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Update on the Management of Keloids

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Keloids are scars, unique to humans, that grow beyond the boundaries of a cutaneous injury, inflammation, burn, or surgical incision. Although benign, keloids are often aesthetically malignant. The etiology of keloids is uncertain. However, we do know that they occur more often in African-American and Asian than Caucasian patients. There is no one therapeutic modality that either prevents the formation of keloids or treats active or inactive lesions. Consequently, there are many therapeutic options. In this review, an approach to medical and surgical management of keloids is provided, as well as a review of experimental therapeutic modalities.

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Keloids are scars, unique to humans, that grow beyond the boundaries of a cutaneous injury, inflammation, burn, or surgical incision. However, spontaneous keloids sometimes develop without a preceding trauma, most commonly over the sternum. Although benign, keloids are often aesthetically malignant, painful, and/or pruritic, but they also may be asymptomatic. They can occur anywhere on the body, most often on the earlobes (Fig. 1), shoulders, mid-chest (Fig. 2), and upper back, but rarely on the hands, feet, axillae, or scalp. Enlargement can be predicted in areas of the keloid that have an erythematous border (Fig. 3).

The etiology of keloids is uncertain, especially because there are no animal models to study. They occur most often in dark-skinned individuals. African Americans form keloids more often than Caucasians by a ratio ranging from 5:1 to 16:1. Keloids do not occur in albinos. The author has treated 2 patients with keloids who developed vitiligo. Some of the vitiliginous lesions were overlying a keloid that resolved in these areas, but the keloid did not improve in areas covered by the patients' normal-colored skin. The incidence of keloids is approximately equal for male and female patients. They can occur at any time of life but most commonly in patients in their 20s and 30s. Although the formation of keloids clearly involves both genetic and environmental factors, they are not yet fully understood.

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Precipitating Events

Both cutaneous viral and bacterial infections can lead to the development of keloids, especially in the lesion sites of African-American children, unless preventative therapy (eg, pressure, topical steroids, and imiquimod) is administered early. Herpes zoster may also cause keloids to form, as well as pseudofolliculitis barbae (ie, razor bumps), which is most common among African-American men who shave, and acne keloidalis nuchae, which is characterized by keloid-like papules and plaques on the occipital scalp and posterior neck. Inflammatory skin conditions, such as varicella, Bacille Calmette-Guerin vaccination, folliculitis, and acne (Fig. 4) may also precipitate the formation of keloids. Other culprits are thermal and chemical burns, ear-piercing, tattooing, and fraternity branding.

Diagnosis

Keloids are characterized by excessive deposition of collagen in the dermis beyond the boundaries of the wound, whereas hypertrophic scars remain within those boundaries (Fig. 5). However, it can be difficult to distinguish between early keloids and hypertrophic scars. Unlike hypertrophic scars, which usually regress in a year or two, keloids typically grow for several years and then become stable. There are, however, some keloids that grow for years or even the lifetime of the patient (Fig. 6). Also, although hypertrophic scars respond well to therapy, keloids may not.

Preventive Measures

Before providing surgical treatment for keloids, the physician should know whether the patient, or his/her immediate family, has a history of keloid formation. One should note that if



Figure 1 The most common site for keloids is the posterior ear lobes. They are usually larger than anterior ear-lobe keloids.

a patient has only earlobe keloids, it does not necessarily indicate that the individual is prone to keloid formation because earlobe keloids are common and may occur without the presence of a positive family history. Other major risk factors that the patient and the physician must be aware of are an infected operative site and the type of precipitating injury (especially thermal or chemical burns). Physicians should warn at-risk patients not to have their ears pierced, get tattoos, or undergo nonessential cosmetic surgery, such as breast reduction or augmentation, face-lifts, or tummy-tucks.



Figure 2 Keloids on the mid-chest are the least responsive to therapy and the most common site for spontaneous keloids.



Figure 3 A keloid on the left flank with erythema of the right inferior border.

Treatment

Although no one therapy works best for all keloids, the standard treatment is intralesional corticosteroids and/or topical corticosteroids, which inhibit the alpha-2-macroglobulin. Alpha-2 macroglobulin, when active, normally inhibits collagenase. Thus, the use of intralesional and/or topical corticosteroids enables collagenase to be active, enabling collagen degeneration. In fact, collagenase may prove to be the best treatment, although a study by Kang et al¹ found that intralesional collagenase was ineffective in treating keloids.

