Keloid Pathogenesis and Treatment

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Background: Keloid management can be difficult and frustrating, and the mechanisms underlying keloid formation are only partially understood.
Methods: Using original and current literature in this field, this comprehensive review presents the major concepts of keloid pathogenesis and the treatment options stemming from them.
Results: Mechanisms for keloid formation include alterations in growth factors, collagen turnover, tension alignment, and genetic and immunologic contributions. Treatment strategies for keloids include established (e.g., surgery, steroid, radiation) and experimental (e.g., interferon, 5-fluorouracil, retinoid) regimens.
Conclusion: The scientific basis and empiric evidence supporting the use of various agents is presented. Combination therapy, using surgical excision followed by intradermal steroid or other adjuvant therapy, currently appears to be the most efficacious and safe current regimen for keloid management. (*Plast. Reconstr. Surg.* 117: 286, 2006.)

Keloidal scarring is one of the most frustrating clinical problems in wound healing. Keloids form following dermal injury and exhibit exuberant, indefinite growth of collagen (Fig. 1).[1,2] They tend to occur in darker skinned individuals with a familial tendency and not in the extremes of age. Keloid formation has been ascribed to altered growth factor regulation, aberrant collagen turnover, genetics, immune dysfunction, sebum reaction, and altered mechanics. No single unifying hypothesis adequately explains keloid formation. The numerous treatments for keloids—surgical excision, steroid injection, radiation therapy, laser, silicone, and pressure therapy, among others—underscore how little is understood about this disease process (Figs. 2 through 5).

This article reviews the history of keloidal scarring, differentiates keloids from hypertrophic scars, explains the theories of pathogenesis, examines the various treatments, and suggests future directions for research.

HISTORY

The first written description of keloids was attributed to the pyramid age in ancient Egypt.[3] In 1806, Alibert coined the term "cheloid" from the Greek word "crab claw."[4] Cosman et al. documented the presentation, characteristics, and treatment of keloids in the first systematic review of keloids in 1961.[5] Mancini and Quaife, and later Peacock et al., delineated the clinical difference between keloids and hypertrophic scars.[6,7]

