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**Review Article**

# Keloids – an extensive review in the light of recent literature

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**Abstract** Keloids are benign but challenging wound healing ailments that manifest clinically in variable and diverse forms. Patients present with one or very few small slow growing lesions on one extreme or else with numerous and very large, life-changing and debilitating lesions covering significant portion of their skin. The keloids require a comprehensive treatment plan and approach and most lesions need more than one modality of treatment. Proper assessment requires accurate quantification of the disease's impact on the patients in terms of physical symptoms, quality of life and psychosocial status. This review focuses on the natural history, clinical features and therapeutic update of keloids in the light of the recent literature

***Key words***
Keloid, hypertrophic scars, fibroblast, collagen, treatment, prevention, biology.

## Introduction

Wound repair represents interplay between cellular processes that act to restore skin integrity and function after trauma and ultimately end in scar formation. Keloid represents the result of an abnormal wound repair when excessive scar tissue is deposited within and beyond the boundaries of the wound. Keloids pose aesthetic as well as functional problems and are psychologically debilitating. This review discusses the epidemiology, pathophysiology, clinical features, and management of keloids in the light of the recent literature.

## Methods

The original articles and case reports dealing with the biology, prophylaxis and treatment strategies for hypertrophic scars and keloids were searched keloids were reviewed in PubMed, HINARI, Google Scholar, Web of Science and Cochrane library databases after search on the keywords: Keloid and hypertrophic scars and treatment and biology. Only the literature published in English was included and all articles in languages other than English were excluded. Time limits were set from 1 January 2012 to till date. In addition, important references from earlier dates and abstracts of non-English articles that appeared as cross references in the included articles were also reviewed and used where ever necessary.

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## Historical background

Keloid scars were first described by ancient Egyptian surgeons in the Edwin Smith Papyrus, dating back to 1700 BC. The East Nigerian Yoruba tribe reported on keloids in the 10$^{th}$ century and the cultural studies have revealed that they were practicing ritual facial marking and recorded characteristics of the keloid. This was followed by Retz in 1790 who referred to keloids as "dartre de graisse" or "fatty hernias"

in his book "Treatise on Skin Diseases and Things of Mind" published in 1790, probably a misnomer since the clinical description was suggestive of keloid.[1]

Baron Jean-Louis Alibert (1768–1837), a French pioneer in dermatology , identified the keloid as an entity in 1806 . He called them 'cancroïde ', but later around 1817 changed the name to 'chéloïde' to avoid confusion with cancer. The term is derived from the Greek χηλή, chele, meaning "hoof", here in the sense of "crab pincers", referring to the claw like extension of the lesions with a tendency to grow in a lateral direction and the suffix -oid, meaning "like".[1]

**Pathogenesis**

Skin injury due to any case such as a surgical incision, a burn or a chronic disease state such as acne, is resolved typically through a process of repair resulting in scar formation.

The classical model of wound repair initially involves hemostasis followed by three distinct, but overlapping phases that follow a time sequence: the inflammatory phase, the proliferative phase and the remodeling phase.

The inflammatory phase lasts for approximately 2–3 days after injury and by its end; the process achieves reepithelialization thereby restoring the skins continuity and protective function.[2]

As the inflammatory phase resolves, the repair process progresses beneath the healed epithelium. Myofibroblasts are formed from the dermal fibroblasts in the dermis adjacent to the wound after they get activated. They migrate into the granulation tissue where they produce Type 3 collagen matrix which leads to wound contraction bringing the wound edges together. The final phase involves remodeling of collagen matrix and replacement with Type 1 collagen, resulting in the formation and maturation of the visible scar tissue and can last a year or more. For a wound to heal effectively, all phases should occur properly and in the right sequence. Scarring is deemed as abnormal when deposition of dermal collagen and fibrosis is excessive or suboptimal. Uncontrolled deposition of dermal collagen results in formation of benign, fibroproliferative lesions, hypertrophic scars and keloids.[3]

