralesional steroids was recommended (by an International Advisory Panel on Scar Management) as the first-line therapy,[44] with the use of localized pressure therapy if possible. For resistant cases, second-line therapy includes specific wavelength laser therapy and surgery with adjunctive silicone gel sheeting, if required.

STEROIDS

Intralesional steroid (triamcinolone) is the most effective and widely used treatment for keloids,[20] and perhaps first-line.[44,45] The main effects of corticosteroids are thought to result primarily from their suppressive effects on the inflammatory process in the wound.[21] Other proposed mechanisms of action include inhibition of nitric oxide synthase transcription with subsequent inhibition of collagen synthesis in fibroblasts,[46] inhibition of keloid fibroblast growth, fibroblast degeneration, and downregulation of collagen gene expression in keloids.[47] Various steroid preparations that can be used for intralesional injection include hydrocortisone acetate, methylprednisolone, and dexamethasone.[21] Triamcinolone acetonide (TAC)

(10–40 mg/ml per course every 4 weeks) is the most commonly used.[48] Depending on the type of lesions, two or three doses of TAC injections may suffice but some may require injections for 6 months or more with 4–6 weeks interval between injections.[49] Intralesional steroids can be used alone or as an adjunct therapy following surgical excision.[42,48] The most efficacious treatment of keloid scars is combined therapy involving steroids and surgical excision with cure rates of 80–100%.[42,44,48,49] Complications include atrophy, telangiectasia formation, and pigmentary alteration, noted more in darker-skinned individuals.[21]

SURGERY

Surgical excision is a common management option,[43] but it is generally not recommended for keloids without adjunctive treatment.[21] Extreme caution is necessary as recurrence rate is between 45% and 100% and can result in a larger and more aggressive keloid.[50,51] The recurrence rate has been reduced to 8% with the use of combination therapy with surgical removal and an additional treatment modality,[11] including corticosteroid injection, pressure dressings, interferon (IFN) injections, or radiation therapy.[11,52] Small lesions can be excised and primary closure done while larger lesions may require skin grafting[43] and complex surgical techniques such as flaps to reduce tension in the surrounding skin.[20,53] Tissue trauma at surgical excision should be minimal[43] because regardless of the surgical technique, the dermis is further injured and this leads to the proliferation of fibroblasts and extreme amounts of collagen formation which results in keloid scar formation.[54] Other factors that enhance the possibility of recurrence include dead space, foreign material, hematoma, infection, and wound tension.[49]

RADIATION

The treatment of keloids with radiotherapy remains controversial, although studies have shown efficacy and decreased recurrence rates, the safety of radiotherapy has been questioned.[21] Radiotherapy has been used as monotherapy or as an adjuvant after surgical excision.[44] Radiation could be by tele- or brachy-therapy.[55,56] When indicated, keloids should be first excised and to prevent recurrence, the resulting scar is irradiated.[57,58] Primary radiotherapy is only effective during the first 6 months after keloid development.[59] Radiation is thought to reduce rate of fibroblast and endothelial cell proliferation[42] resulting in a decreased amount of collagen production.[60] Superficial X-rays, electron beam, and low- or high-dose-rate brachytherapy have been used primarily as an adjunct to surgical removal of keloids with good results.[61] The adverse effects of radiation therapy include pigmentary alteration, radiation dermatitis, and potential risk of carcinogenesis.[21,41] Adjuvant radiotherapy is not recommended for pregnant patients, keloids located close to the thyroid gland, or the female breast.[55]

LOCALIZED PRESSURE THERAPY

Localized pressure therapy or mechanical compression has been shown to be effective in preventing recurrence after surgical excision, especially of earlobe keloids.[21,62] Positive pressure therapy is thought to reduce oxygen availability, increase underlying temperature, increase skin hydration, and inhibit angiogenesis and formation of new telangiectasias.[21] Compression earrings may be worn on the lobules of the ears during the wound healing phase to avoid excessive scar formation[21] and the pressure should be maintained between 24 and 30 mmHg for 6–12 months.[44] Whether used on the earlobe or for keloids on other parts of the body, pressure therapy has minimal adverse effects and though simple, is highly efficacious.[20] Good results have also been obtained when the earrings are combined with silicone gel sheeting.[63]

SILICONE GEL SHEETING

This is a noninvasive approach to the prevention and treatment of keloids and hypertrophic scars.[1] Silicone sheets are thought to work by increasing the temperature, hydration, and perhaps the oxygen tension of the occluded lesion, causing it to soften and flatten.[14,64] To be effective, the silicone sheets must be worn over the scar for 12–24 h/day for 2–3 months.[65] The use of silicone gel sheets is limited by daily patient compliance.[20] Silicone sheets may also be used as an adjunct to surgical excision, intralesional corticosteroids, and laser therapy.[41]

LASER

Laser therapy for keloids has yielded varying success.[21] Lasers such as carbon dioxide (CO_2) and erbium: Yttrium aluminium garnet (YAG) are ablative nonselective lasers that target water molecules while those like 585 and 595-nm pulsed dye and neodymium (Nd):YAG lasers are nonablative and chromophore (usually oxyhemoglobin) selective.[66] The 585-nm pulsed-dye laser (PDL) currently gives the most encouraging results.[67] It targets oxyhemoglobin causing selective photothermolysis to the scar vasculature, with subsequent ischemia and necrosis.[51] The main problem with the 585-nm PDL is that melanin is a competing chromophore, it, therefore, loses efficacy in darker skinned individuals, who are at risk for keloids.[20] For dark-skinned patients, the 595-nm PDL is an alternative vascular specific laser.[21] Improvement rates of 83–88% efficacy have been reported.[68,69] Transient hyper- or hypopigmentation and blistering are some of the adverse effects.[67-69] Postoperative purpura is the most common side effect of 585-nm PDL treatment.[21]