KELOID VERSUS HYPERTROPHIC SCAR

Keloids and hypertrophic scars are separate clinical and histochemical entities. Clinically, hypertrophic scars remain within the confines of the original scar border, whereas keloids invade adjacent normal dermis.[7] Hypertrophic scars generally arise within 4 weeks, grow intensely for several months, and then regress. In contrast, keloids may appear later following the initial scar and then gradually proliferate indefinitely.[5,8,9] Although both keloids and hypertrophic scars show increased fibroblast density, only keloids have increased fibroblast proliferation rates.[10] Collagen fibers in keloids are larger, thicker, and more wavy than those found in hypertrophic or normal scars[11] and assume a random orientation, whereas those in hypertrophic scars orient parallel to the epidermal surface.[12] Enzyme concentrations, such as alanine transaminase and metabolic activities marked by adenosine triphosphate, are elevated in keloids compared with normal scar tissue and hypertrophic scars.[13,14] Fibroblasts isolated from keloid and hypertrophic scar tissue exhibit increased gene transcription of $\alpha 1$ (I) procollagen. However, the increased mRNA concentration is compensated at the posttranscriptional level in hypertrophic scars, but not in keloids. The post-
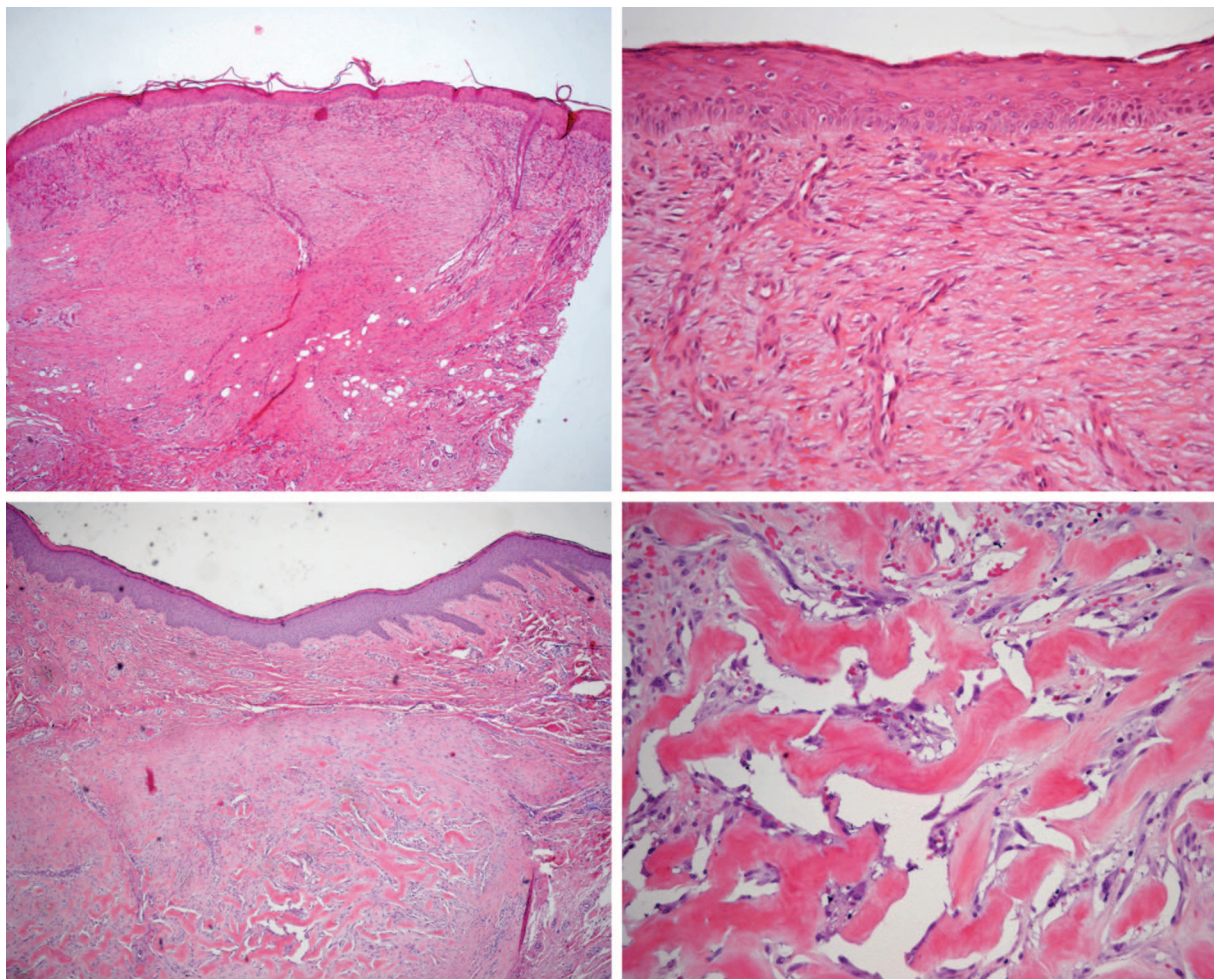
Fig. 1. Clinical samples of normal and keloid scar tissue stained with hematoxylin and eosin. Microscopic anatomy reveals markedly increased, disordered collagen bundles in the keloid specimen, which contribute to its clinical phenotype. (*Above*, *left*) Normal scar (hematoxylin and eosin; original magnification, ×40). (*Above*, *right*) Normal scar (hematoxylin and eosin; original magnification, ×200). (*Below*, *left*) Keloid (hematoxylin and eosin; original magnification, ×40). (*Below*, *right*) Keloid (hematoxylin and eosin; original magnification, ×200).

transcriptional difference results in an increased ratio of type I to type III collagen found in keloids, but not in hypertrophic scars.[15]

PATHOGENESIS

The following hypotheses have been proposed for keloid formation and growth.

Altered Growth Factor Milieu

The exuberant scar tissue found in keloids has been attributed to augmented growth factor activity (transforming growth factor-β and platelet-derived growth factor) and alterations in extracellular matrix (fibronectin, hyaluronic acid, and biglycan).

Growth Factor Differences

Transforming growth factor (TGF)-β and platelet-derived growth factor are growth factors normally produced during the proliferative phase of wound healing[16] and whose activities are both significantly abnormal in keloids. Keloid fibroblasts have heightened sensitivity to and dysfunctional regulation of TGF-β.[17–19] Areas of enhanced proliferation and collagen deposition within keloid tissue have distinctly elevated levels of TGF-β.[20] Similarly, keloid fibroblasts have four- to five-fold increased levels of platelet-derived growth factor receptor, and the growth-stimulatory effects are synergistic with TGF-β.[21]

Extracellular Matrix Differences

The components of the extracellular matrix regulate growth factor activity. The extracellular

Fig. 2. Keloids classically occur on certain parts of the body, specifically, on the shoulder, anterior chest wall, and earlobes. Surface tension and sebaceous gland density are among the characteristics that have been hypothesized to predispose these anatomical sites to keloid formation. Image shows keloid on the shoulder.

Fig. 4. Keloid on earlobe.

Fig. 3. Keloid on anterior chest wall.

matrix of keloids is abnormal, with elevated levels of fibronectin and certain proteoglycans and decreased levels of hyaluronic acid.[22] Fibronectin and hyaluronic acid are proteins expressed during normal wound healing, and their dysfunctional regulation in keloid contributes to the fibrotic phenotype.[23,24] Biglycan and decorin are proteoglycans that bind collagen fibrils and influence collagen architecture. Keloids have aberrant production of these proteoglycans, resulting in disorganized extracellular matrix and collagen architecture.[25]

Why is the growth factor milieu in keloids abnormal? Three concepts address why the environment is altered.