After the initial injury and the formation of a wound clot, the balance between granulation tissue degradation and biosynthesis becomes essential to adequate healing. Keloids as compared to normal mature scar tissue have an increased blood vessel density, higher mesenchymal cell density, a thickened epidermal layer, and increased mucinous ground substance. The alpha–smooth muscle actin fibroblasts, myofibroblasts important for contractile situations are very few. The collagen fibrils in keloids are more irregular, abnormally thick, and have unidirectional fibers arranged in a highly stressed orientation.[4]

Growth factors and cytokines are intimately involved in the cycle of wound healing and various factors attenuate or accelerate fibrosis . Keloids display an amplified production of tumor necrosis factor (TNF)-α, interferon (INF)-β, and interleukin-6 and diminished production of INF-α, INF-gamma, and TNF-β. INF-α, INF-β, and INF-γ lead to reduce synthesis of collagen types I and III. A relationship appears to exist between immunoglobulins and keloid formation; while levels of immunoglobulin G and immunoglobulin M are normal in the serum of patients with keloids, the concentration of immunoglobulin G in the scar tissue is elevated when compared to hypertrophic and normal scar tissue.[4]

In keloids, TGF-B1 causes an increase in type-1 collagen through activation of COL1 genes, but a decrease in matrix metalloproteinase-1 (MMP-1, interstitial collagenase). The net result is deposition of collagen and fibrosis. Furthermore, it has also been seen that TGF-B1 increases MMP-2 (gelatinase), allowing keloid fibroblasts to migrate 2.5 times faster than normal dermal fibroblasts. This may partially explain the proliferative and spreading nature of keloids over time. Similarly Type III collagen, chondroitin 4-sulfate, fibronectin and glycosaminoglycan content are higher in keloids. Collagen cross-linking is greater in normal scars, while keloids have immature cross-links that do not form normal scar stability. Mast cell population and hence histamine production within keloid scars is increased which explains the pruritus associated with these lesions.[4-5]

**Recent advances in understanding of biology of wound healing with relation to keloids**

Various factors have been proven to influence the pro-fibrotic or anti-fibrotic pathways and hence determine the outcome of wound repair process.

***Hypoxia***

Oxygen has been known to be an important factor in wound repair.[6] There have been many reports in literature suggesting that a hypoxic environment is associated with keloid formation. A recent study by Touchi et al indicated that the central portion of keloids is severely ischemic as compared to that of normal scar or hypertrophic scar. The investigators found greater expression of hypoxia-induced factor-1α (HIF-1 α) as well as lesser vascular density, in the center than along the periphery of these lesions.[7]

Zhao et al. conducted a study to investigate if hypoxia drives the transition of dermal fibroblasts to myofibroblasts and to clarify the potential transduction mechanisms involved. They observed that keloids are relatively hypoxic and that hypoxia drives the transition of normal dermal fibroblasts to a myofibroblast-like phenotype [high expression of α-smooth muscle actin (α-SMA) and collagen I and III]. Hypoxia effectively facilitated the nuclear import of the Smad2 and Smad3 complex, while blockade with the Smad3 inhibitor, SIS3, significantly impaired the expression of hypoxia-induced fibrosis-related molecules. Hence the study demonstrated that hypoxia facilitates the transition of dermal fibroblasts to myofibroblasts through the activation of the TGF-β1/Smad3 signaling pathway and these findings are expected to provide a potential target for the treatment of keloids.[8]

A recent study by Okuno et al suggested that keloids have a prosurvival mechanism in which enhanced autophagy and glycolysis in the fibroblasts of a keloid's hypoxic central zone aids in the extrusion of lactate to fibroblasts in the normoxic peripheral zone via metabolic coupling.[9] Increased autophagy also appears to inhibit central-zone apoptosis. The study results indicate that autophagy inhibitors and MCT4 blockers may have potential therapeutic implications in keloid treatment.[9]

***Angiogenic imbalance and Periostin***

Keloid exhibits unregulated and abnormal angiogenesis which is attributed to an imbalance between proangiogenic and antiangiogenic factors. The Angiogenic imbalance in keloids was explored with reference to circulating and tissue level expression of vascular endothelial growth factor (VEGF) and endostatin/collagen XVIII by Mogli N S et al . It was observed that VEGF levels were upregulated and endostatin

levels were downregulated in keloid patients in comparison to normal controls in both sera and tissue. The study suggested that the antiangiogenic therapeutics based on endostatin in combination with current curative strategies could present a scope for the effective management of keloids.[10]