The patient should be warned that the corticosteroid injection sites may become hypopigmented and/or atrophic for 3 to 6 months. An hour before injection, the physician should apply a thick coating of a topical anesthetic cream such as EMLA (Rx. AstraZeneca, Wilmington, DE) or LMX4 (Rx. Ferndale, Ferndale, MI) to the keloid and cover with plastic wrap. Thereafter, triamcinolone, 10-40 mg mL⁻¹, should be



Figure 4 Keloids on the back, chest, and shoulder secondary to acne.

injected every 2 to 3 weeks with a 27- to 30-gauge needle. (Note that larger needles will clog more often when inserted into hard keloids.)

The needle is inserted into the papillary dermis, where collagenase is produced. Then, the needle should be placed a little deeper into the dermal-epidermal plane, where the triamcinolone will insert more easily. The physician should inject the contents of the needle while withdrawing. One easy way to inject triamcinolone is to use half 10 mg/mL and half 40 mg/mL. This ratio provides adequate strength of triamcinolone and ease of injection without clogging the needle as much as when triamcinolone, 40 mg mL⁻¹, alone is injected. If, after 4 injection sessions, the keloid has not begun to regress or get softer, surgery is recommended.

Other injectable therapies that have been reported to have varying success are bleomycin, 5 fluorouracil (5-FU), and interferon. Small isolated keloids have been successfully treated with 5-FU. The response is best when 0.1 mL of triamcinolone acetonide, 10 mg mL⁻¹, is added to 0.9 mL of 5-FU, 50 mg mL⁻¹. This mixture is initially injected into the keloid 3 times per week and is then adjusted according to the response. Most keloids require 5 to 10 injections, which are painful. This type of therapy should be limited to small keloids. Interlesional bleomycin has been successful in flattening keloids via a multipuncture technique at a concentration of 1.5 IU/mL with the use of a needle and syringe or Dermajet (Robbins Instruments Inc, Chatham, NJ).^{2,3} Complete flattening occurred in 6 of 13 cases.

Surgical Excision

When performing surgery, the physician should avoid making mid-chest incisions and crossing joint spaces, should follow skin creases where possible, and should close the wound with minimal tension. Patients who have used systemic steroids or isotretinoin during the previous 6 months can have poor treatment results with surgery because both of these medications can impair wound healing. All patients who undergo excisional surgery must have explicit preoperative and postoperative instructions because postoperative compliance is an extremely important part of successful sur-



Figure 5 Hypertrophic scar of the forearm.



Figure 6 Keloid on the chest that has been slowly growing for 15+ years.

gical therapy. Prolonged pressure is often effective in preventing recurrence of keloids after surgical excision. An elastic garment covering the postoperative site should be worn 16 to 20 hours a day, beginning immediately after complete wound healing. Pressure seems to decrease α -macroglobulins, which normally would inhibit collagenase breakdown of collagen. Pressure also reduces mast cells, which are increased in keloids and may be the cause of keloid pruritus.

To anesthetize the site, the physician should use a mixture of equal parts triamcinolone acetonide, 40 mg mL⁻¹, and 2% lidocaine with epinephrine (1:1000). For patients with a history of keloid formation, as noted previously, one should avoid making mid-chest incisions and crossing joint spaces and should follow crease lines, if possible. If the keloid has a narrow base, it is usually sufficient to make a simple elliptic excision and undermine the base, then close with sutures.

For keloids with large bases or large nonpedunculated earlobe keloids, the procedure is more complex. A tongue-line incision approximately one-fifth the size of the keloid from its border to the flattest-looking surface should be made, the keloid excised, and then the site closed with the tongue-like flap of keloid tissue (Fig. 7). In cases in which the skin is not smooth, the physician can insert a tissue expander and wait several months before excising the keloid and closing the



Figure 7 The postexcision site is closed with a tongue-like flap.



Figure 8 A recurring keloid; each time after surgery, it grew larger. However, the patient did not use adjunctive therapy as prescribed. On her initial visit, the keloid measured a 3 by 20.3 cm; it subsequently tripled in size after 3 surgeries.

wound primarily with the least amount of tension possible. One should wait 10 to 20 days to remove sutures, especially after earlobe keloid excision.