Concept 1: Epithelial-mesenchymal interactions likely play a fundamental role in keloid pathogenesis. Studies using keratinocyte-fibroblast in vitro coculture systems have revealed that keloid keratinocytes can induce the keloid phenotype in normal fibroblasts. Furthermore, histologic changes in the epidermis of abnormal scars in vivo correlate with dermal fibroblast activity.[26]

Concept 2: Proliferative pathways active in fetal cells and disabled in the adult possibly reemerge in the keloid. Unlike normal adult skin fibroblasts, fetal and keloid tissue can survive and proliferate in vitro in a reduced serum environment.[19]

Concept 3: Hypoxia found in keloid tissue could trigger the release of angiogenic growth factors, spurring endothelial proliferation, delayed wound maturation, and increased collagen production by fibroblasts.[16,27,28] The hypoxia appears to be caused by endothelial overgrowth partially to fully occluding the microvessel lumens in the keloids.[29]

Collagen Turnover Hypothesis

Abnormal regulation of the collagen equilibrium leads to the characteristic physical appearance of a keloid, the large collagenous mass that distinguishes it from normal scar.[7]

Fig. 5. "Dumbbell" keloid on earlobe.

Collagen content in keloids is elevated compared with normal tissue or scar.[17] Light and electron microscopic studies demonstrate that collagen in keloids is disorganized compared with normal skin. The collagen bundles are thicker and more wavy, and the keloids contain hallmark "collagen nodules" at the microstructural level.[30,31] The ratio of type I to type III collagen is increased significantly in keloids compared with normal skin or scar, and this difference results from control at both the pretranscriptional and posttranscriptional levels.[15]

Collagen is produced mainly by fibroblasts and also by endothelial cells.[6,32–34] Keloid fibroblasts have a greater capacity to proliferate because of a lower threshold to enter S phase and produce more collagen in an autonomous fashion.[2,17,34–39]

Matrix metalloproteinases and their inhibitors (tissue inhibitors of matrix metalloproteinases) potentially play a major role in keloid formation. Collagen is degraded by collagenase produced in fibroblasts and in inflammatory cells.[32,34] Enzymes that inhibit or degrade collagenase exert an additional level of collagen regulation.[34,40] Concentrations of collagenase inhibitors, α-globulins and plasminogen activator inhibitor-1, are consistently elevated in both in vitro and in vivo keloid samples, whereas levels of degradative enzymes are frequently decreased.[34,40] Steroid-treated and irradiated keloids exhibit a decrease in collagenase inhibitors and an increase in apoptosis of fibro-

blasts, leading to normalization of net collagen levels.[31,34] Furthermore, matrix metalloproteinase activity differs between keloid and normal fibroblasts, and these differences appear to directly affect phenotype.[41] Because collagen predominates in the phenotypic appearance of keloids, collagen metabolism and particularly modulation of matrix metalloproteinases serve as valuable targets of therapeutic intervention.

Tension Hypothesis

Mechanical tension placed on the healing wound misaligns the orientation of collagen formation and results in keloid formation.

Mechanical tension drives fibroblast proliferation and collagen synthesis.[42,43] In vitro and in vivo studies have suggested that stretch and tension not only promote collagen production but also dictate collagen architecture and orientation and affect dermal remodeling.[44] Collagen is oriented perpendicular to the muscle contraction; therefore, incisions perpendicular to the muscle fibers theoretically heal with collagen oriented naturally.[45] Anecdotal evidence suggests that incisions created parallel to skin tension lines rarely form abnormal scars, whereas those placed at sites of joint motion frequently do.[46,47] Keloid and hypertrophic scar formation can also be minimized through the use of absorbable subcuticular suture closure instead of interrupted nonabsorbable su-

turing, thereby limiting suture trauma to the skin.[47] Furthermore, abnormal scarring rarely develops in elderly patients, whose skin characteristically has poor tension.[7]

This hypothesis implies that nonaligned tension forces disrupt scarring into an abnormal pathway. Without objective evidence, there is disagreement regarding whether sites of frequent keloid formation, such as the earlobe and the chest wall, are under tension or not.[7,48,49] Indeed, although stretch and tension are important determinants of final scar appearance, they may play a more dominant role in the pathogenesis of hypertrophic scarring than they do in keloid formation.[7,44] Nonetheless, stretch and tension forces must be carefully considered in all models of skin healing, and future research may reveal more complexity to this hypothesis than the current two-dimensional paradigm.

Genetic Immune Dysfunction

An inherited abnormal immune response to dermal injury may cause keloid formation, as keloids are associated with particular human leukocyte antigen subtypes.