Periostin is a secreted extracellular matrix (ECM) protein involved in angiogenesis and was originally identified in osteoblasts, periosteum and periodontal ligament. This matricellular protein has lately been found to be expressed in the basement membrane, dermis and hair follicle.[11]

Zhang Z et al in an effort to elucidate the underlying regulatory mechanism of keloid angiogenesis and its imbalance conducted a study aimed at examining the impact of periostin on angiogenesis in keloids. The study found that the vessel density was higher in keloids compared with normal tissue, observed following staining with CD31 and CD105. Further, the expression of periostin was upregulated and demonstrated a markedly positive correlation with blood vessel density. The upregulated periostin activates the ERK1/2 and FAK signaling pathways leading to increased secretion of vascular endothelial growth factor and angiopoietin-1 in the keloid fibroblasts, thereby promoting angiogenesis. The study suggested that upregulation in the level of periostin may be a key factor in keloid development and hence periostin may, therefore, be a novel therapeutic target in the treatment of keloids.[12]

***MicroRNAs***

MicroRNAs (miRNAs) are a class of small non-coding RNAs which play a role in the regulation of gene expression at the posttranscriptional level by degrading their target mRNAs and/or inhibiting their translation. Recently researchers have performed miRNA expression microarrays in keloids and reported miRNAs to be deregulated (upregulated or downregulated) in keloids, suggesting a potential in the treatment of keloids.[13-15]

***Decorin***

Decorin is a proteoglycan component of dermal connective tissue that binds to type I collagen fibrils and neutralizes the stimulatory effects of TGF-β on collagen, fibronectin and glycosaminoglycan synthesis. This protein has been found to be decreased in keloids. Decorin also displays inhibitory action on angiogenesis by interacting with VEGF receptors (VEGFR2) and by inhibiting hepatocyte growth factors and PDGF. Decorin, due to these antifibrotic properties. Hence Decorin is currently being investigated as a potential future therapeutic agent.[16-17]

***Fibroblast activation protein-alpha (FAP-α)***

Fibroblasts are proven to be the key cellular mediators of fibrogenesis in keloid .Fibroblast activation protein alpha (FAP-α) and dipeptidyl peptidase IV (DPPIV) are proteases located at the plasma membrane promoting cell invasiveness and have been previously associated with keloid scars. Dienus K et al analyzed in detail the expression of FAP-α in keloid fibroblasts compared to control skin fibroblasts and found a significantly increased expression of FAP-α in keloid fibroblasts compared to control skin fibroblasts. Inhibition of FAP-α/DPPIV activity using the irreversible inhibitor H(2)N-Gly-Pro-diphenylphosphonate reduced the increased invasiveness of keloid fibroblasts indicating that keloid invasiveness may potentially be partly FAP-α/DPPIV mediated. The study concluded that since FAP-α expression was found to be restricted to reactive

fibroblasts in wound healing and normal adult tissues are generally FAP-α negative, inhibiting FAP-α/DPPIV activity may be a novel treatment option to prevent keloid progression.[18]

***Adiponectin***

Adiponectin is an adipocyte-derived protein hormone that is known to exert pleiotropic biological effects on metabolism, inflammation, vascular homeostasis, apoptosis and immunity. Recently, adiponectin has been suggested to attenuate the progression of human dermal fibrosis and studies have been undertaken to understand the underlying mechanism. Limin L et al in their study investigated the expression of adiponectin and adipoRs in keloids and normal skin tissues and revealed the signal transduction pathway by which adiponectin mediated Connective Tissue Growth Factor (CTGF )activity. The study suggested that adiponectin may become a potential focus for studies of the pathogenesis of keloids.[19]

***Wnt/beta-catenin pathway***

There are evidences that suggest that Wnt signalling and its effector beta-catenin play an important role in wound healing. Sato M studied the role of Wnt/beta-catenin signaling in TGF-β induced collagen deposition in hypertrophic scars and keloids. The study provided evidence that beta-catenin protein levels are elevated in keloid and that TGF-beta induces activation of beta-catenin mediated transcription in human dermal fibroblasts via the Smad3 and p38 MAPK pathways. These findings may prove in future to be relevant in understanding the pathogenesis of keloids.[20]