Adjunct Therapy

Unfortunately, excision alone has a recurrence rate of $>50\%$, so adjunct therapy is advised (Fig. 8). The most common adjunct is the injection of triamcinolone acetonide, 40 mg mL^{-1} , into the postoperative site every 2 to 3 weeks $\times 4$, beginning 1 week after suture removal. The maximum dosage advised per injection session is 5 mL. To anesthetize the site, use a mixture of equal parts triamcinolone acetonide, 40 mg mL^{-1} , and 2% lidocaine with epinephrine. If injection is still too painful, inject 1% lidocaine into the perilesional area of the keloid. The steroid slows wound healing; therefore, sutures should remain in place for 10 to 20 days. Later, if the postoperative site begins enlarging, intralesional triamcinolone should be readministered. Daily use of flurandrenolide (Cordran) tape (Rx. Watson Laboratories, Corona, CA) or a potent topical steroid is recommended as an adjunct to the injections.

Other adjunct therapies include the following:

- Pressure garments combined with a class 1 topical steroid, beginning 1 week after suture removal, helps prevent recurrence.
- Flurandrenolide tape can be applied daily and left on 12 to 20 hours.
- Daily use of silicone gel sheeting can also be effective.
- Another topical agent that may be successful for treating keloids is Curad scar therapy (Beirsdorf, El Paso, TX). It is a polyurethane, silicone-free adhesive that can be used on new or old keloids and may be applied to any part of the body, including the face. It is left on for 12+ hours a day for as long as the keloid is becoming flatter and then applied weekly to prevent recurrence.
- For posterior pedunculated earlobe keloids, shaving followed by pressure hemostasis and postoperative daily

use of a pressure earring with silicone backing may prevent recurrence.

- A million units of interferon alpha- 2β per linear centimeter injected into the excision site immediately after surgery and 1 to 2 weeks later is also effective, according to Berman and Flores,⁴ who reported an 18.7% recurrence rate, whereas their recurrence rate with excision alone was 51%. (If the site is long, requiring more than 5 million U of interferon alpha- 2β , the physician should premedicate the patient with acetaminophen to help prevent the flulike symptoms that can be caused by the interferon.) The major limiting factor in the use of alpha-interferon is its high cost.
- Imiquimod cream, applied immediately after surgery and daily for 8 weeks, is another adjunct therapy. Its use is not advised until 4 to 6 weeks after surgery for patients with incisions that are large, under tension, or closed with flaps or graphs, which may splay or dehisce. According to Berman and Kaufman,⁵ one half of the patients also developed hyperpigmentation. Some subjects also experienced marked irritation for 3 to 7 days before being able to resume treatment.
- Topical tacrolimus has been touted as preventing the recurrence of keloids, whereas pentoxifylline (Trental) 400 mg t.i.d. has shown limited success.^{6,7}
- Two older therapies that deserve mention are methotrexate and colchicine, both of which have shown some success. Methotrexate, 15-20 mg, in a single dose every 4 days, starting a week after surgery and continuing for 3 to 4 months, induces folic acid deficiency, resulting in poor collagen formation. Colchicine may work by inhibition of collagen synthesis and collagenase stimulation. (However, Kang et al¹ found that collagenase, when injected intralesionally, was ineffective in the treatment of keloids.)
- Super potent (class 1) topical corticosteroids, such as clobetasol propionate, are useful when applied daily or b.i.d.
- Antihistamines can be used for pruritus, although possible drowsiness may be a problem for some patients. Sting stop is an herbal remedy that sometimes stops the pruritus when applied 3 to 4 times a day (Google “Sting Stop” for more information).

Other Medical Therapies

Verapamil, a calcium-channel blocker or calcium-ion antagonist, blocks the synthesis of collagen, glycosaminoglycans, and fibronectins. In one study, patients were treated with intralesional verapamil, 2.5 mg/mL, after excision during a 2-month period.⁸ Twenty-two keloids (55%) in 16 patients (52%) were cured by this treatment modality. Relaxin is a growth factor that can stimulate collagenase activity. It has been used in several trials for the treatment of scleroderma.⁹ D-penicillamine, another drug that has been used in the treatment of scleroderma,¹⁰ is an immunosuppressive agent that interferes with the cross-linking ability of collagen. It may be useful in the treatment of keloids. Clinical trials with

topical zinc, tretinoin, and cyclosporin have provided mixed results in their therapeutic effectiveness.¹¹⁻¹⁴ Alternatives to excision are cryosurgery, laser surgery, and radiation. They can also be useful adjuncts to excision.