Keloids tend to occur in darker skinned individuals, and familial tendencies suggest a polygenic inheritance pattern. However, darker complexion does not correlate directly with a higher rate of keloid formation, as seen in a study of 175 Malaysian keloid patients.[50] A genetic influence is probably directed through an immune phenotype. Studies suggest association of group A blood type and human leukocyte antigen B14, 21, BW35, DR5, and DQW3 in patients with a keloid diatheses.[51–54] Patients who develop keloids have a disproportionately high incidence of allergic diathesis and elevated levels of serum immunoglobulin E.[55,56] Multiple reports have found trends in patterns of serum complement, immunoglobulin G, and immunoglobulin M levels in patients with keloids,[51,57,58] suggesting a systemic immune state genetically predisposed to keloid formation.

Keloid formation could be considered an autoimmune connective tissue disease.[58] Circulating non–complement-fixing antifibroblast antibodies could bind to fibroblasts and stimulate proliferation and collagen production, similar to antithyroid antibodies in Hashimoto's thyroiditis.[59] Keloids have been found associated with a number of other genetic connective tissue diseases, including Rubinstein-Taybi syndrome, Ehlers-Danlos syndrome, progeria, osteopoikilosis, scleroderma, and pachydermoperiostosis.[60–64] Clinical evidence

also suggests that patients who develop keloids have an inherently hypersensitive cell-mediated immune system.[57,65,66]

The growth of keloids, characterized by a slow initial phase followed by rapid secondary growth, suggests the occurrence of a local immune reaction.[55] Use of monofilamentous suture material in closure of surgical incisions results in fewer abnormal scars compared with multifilamentous suture, presumably attributable to less local inflammation.[67] Furthermore, actively growing keloid explants, placed into nude mice that lack an immune system, grow initially and then regress despite revascularization. Keloid regression in nude mice supports the theory that a systemic immune response directed their growth before explantation.[68–70]

Sebum Reaction Hypothesis

Keloids could arise from an immune reaction to sebum. Dermal injury exposes the pilosebaceous unit to systemic circulation, and in individuals who retain T lymphocytes sensitive to sebum, a cell-mediated immune response is initiated.

Release of cytokines, in particular interleukins and TGF-β, stimulates mast cell chemotaxis and fibroblast production of collagen. As the keloid expands, further pilosebaceous units on the advancing border are disrupted, and the process propagates.[71–73] Keloids preferentially occur on anatomical sites with high concentrations of sebaceous glands, such as the chest wall, shoulder, and pubic area (Fig. 6), and rarely occur on anatomical sites lacking sebaceous glands, such as the palm and sole. The sebum reaction hypothesis explains why an individual with two otherwise identical incisions could develop one keloid and one normal scar.[72,73] The sebum reaction hypothesis also explains why only human beings, the only mammals with true sebaceous glands, are affected by keloidal scarring. Patients with keloids demonstrate a positive skin reaction to intradermal sebum antigen[71] and tend to have a greater resultant weal size than patients without a keloid diathesis.[74] Furthermore, keloids can form following immunization with autologous skin,[75] and a sebum vaccine can successfully desensitize patients from keloid recurrence following excision.[71]

The success of radiation therapy and steroids in the treatment of keloids, the former reducing sebum production[76] and the latter inhibiting local lymphocyte activity, is consistent with a sebum reaction as the cause. It has been speculated that ablation of the pilosebaceous unit before elective

Fig. 6. Spontaneous keloid formation in the pubic area of male (*above*) and female (*below*) patients.

Fig. 7. An earlobe keloid is injected with steroid (triamcinolone acetate) using a syringe with a 25-gauge needle.

surgical excision may provide prophylaxis against the later formation of keloids.[72]

TREATMENT STRATEGIES

Steroids

Intralesional steroid (triamcinolone) is the most effective and widely used treatment for keloids.

Intralesional triamcinolone acetonide, a potent anti-inflammatory hydrocortisone fluoridated at its ninth carbon, is first-line therapy for keloids (Fig. 7).[77–79] Large trials in the 1960s and 1970s demonstrated that the efficacy of triamcinolone against keloids exceeds 80 percent.[80–85] Triamcinolone acetonide (Kenalog, 10 mg/cc; Bristol-Myers Squibb, Princeton, N.J.) is injected intralesionally, typically 10 mg per linear centimeter of keloid every 2 to 6 weeks, until clinical resolution or until side effects prohibit use.

Triamcinolone inhibits the proliferation of normal and keloid fibroblasts, inhibits collagen synthesis, increases collagenase production, and reduces levels of collagenase inhibitors.[83,86–89]

Working through fibroblast glucocorticoid receptors, steroids also induce ultrastructural changes in collagen synthesis that enhance the organization of collagen bundles and degenerate the characteristic keloidal collagen nodules.[88,90]

Adverse effects, including subcutaneous atrophy, telangiectasis, and pigment changes, occur in approximately half of all patients treated with triamcinolone but frequently resolve without intervention.[77,78,84,91–93] Systemic effects of steroids (Cushing's syndrome) generally do not occur with intralesional triamcinolone treatment, but rare cases have been reported.[94,95]

Surgery

Surgical excision of keloids by itself generally results in lesion recurrence.