**Epidemiology and Clinical features**

Keloids are formed when the pathological scarring process extends beyond the margin of the original wound and is the most extreme type of scarring. Keloids can develop in predisposed individuals at any site where skin trauma has occurred though they occur more frequently on shoulders, chest, neck, upper arms and cheeks.[21] Keloids have also been reported in literature to occur on eyelids, genitalia, palms, soles, cornea or mucous membranes.[22-24]

The precipitating factors include pimples, body piercing, insect bites, scratching, burns, surgical incisions, vaccination or other skin injury. Pruimboom T and Scheltinga M R even reported keloid formation due to repeated mammographies.[25] Rarely cases are reported in literature proving that keloids can also develop spontaneously without any precipitating injury.[26-28]

They are more frequent in Africans /African Americans and Asians with incidence rates as high as 15–20% in the black skinned population. Although they can occur in all skin types, there are no reports of keloid formation in albinos 29. Keloids occur in all age groups although mainly seen around the puberty and both the genders are equally affected.

On physical examination, keloids are characterized by a well-circumscribed, firm, irregular, mildly tender, bosselated and pink-purple lumps usually accompanied by hyperpigmentation, and a glossy surface with occasional telangiectasias.[30]

Keloids are often asymptomatic but may cause pain (throbbing, sharp needle like or else aching), burning sensation, pruritus, or hyperesthesia, the degree of sensation varying from person to person. The precise etiology of keloid related pain is unclear, but studies suggest a small nerve fiber neuropathy affecting the perikeloidal skin as a possible explanation.[31,32]