Cryosurgery

Cryosurgery can be used as a monotherapy or to produce mild edema of the keloid for easier injection of intralesional steroids. When used before injections, the freeze time is 10 to 15 seconds. As a monotherapy, use 2 courses of 15-20 second freeze-thaw cycles every 3 weeks. The patient should be warned of the possibility of hyperpigmentation for 6 to 12 weeks, which may occur with a freeze time of <20 seconds. However, a longer freeze time may cause hypopigmentation lasting longer than a year. To decrease morbidity, the patient should take 2 adult aspirin 1 hour before treatment and apply clobetasol propionate, 0.05% ointment t.i.d. ×2 days, after cryosurgery.

Laser Therapy

The jury is still out on the success of lasers in keloid therapy. Although numerous studies have been published on the subject, so far no laser has proved to be a panacea. The carbon dioxide laser can be used to debulk large lesions but when used as monotherapy, there is often a recurrence rate of >70%. The Nd:YAG 1064-nm laser was successful in improving keloids in 16 of 17 patients, according to Sherman and Rosenfeld,¹⁵ but their study provides little follow-up information. The 585-nm flash lamp pumped pulsed-dye laser has shown some success in treating sternotomy scars,¹⁶ especially when used in conjunction with intralesional triamcinolone injected every 3 weeks.¹⁷

Radiation

Radiation as a monotherapy has not shown much success except in large doses. However, large doses can increase the risk of squamous-cell carcinoma at the treated site 15 or more years later. Radiation is more successful as an adjunct to surgery, used during the first 2 weeks after excision when the fibroblasts are proliferating. The usual dosage is either 300 rads (3 Gy) q.o.d. for 5 courses or 500 rads (5 Gy) q.o.d. for 3 courses starting immediately after surgery. Use of interstitial radiotherapy with iridium 192 postoperatively reduced the recurrence of keloids by 20 to 30%. Single-fraction radiotherapy after extralesional excision was reported by Ragoowansi et al¹⁸ to be effective in preventing recurrence of high-risk keloids that did not respond to prior treatment. Although keloid therapy consists of many different combinations and permutations (Table 1), there is no universally efficacious monotherapy that will either cure keloids or prevent their formation.

Possible Future Therapeutic Agents

Several possible treatments still in the experimental stage include hydroquinone, G6PD, and hyperbaric oxygen.

Table 1 Keloids: Therapeutic Options

Topical
Corticosteroids
Imiquimod
Tacrolimus
Flurandrenolide tape
Silicone gel sheeting
Curad scar therapy
Intralesional
Corticosteroids
5-FU
Bleomycin
Interferon alpha-2b
Surgical
Excision with primary closure
Excision with second-intention closure
Excision with flaps or grafts
Laser surgery
Cryosurgery
Physical
Pressure garments
Pressure earrings
Suture amputation
Oral medications
Methotrexate
d-Penicillamine
relaxin
colchicine

Hydroquinone or Other Bleaching Agents

Bleaching appears to be a promising therapy. The rationale is that albino patients do not develop keloids and vitiligo often causes the underlying keloid to regress. Hydroquinone works best if used within the first 5 months of keloid formation. If an excision is performed first, treat the excision site plus a 1- to 2-cm margin, being sure to include all suture sites.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)

African-American patients have a greater incidence of G6PD than Caucasian patients and, in the author's experience, patients with keloids have a greater incidence than those who don't. Thus, an agent to lower or block G6PD might be successful in treating keloids.

Hyperbaric Oxygen

Because low oxygen tension (hypoxia) stimulates fibroblasts, high oxygen tension may do the opposite. Studies are being conducted to compare how fibroblasts respond to low and high oxygen tension.

Future Research

There is a need for further research to determine the etiology of keloids. Unfortunately, there is no animal model for research. Hoof animals do develop keloid-like lesions on their extremities, as do eagles and the vulture family of birds. How-

ever, in these animals, the lesions clear without therapy when the offending agent is withdrawn.

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