Surgical excision of keloids alone has consistently shown poor results, with recurrence rates of 40 to 100 percent.[5,7,48,96] Simple excision is believed to stimulate additional collagen synthesis, resulting in rapid regrowth and often a larger keloid.[48,97]

Subtotal excision along with lateral undermining has been credited with improved outcome and fewer recurrences (Fig. 8). Because the rim of the keloid scar serves to splint the wound and relieve tension, the stimulus for collagen synthesis is decreased.[92] However, an earlier study comparing

Fig. 8. Serial views of a subtotal surgical excision of a large keloid around the left ear. (*Left*) Preoperatively; (*center*) after surgical excision; and (*right*) postoperatively after primary closure.

different excisional strategies did not find merit in subtotal excision,[96] and currently both subtotal and complete surgical excision are practiced.

Surgical excisions can be closed either primarily or through a number of reconstructive techniques. In general, sutures are removed as early as possible and intradermal, subcuticular closure is preferred, to avoid suture marks that subsequently develop keloids.[47] Monofilamentous suture is preferred to braided suture to minimize local inflammatory reaction.[67] If primary closure does not suffice, the wound from the surgical excision of keloids can be closed with flap advancement, autograft, or composite allografts, including Integra (Life Sciences, Plainsboro, N.J.).[98]

Radiation

Radiation therapy effectively reduces keloid recurrence rates. Its use has been limited by the theoretical risk of inducing malignancy.

Radiation therapy as an adjunct to keloid excision has efficacy rates of 65 to 99 percent in long-term follow-up, with results consistently better than matched controls of surgical excision alone.[93,99–102] Radiation therapy is generally administered immediately after keloid excision, using fractionated therapy with a total dose of 10 to 15 Gy.

Radiation of keloids damages the fibroblasts directly and affects collagen structure and organization.[31,100] In vitro studies demonstrate that radiation increases the rate of apoptosis in keloid fibroblast to normal, reestablishing cell population equilibrium.[31] One study suggests adjuvant radiation should be used selectively in early keloids,[103] reflecting the increased number of proliferating fibroblasts in younger keloids.

Skin pigmentation changes and ulceration occasionally occur and frequently resolve without treatment.[5,49,93,96,99–101,103,104] Wound dehiscence has not been noted with early postoperative radiotherapy of keloids.[49,100,102] Radiotherapy is contraindicated for keloids in pediatric patients and pregnant women and on sites with underlying visceral structure. Despite the theoretical risk of cancer and a few documented cases, there has been no association of radiation therapy for keloids and carcinogenesis in multiple large clinical trials, totaling thousands of patients treated.[49,99–102,104] Radiation therapy should probably be used more frequently in the management of keloids when exposure of visceral structures can be avoided.

Silicone Gel

Silicone gel is effective in the management of keloids, although its mechanism of action is unknown. The use of silicone gel, especially as sheets, is limited by daily patient compliance.

Silicone gel, a U.S. Food and Drug Administration–approved, cross-linked polymer of dimethylsiloxane, is an effective adjunct to keloid excision and a prophylaxis to abnormal scarring in

elective incisions.[105–110] Use of silicone gel either as a topical gel or impregnated elastic sheet requires covering the entire scar for at least 12 hours each day, and ideally 24 hours per day except when the skin is being cleaned (Fig. 9). Silicone gel can be used alone or as adjuvant therapy after excision and is effective after 4 to 6 months of treatment.[109,111,112] Use of silicone gel has resulted in more rapid healing and can be used in conjunction with carbon dioxide laser excision to decrease recurrence rates.[111,112]

Silicone gel probably acts as an impermeable membrane that keeps the skin hydrated, functioning in a manner analogous to the stratum corneum.[113–115] In vitro experiments have documented that silicone is inert, with no effect on fibroblast function or survival, but enhanced keratinocyte hydration alters growth factor secretion, which in turn affects fibroblast function and collagen production.[115] The clinical effects of silicone gel do not appear to be mediated by changes in pressure, temperature, tissue oxygenation,[106,107] or silicone entry into the dermis.[106,107,109,116]
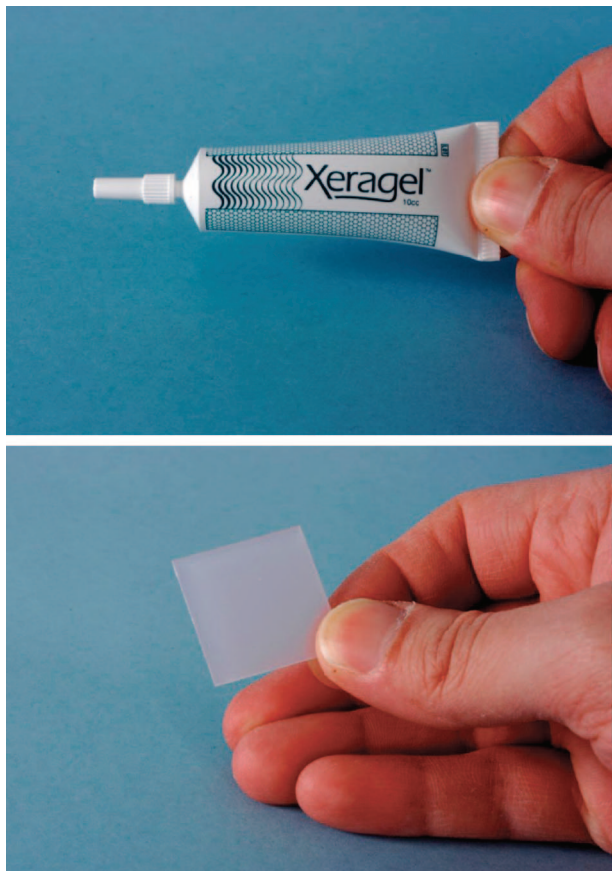