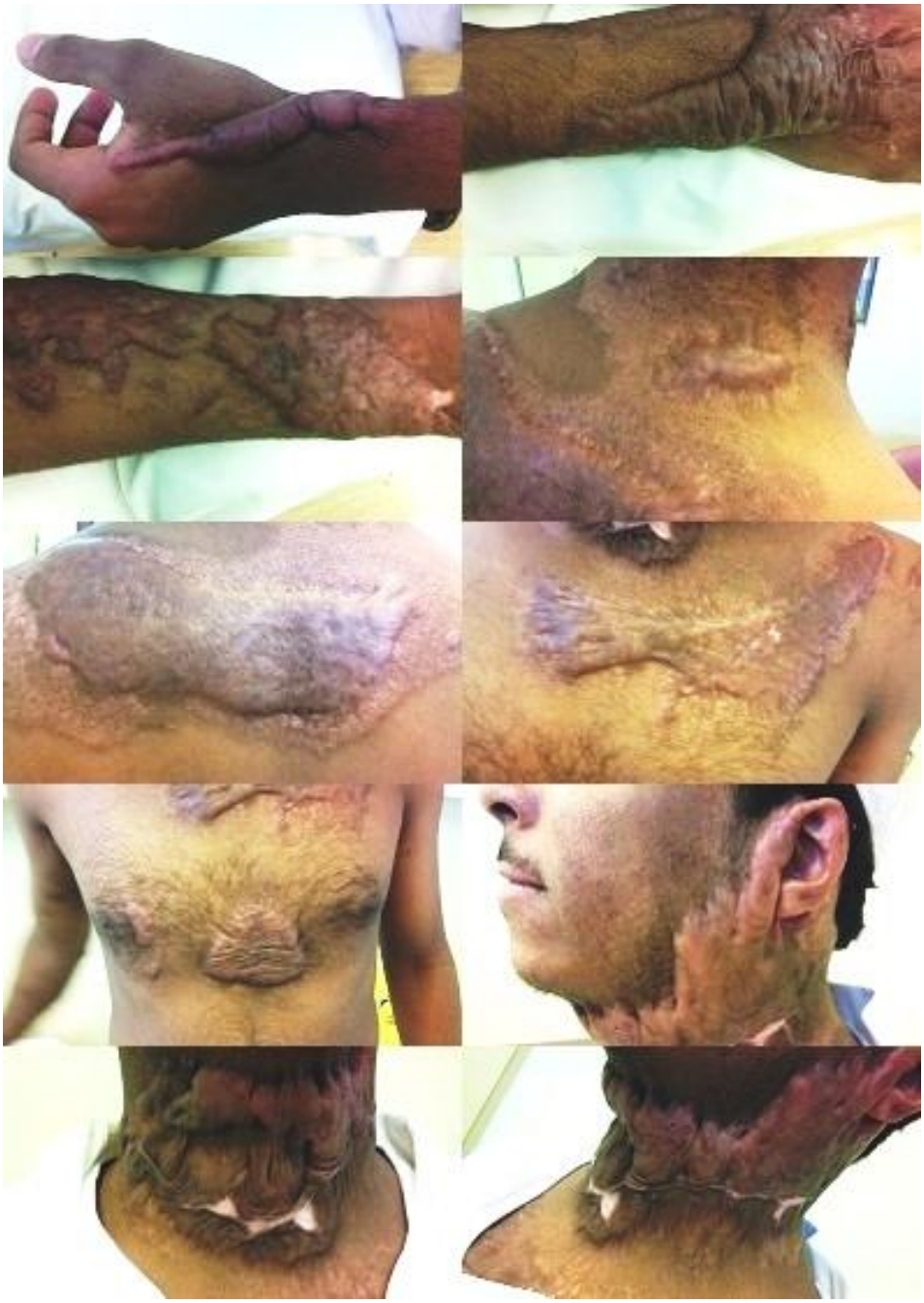

**Figure 1** Keloids over multiple areas after nine months of sustaining burn injuries

Individuals may report experiencing some relief in symptoms when taking a hot shower.[25]

Besides leadings to significant physical and esthetic disabilities, keloids can have significant psychological and social ill-consequences for patients, and may be associated with substantial emotional and financial burden. Keloids may lead to sleep disturbances, anxiety, depression, and significant disruption of routine life. Besides, the lesion has a potential to deteriorate creating contractures, restriction of joint movements and severe deformities. The combination of the factors ultimately result in a compromised quality of life and diminished functional performance. However Olaitan PB in

his study concluded that even though keloids do not have a significant negative impact on overall quality of life in communities like a black African population where keloid exists in endemic form but about 47 (35.8%) of the patients believed that keloid swelling limit their social interaction and females (59.1%) felt stigmatized.[33]

**Histopathology of keloids**

Butler et al in 2008 summarized four histologic features that are consistently found in specimen of keloid and therefore are deemed pathognomonic for keloid diagnosis[34]:

i. presence of keloidal hyalinized collagen.
ii. tongue-like advancing edge underneath the normal-appearing epidermis and papillary dermis.
iii. horizontal cellular fibrous bands in the upper reticular dermis.
iv. prominent fascia-like fibrous bands.

**Differential Diagnosis**

*Hypertrophic scar*

Hypertrophic scars are the most important differential diagnosis. They are raised and often discolored, but do not extend beyond the boundary of the initial wound. Hypertrophic scarring typically develops in wounds at locations on the body which are under tension, such as shoulders, ankles, knees, and the neck. Histopathological and immune-histochemical analysis can clear the diagnosis in doubtful case.

*Neoplastic lesions*

Cases in the literature suggest the presence of various types of malignant tumors that resemble keloid, including dermatofibrosarcoma protuberans, trichilemmal carcinoma, and keloidal basal cell carcinoma. And the careful differential diagnosis is particularly challenging in African-Americans since the skin and tumor color is often similar and hence biopsy is recommended in anomalous cases.

*Keloidal blastomycosis (syn:Lobomycosis, lacaziosis, Lobo's disease )*

Keloidal blastomycosis is a chronic keloid-like lesions, slowly growing mycosis of the skin and subcutaneous tissue which produces plaques, nodules, verrucoid lesions, or ulcerated lesions, usually at a site of trauma.[35-36]

The essential element in the patient's history that should raise suspicion is the exposure to aquatic environments and animals of the Amazon River basin, particularly fresh water dolphins. Histopathology reveals abundant fungi and giant cells in the lesions which are granulomatous and devoid of collagenous fibrosis unlike that in keloids.[35-36]