CRYOTHERAPY

Cryosurgery is widely used for the treatment of keloid and hypertrophic scars.[43] The mechanism of action is the rapid, repeated cooling and rewarming of tissue, leading to cell death and tissue sloughing.[20] It has been used as monotherapy and in conjunction with other forms of treatment for bigger scars.[21] Cryosurgery has been reported to have an efficacy of 50–85% on keloids, with moderate flattening and symptomatic relief.[70] Acute adverse effects of cryotherapy include pain, necrosis, edema and infections while the chronic effects include atrophy, hyperpigmentation, and hypopigmentation.[12,20]

EMERGING THERAPIES

Emerging therapies with limited studies[1,12] include intralesional IFN, bleomycin, FU, and verapamil injections.

Interferon therapy

IFNs are cytokines with antiproliferative, antifibrotic, and antiviral effects.[71] They decrease the synthesis of collagen types I and III.[52] The antifibrotic effect is thought to be mediated through the antagonizing effects on transforming growth factor-beta (TGF-β) and histamine.[72] IFN alfa-2b injected intralesionally (1.5 million IU twice daily for 4 days) reduced keloid size by 50% over 9 days, proving superior to intralesional corticosteroids.[22] It was also found that after excision of keloid IFN alfa-2b was more effective than corticosteroids for preventing recurrence.[1] Some other clinical studies, however, have not demonstrated a long-term efficacy of intralesional IFN in the management of keloidal scars.[72,73] IFN therapy is costly (about $100 per treatment)[1] and has adverse effects which include painful injections requiring local anesthesia and dose-dependent fevers, chills, night sweats, fatigue, myalgia, headaches, and flu-like symptoms for 48–72 h postinjection.[74]

Bleomycin

Bleomycin directly inhibits collagen synthesis through decreased stimulation by TGF-β1.[75] Bleomycin has antitumor, antiviral, and antibacterial activity and is a secondary metabolite of a strain of streptomyces obtained from soil.[21] Intralesional injections of bleomycin resulted in significant improvement in scar height and pliability as well as a reduction in erythema, pruritus and pain.[75,76] Dermal atrophy and hyperpigmentation may occasionally occur as side effects.[12]

5-Fluorouracil

5-FU is a pyrimidine analog with antimetabolite activity used in cancer chemotherapy.[77] Intralesional 5-FU among other actions inhibits fibroblast proliferation and decreases fibrogenetic markers and TGF-alpha.[78] 5-FU produces better results in combination with steroids or lasers[79] than as monotherapy.[78,80] Adverse side effects of intralesional 5-FU include pain, ulceration, and burning sensations.[81]

Verapamil

Verapamil is a calcium channel antagonist which inhibits the synthesis and secretion of extracellular matrix molecules (e.g., collagen, fibronectin) and increases fibrinase.[21] It has been demonstrated that intralesional verapamil is effective in reducing the size of keloids relative to intralesional triamcinolone without the side effects of pain at the injection site or hypopigmentation.[82] In conjunction with silicone sheeting, intralesional verapamil yielded better results when compared with silicone sheeting alone.[83]

OTHER THERAPEUTIC MODALITIES

Imiquimod

Imiquimod is an agent that induces the local production of proinflammatory cytokines (e.g., IFN-a, tumor necrosis factor-a) and other mediators and causes a T-helper (Th) type 1 immune response, resulting in antifibrotic, and proapoptotic effects.[84,85] Imiquimod, 5% cream, has been shown to have the potential to prevent recurrence after excision of keloids.[66]

Retinoids

Topical and intralesional Vitamin A and its retinoid derivatives aid in wound healing and reduce pathologic scar tissue.[86] Retinoic acid solution (0.05%) applied daily on scars demonstrated a reduction in size and a decrease in itching.[87] Another study with topical 0.05% tretinoin showed a significant decrease in scar size.[88] Adverse effects included photosensivity, skin irritation and skin atrophy.[87-89]

Other agents that have produced various results include tacrolimus, an immunosuppressor,[90] Botulinum toxin A, a neurotoxin,[91] ultrasound therapy,[92] and nonprescription agents such as onion extract[93] and topical Vitamin E.[94] Some of the successes recorded with some of these agents are anecdotal.

CONCLUSION

The multiple modalities of treatment available for the treatment of keloids suggest that there is still no single method that is completely satisfactory. The fact remains that prevention is the best treatment. Unnecessary surgeries should be avoided. It has been suggested that parents from keloid-prone families should consider their children's ears pierced in infancy or early childhood or perhaps not at all.[95] This last option of not piercing at all should be considered because bilateral ear lobe keloids have been reported in a 9-month-old patient following earlobe piercing that had been performed at the age of 3 months.[96] Nevertheless, combination therapies yield the best results. Steroidal therapy with TAC alone for small lesions, or combined with surgery or other modalities of treatment for bigger lesions, have been useful in controlling the growth of keloids.

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Conflicts of interest

There are no conflicts of interest.

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