Fig. 9. Silicone gel can be used either alone or in combination therapy, including postresection, and can be applied to the scar as a gel (*above*) or as an impregnated sheet (*below*).

Adverse effects of silicone gel include occasional skin maceration, erosion, rash, and pruritus, all of which resolve with removal of the gel for several days followed by reapplication.[109–112,116,117] Silicone gel is comfortable, but it requires active patient compliance and long-term application that can be especially challenging on mobile and angled anatomical sites such as the neck.[111]

Pressure Therapy

Pressure therapy following excision is effective with minimal adverse effects, but its practical use is limited to earlobes.

Pressure therapy is an effective therapy for keloids and has found its widest use as a postoperative adjunct for earlobe keloids. Recurrence-free rates of excision followed by earlobe pressure therapy generally exceed 80 percent.[118–126] In a controlled trial in 1942, Nason found that adjuvant postoperative pressure reduced recurrence rates of keloids excised from various parts of the body from 67 percent to 18 percent.[127] The mechanism of pressure therapy has not been determined. Because tension affects collagen production and organization,[42,43] some of the therapeutic benefit of pressure might be a result of altered wound tension. An additional mechanism may be through pressure-induced ischemia that promotes collagen degradation and modulates fibroblast activity.[128] Because compression earrings should be worn 24 hours per day after suture removal, patient compliance can be an issue. Nevertheless, whether used on the earlobe or for keloids on other parts of the body, pressure therapy is simple and highly efficacious, with minimal adverse effects.

Laser

Laser therapy has been advocated but has not been shown to be effective in keloid management.

The carbon dioxide laser has the reported advantages of reduced blood loss, decreased postoperative pain, and less scarring.[129–131] However, carbon dioxide laser excision alone yields unremarkable results, with over 50 percent recurrence rate, suggesting no advantage over scalpel excision.[103,129] Some investigators combined the carbon dioxide laser with modalities including interferon, triamcinolone, and silicone gel,[103,112,132] and reported success rates similar to scalpel excision with respective adjuvant therapy. The cost of the carbon dioxide laser and the recurrence rate prohibit its use over the scalpel.

In numerous studies, keloids respond to the 585-nm flashlamp-pumped pulsed-dye laser with efficacy exceeding 75 percent and minimal morbidity in selected patients.[133–137] The mechanism of the flashlamp-pumped pulsed-dye laser is selective thermolysis of hemoglobin molecules, which results in microvascular damage and coagulative necrosis, and ultimately tissue hypoxia; the laser may also cause dissociation of collagen bundles.[134,136,138] The main problem with the 585-nm flashlamp-pumped pulsed-dye laser is that melanin is a competing chromophore. Therefore, the flashlamp-pumped pulsed-dye laser loses efficacy in darker skinned individuals, who are at risk for keloids.

5-Fluorouracil

Intralesional 5-fluorouracil is an experimental therapy for keloids that has shown some potential in preliminary trials.

5-Fluorouracil is an antimetabolite that inhibits fibroblast proliferation and modestly improves keloidal scarring.[139–141] 5-Fluorouracil has been successfully used to inhibit postsurgical scarring in glaucoma surgery.[142] Intralesional administration of 5-fluorouracil as single therapy for keloids has been reported in one retrospective study of more than 1000 patients where an initial response was almost uniformly present but was followed by recurrence, necessitating serial administrations.[139] 5-Fluorouracil (50 mg/ml) was injected at 0.05 ml per linear centimeter or until blanching appeared every 3 weeks up to 10 times. A small placebo-controlled prospective trial of surgical excision followed by topical administration of 5-fluorouracil suggested clinical improvement in the treatment arm after 6 months of follow-up, along with a trend toward normalization of immunohistochemical markers.[140] Wounds were exposed to a pledget soaked with 5-fluorouracil (50 mg/ml) for 5 minutes, then closed. Adverse effects have been rare and include superficial skin irritation without any discernible hematologic changes.[139–141]

Interferon

Intralesional interferon is an experimental therapy with considerable systemic adverse effects. Its efficacy in keloid management has not been demonstrated.