*Nodular contact dermatitis*

Contact dermatitis secondary to metallic earrings may produce nodular lesions resembling keloids on the earlobes but histopathological analysis of these lesions shows a dense infiltration of lymphocytes and formation of lymphoid follicles rather than dense collagen tissue. Allergic reaction is more pronounced with nickel and gold is relatively safe material due to its stability and low tendency to ionization. However sporadic reports of allergic contact dermatitis to gold do appear in literature.[37,38] Cases of palladium induced epithelioid granulomas in the earlobes with a positive patch test are also reported.[39]

*Cutaneous sarcoidosis*

Cutaneous sarcoidosis presents in 9-37% of patients with systemic sarcoidosis, and may mimic keloids or hypertrophic scars. This granulomatous disease of unknown etiology most commonly affects the lungs and is more prevalent in African-Americans than in Caucasians though recent studies have shown cutaneous involvement up to 30% in Germany and about 33% in France.[40] Lesions are typically pink to yellowish-brown or purple, and on diascopy display a classic "apple jelly" appearance. The lesions have a predilection for localization in scars or sites of injury, particularly those containing foreign material (e.g. splinters, suture material, or even silica).[40]

*Atypical mycobacterial infections*

Atypical mycobacterial infections are indolent slowly enlarging cutaneous and subcutaneous infections that can mimic keloids. They frequently occur after trauma or surgery, and acid-fast organisms such as Mycobacterium chelonae (subspecies abscessus) have been found in the tap water , disinfectants used in hospital settings and even gentian violet used by surgeons to mark the patients preoperatively.[41] Erroneous sterilization of surgical instruments can lead to outbreaks and make it a problem mainly affecting developing countries such as Africa where keloid is otherwise more prevalent. A high index of suspicion is required to accurately diagnose atypical mycobacterial infections, since the usual hallmarks of surgical site infections (pain, fever, worsening erythema) may be absent.

*Spitting suture, suture abscess and suture granuloma*

These are common causes of postoperative nodularity and hyperplastic growth in surgical wounds and scars. These changes frequently occur weeks to months after surgery. Subcuticular sutures may "spit" or cause excess granulation tissue to protrude through the skin and often appear as a shiny red or purple nodule with focal tenderness or pruritus. Spitting sutures may express serosanguinous pus or spicules of partially degraded suture material leading to immediate decompression of the nodule, differentiating it from a keloid. Suture granuloma may present with classic inflammatory reaction with erythema, swelling, pain and finally rejection of the suture material or else as a chronic inflammatory reaction with granuloma formation that may present as a solid mass, usually painless and gradually increasing in volume.[42]

**Clinical Genetics of Familial Keloids**

Most keloids occur sporadically, but some cases are familial. Various studies have been undertaken to document the genetics and the mode of inheritance of keloid formation and several lines of evidence (increased familial clustering in KD, its increased prevalence in certain races and concordance in identical twins) do suggest that keloid scarring is influenced by genetic factors.[43]

Marneros et al studied the clinical and genetic characteristics of 14 pedigrees with familial keloids and found the pattern of inheritance to be consistent with an autosomal dominant mode with incomplete clinical penetrance and variable expression. Chen et al arrived at the similar conclusion by studying the clinical and genetic information of six Han Chinese pedigrees with familial keloids with all the family members having no recorded marriage history to other races except Han people.[44,45]

Clark et al studied three African American families, one Afro-Caribbean family and one Asian-American family to determine the inheritance pattern and phenotype of keloids

among multigenerational families, as a prelude to a positional mapping strategy to identify candidate genes. The study concluded that familial keloids appear to most commonly manifest autosomal dominant or semidominant inheritance, and there may be familial patterns of keloid distribution.[46]

Brown et al have demonstrated that a genetic association exists between HLA-DRB1 status and the risk of developing keloid scarring in Caucasians of Northern European origin but a similar association is absent in Afro-Caribbean population.[47,48]

A study by Lu et al supports an association between HLA-DRB1 alleles and susceptibility or resistance to keloids in Chinese Han individuals.[49]

**Systemic Implications and Complications**

Hypertrophic scars and keloids alone do not predispose an individual to systemic disorders or complications; however, certain dermatoses may present with an increased number of keloids. Spontaneous keloids have been reported in association with syndromes such as Rubinstein-Taybi syndrome (RSTS), Dubowitz syndrome, Noonan syndrome, Goeminne syndrome, Bethlem myopathy, conjunctivo-corneal dystrophy, X-linked recessive polyfibromatosis, novel X-linked syndrome with flamin A mutation, Ehlers-Danlos syndrome, and the third stage of yaws.[31]

In Rubinstein-Taybi syndrome (RSTS), keloids occur in 24% of individuals, either spontaneously or after a minor trauma, usually starting in early puberty.[50]

**Treatment Strategies**

*Corticosteroids*

Corticosteroids have been a popular treatment for pathological scars since the mid-1960s, and this treatment still continues to play a major role in the management of keloids. Triamcinolone acetonide after its introduction in 1990s has been most popular and is administered intralesional most commonly or else in the form of steroid tapes/ plasters.[51]

Triamcinolone can suppress vascular endothelial growth factor (VEGF), inhibit fibroblast proliferation, and induce scar regression, which may be the most important mechanism of action. Triamcinolone has also been found to inhibit transforming growth factor (TGF)-β1 expression and to induce apoptosis of fibroblasts. Depending on the size and site of the lesion and age of the patient, dosage has varied from 10 to 40 mg/mL, and the dose is administrated at intervals of 3 to 6 weeks for several months or until the scar is flattened. Kontochristopoulos et al. however treated 20 patients with intralesional injections of 5-FU (50 mg/mL) at shorter interval i.e., once weekly for 7 weeks and the follow-up at 12 months revealed that 85% of the patients experienced greater than 50% improvement though recurrence rate was 47%.[52]

Dexamethasone was found by Wu WS et al to cause keloid regression via interaction with the GR and suppression of endogenous VEGF expression and fibroblast proliferation.[53]

Furthermore, all corticosteroids exhibit suppressive effects on the inflammatory process in the wound and inhibit collagen and glycosaminoglycan synthesis, fibroblast growth, and enhance collagen and fibroblast degeneration. Another mechanism is induction of vasoconstriction mediated by binding of the

topical steroid to the classical glucocorticoid receptors.[54]

Resolution rates for keloids treated with steroids are variable and range from 50-100% and recurrence is seen in 9-50%. Syed F et al. compared the single and combined efficacy of glucocorticoids-dexamethasone (Dex), triamcinolone (TAC), and methylprednisolone (Medrol)-on primary keloid fibroblasts (KFs) and normal skin fibroblasts at cellular, protein, and messenger RNA levels in vitro. The study reported the superior efficacy of three well-known steroids on KF and suggested that the combination may be superior than using a single steroid in treating keloids.[55]

The adverse effects include the pain at injection site, thinning and atrophy of the skin and subcutaneous tissues, the development of steroid acne, capillary dilation, telangiectasia, moulting, the development of secondary lymphogenous and linear hypopigmentation (temporary/ permanent), high recurrence rates of 9-50%, local skin necrosis /ulceration and Cushing's syndrome .

Significant pain at injection site is a concern as it causes many patients to discontinue treatment and many studies have been undertaken recently to find means to alleviate the pain. Topical application of anesthetic creams, such as Tetracaine and EMLA cream (lidocaine and prilocaine) to prevent pain on steroid injection site, has limited efficacy in bigger lesions because of poor drug penetration.

Tosa M et al. achieved significant reduction in pain by pretreatment with topical 60% lidocaine tape.[56] Wang X et al applied cryoanesthesia (cryotip) as pretreatment before injection and found it to be a rapid and effective means of reducing the pain associated with steroid injections.[57] Park et al found vibration anesthesia to be a promising option to effectively and safely alleviate pain, likely by reducing pain transmission from peripheral receptors to the brain.[58] Usanakornkul A and Burusapat C. administration of mixture of 1% lidocaine and TA did not find it effective in pain relief.[59]

Park et al. in 2012 in a study concluded that the anatomic location of facial keloids could play a role in re-development, because recurrence rates were greater in perioral regions and that the possible reason for this greater recurrence could be skin tension and wound strain in the highly mobile perioral region.[60]

To minimize the side effects without diminishing the effect, steroids are administered in lowest possible doses and in combination with other modalities.