Interferons are cytokines secreted mainly by T-helper lymphocytes that produce an antifibrotic profile.[143–146] Interferon-γ and interferon-α2b have been used in the experimental treatment of keloids. Interferon-α2b has a more comprehensive effect on enzymes that modulate collagen levels.[145] Three trials of intralesional interferon-γ only demonstrated keloid softening or modest size reduction.[147–149] Interferon-α2b was demonstrated to decrease keloid surface area following serial intralesional injections.[144] However, three subsequent clinical trials using intralesional interferon-α2b alone failed to demonstrate any efficacy.[150–152] After carbon dioxide laser excision, a small trial of adjuvant intralesional interferon-α2b suggested a 66 percent cure rate with 3 years of follow-up; one arm of the study group with ear keloids had no recurrences.[132] However, a clinical trial of postexcisional interferon-α2b versus triamcinolone therapy was prematurely terminated because of a 46 percent recurrence in keloids treated with interferon-α2b versus 15 percent with triamcinolone ($p < 0.05$) (this issue, p. 247).

Unlike other treatment modalities for keloids, intralesional interferon produces adverse systemic effects. Dose-dependent flu-like symptoms, including pyrexia, headache, and myalgias, may develop after therapy. Patients can be either treated or prophylactically pretreated with acetaminophen for relief of symptoms.[144,147,148,153]

Retinoids

Retinoids, an experimental therapy, have produced responses in limited clinical trials, but there has been no general acceptance in clinical practice.

Topical and intralesional vitamin A and its retinoid derivatives enhance new wound healing and promote regression of pathologic scar tissue.[154–156] Two clinical trials show significant responses of established keloids to 0.05% topical retinoic acid applied twice daily for 3 months.[59,157,158]

Retinoids enhance epidermal proliferation while inhibiting that of fibroblasts and shift the healing process to normal regeneration.[154,155] In vitro data have suggested that retinoids can modulate proliferation of normal and keloid fibroblasts and modulate collagen production.[87,155,159,160] Interestingly, retinoids also suppress sebum production,[161] which could have a role in keloid pathogenesis. Adverse effects included photosensitivity, skin irritation in 50 percent, and slight skin atrophy in 10 percent of patients.[59,157]

Other Therapies

Additional strategies for keloid management have been reported in the literature, including the following.

Calcium Channel Blockers

Intralesional injection of phenylalkylamine calcium channel receptor antagonists after keloid excision has shown promising early results in three clinical trials.[124,162,163] Intralesional verapamil was also successfully used in one of these trials with pressure therapy and in another with topical silicone. No significant adverse events of intralesional verapamil were reported in these trials. The mechanism of action likely involves inhibition of calcium-dependent reactions involved in extracellular matrix production and enhancement of extracellular matrix degradation.[164–166]

Cryosurgery

Cryosurgery uses rapid, repeated cooling and rewarming of tissue, leading to cell death and tissue sloughing. The efficacy of cryosurgery on keloids has been reported to range from 50 to 85 percent, with moderate flattening and symptomatic relief.[167,168] Unlike surgical excision, cryosurgery also has a direct beneficial effect on the keloidal collagen, resulting in improved collagen bundle organization.[168] Cryotherapy can cause hypopigmentation or depigmentation.

Antihistamine

Histamine antagonists, particularly those specific to the H_1 subtype receptor, can relieve some of the burning and pruritus associated with keloids and may modulate keloid size.[169–172] The problematic pruritus of keloids[5] probably results from mast cell degranulation and histamine release.[96] Histamine may also contribute to keloid formation through stimulation of collagen synthesis and other processes.[169,170]

Penicillamine, β-Aminopropionitrile, and Colchicine

Penicillamine and β-aminopropionitrile are lysyl oxidase inhibitors that interfere with collagen crosslinking, making collagen more susceptible to collagenases. These oral agents are used in conjunction with colchicine, which increases collagenase activity. This strategy shifts the collagen turnover ratio by manipulating extracellular enzymes. In a small case series, no keloids recurred after 18 months and there were no documented adverse effects.[173]

Experimental Therapies

Several other experimental therapies for abnormal scarring have been attempted in single case reports or small trials, some of which will likely undergo further investigation on keloids in the future. These therapies include bleomycin, imiquimod, and cyclosporine.[174–179]

Combination Therapy

The most effective management for keloids uses combination therapy, generally excision with adjuvant treatment.

Surgery Plus Steroids

Scalpel excision of the lesion followed by injection of triamcinolone (10 mg per linear centimeter) into the wound bed, often with repeat injection at follow-up, is the most successful management for keloids. Cure rates exceeding 80 percent have been consistently reported using this combination regimen.[80,83–85] The same adverse effects found with steroid treatment alone (atrophy, telangiectasias, and pigment changes) can be seen following this combination therapy, and tend to resolve themselves.

Carbon Dioxide Laser Plus Steroids

Excision of keloids using carbon dioxide laser followed by postoperative injection of steroids into the wound bed yields cure rates comparable to those of scalpel excision followed by steroid injection.[103] Use of the carbon dioxide laser has been reported to result in decreased postoperative pain.[129,130]

Surgery Plus Radiation Therapy

Surgical excision with immediate postoperative radiotherapy can be used for keloids without any underlying visceral structures, particularly the extremities. This combination therapy yields cure rates ranging from 65 to 99 percent, with minimal adverse effects of occasional skin pigment changes and ulceration.[93,100–102,104,180,181] Radiation therapy should not be used in the treatment of keloids in the pediatric population or pregnant women, because of the theoretical risk of malignancy.

Surgery Plus Compression Earrings

Surgical excision of earlobe keloids followed by the use of compression earrings results in cure rates exceeding 80 percent, with minimal adverse effects.[118,120] This combination regimen is the preferred method of managing earlobe keloids.

Surgery Plus Silicone Gel Sheeting

Excision of the keloid followed by application of a silicone gel sheet for up to 24 hours per day for 4 to 6 months results in recurrence-free rates exceeding 80 percent.[109,111,112] Adverse effects of this treatment regimen include minor skin irritation and occasional maceration. Patient compliance is frequently a problem.

Surgery Plus 5-Fluorouracil

Injection of 5-fluorouracil into the wound bed after surgical excision of the keloid is an experimental treatment resulting in cure rates exceed-

ing those with surgical excision alone, with rare adverse effects including minor skin irritation.[140]

FUTURE DIRECTIONS

Current research aims to determine the molecular basis of wound healing and keloid pathogenesis. Four topics deserve special attention in future keloid research.

Animal Model

No adequate animal model has been developed for keloids. Humans are the only mammals that develop keloids, and attempts to create an animal model such as the nude mouse have failed. Even though increased knowledge of keloid pathogenesis suggests a systemic immune component to their cause, the nude mouse continues to be used to study the molecular effects of experimental therapeutics.[68–70,182] Animal models using explanted human tissue would likely require transgenic technology to produce a permissive host environment, and the components of such an environment are poorly understood.

Immunologic Factors

There is a strong immunologic component to keloid formation. Investigation of the role of the immune system could result in a paradigm shift from viewing keloids as a local phenomenon to considering them a systemic autoimmune disease. Furthermore, immunologic research could clarify the genetic component of keloid formation. Interestingly, a propensity to form keloids may confer immunity against melanoma and other skin malignancies[65]; potential insight into any such mechanism would have enormous implications.

TGF-β Subtype Agonists and Antagonists

TGF-β appears to be the growth factor most central to keloid pathogenesis. Increased understanding of the role of TGF-β signaling in fibrotic diseases and elucidation of the characteristics of the different TGF-β subtypes make manipulation of these molecules an attractive therapeutic strategy.[146,183] TGF-β1 and TGF-β2 promote fibrotic scarring in in vivo animal models, and TGF-β3 has the opposite effect of enhancing physiologic healing.[184–187] Investigation into novel TGF-β3 agonists and TGF-β1 and TGF-β2 antagonists may produce new therapeutic tools with enhanced efficacy and specificity.

Mesenchymal-Epidermal Interactions

Keratinocytes play a critical role in keloid pathogenesis. The role of epidermal components such as keratinocytes and Langerhans cells has probably been underestimated, because keloids have been perceived as a dermal, fibroblastic disease. The keratinocyte-fibroblast coculture techniques in the Longaker Laboratory and the rabbit ear scarring models in the Mustoe Laboratory will allow investigation into mesenchymal-epidermal interactions.[188–191] Knowledge of the mesenchymal-epidermal interaction will likely drive development of future therapies.

CONCLUSIONS

No ideal therapy exists for keloids, reflecting our poor understanding of keloid pathogenesis. Although evidence supports each of the hypotheses presented, the cause of keloids and a targeted therapy remain elusive. Optimal treatment continues to be various combinations of triamcinolone, surgical excision, pressure therapy, silicone gel, and occasionally radiotherapy. Current combination therapies appear to decrease recurrence rates as compared with monotherapy. The most effective combination needs to be identified in future clinical trials. Ideally, a regimen of surgical excision minimizing tissue trauma, inflammation, and tension could be combined with an injectable modulator, steroids, and 5-fluorouracil, external beam radiation when applicable, and a hydrating pressure dressing to address the cellular mechanisms. Furthermore, an oral adjuvant therapy (antihistamine, colchicines) to modify host response may improve outcomes. The ideal combination of intradermal, extradermal, and systemic treatments will provide keloid patients more reliable and effective therapy.

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