Davison et al. found that the combination of 5-FU and triamcinolone is superior to triamcinolone alone (15% vs. 40%).[61] Furthermore, the triple combination of 5-FU, corticosteroids, and the pulsed-dye laser has been found to be even more effective. Fibroblast activity is suppressed by 5-FU, corticosteroids suppress inflammation and fibroblast activity, and the pulsed-dye laser suppresses angiogenesis and endothelial cells.[62]

*Scar Revision Surgery*

Surgical excision is one of the traditional modes of management for keloids. The remodeling phase of wound healing may last for more than one year; hence, excision of keloids is to be considered only after a delay of at least one year. Surgical excision alone frequently results in disappointing outcomes with reported recurrence rate of 45-100% and to improve postoperative surgical outcomes, multimodal combination therapy such as postoperative steroid application or radiotherapy is to be added.

During scar revision surgery, tension-free wound closure should be established in order to decrease tension-related inflammation and thereby reduce recurrence and wide range of techniques including three-layered sutures, subcutaneous/fascial tensile reduction sutures, Z-plastics or local flap reconstruction have been proposed , depending upon the case.[63]

*Cryotherapy*

Cryotherapy has been used to treat keloids as a monotherapy or in conjunction with other therapies such as intralesional steroid injections.

Treatments that combine cryotherapy and intralesional triamcinolone injections significantly improve keloids.

Delivery methods for cryotherapy are variable and include contact, spray or the intralesional-needle cryoprobe method. The intralesional-needle cryosurgery device (cryoprobe) was introduced by Zouboulis et al. in 2004 and has since become the most preferred mode of delivery.[64]

The suggested mechanism underlying cryotherapy is vascular damage leading to tissue necrosis. The tissues necrotized by cryotherapy secrete unique inflammatory cytokines that alter the responses of myofibroblasts and hence result in transformation of the scar architecture. The collagen fibers become aligned in a more parallel arrangement and the structure tends to mimic a normal, organized dermis.[65] van Leeuwen et al. in 2015 published the results of a comprehensive review of the articles published on intralesional cryotherapy, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. PubMed and EMBASE. The review showed that this mode produce favorable results in terms of volume reduction (from 51-63%) and alleviate complaints of pain and pruritus. However, complete scar eradication was not established, and recurrences are seen in upto 24%. Also, persistent hypopigmentation proved a problem in Fitzpatrick IV-VI skin type patients. Hence, the evidence proved limited and inconsistent resulting in an American Society of Plastic Surgeons grade C recommendation for this type of the treatment of keloid 66.Similar results were found in the study conducted by O'Boyle et al.[67]

Van Leeuwen et al. in another study have introduced an Argon gas-based system to achieve accurate and highly controlled freezing and found the method to be effective in the treatment of keloid scars, yielding volume reduction and low recurrence rates.[68]

*Radiotherapy*

Studies have proven the effectiveness of external beam radiotherapy and brachytherapy in the treatment of keloids. Radiotherapy is generally delivered as an adjuvant treatment one or two days after scar revision surgery, and the recommend radiation dose is 40 Gray over several divided sessions to minimize adverse effects.

Radiotherapy suppresses angiogenesis that results in decreased delivery of inflammatory cytokines, and successive inhibition of fibroblast activity resulting in decreased collagen synthesis and hence suppression of keloid development. The recurrence rate for this modality is around 10%.[69,70]

Radiotherapy carries an inherent risk of carcinogenesis. The risk is low but still warrants precautions while dealing with keloids over the radiation-vulnerable areas including the thyroid and breast.[71]

Recently, studies have shown effective use of radioactive skin patches that use various kinds of radionuclides like Re-188 and P-32. These patches are used as painless, cost effective monotherapy or else in combination with other modalities. The adverse effects include hyper or else hypopigmentation.[72,73]

*Laser Therapy*

Laser treatment involves the use of light energy of a specific wavelength and pulse duration to ablate targeted tissues and vaporize blood vessels, thereby limiting the ability of the inflammatory cytokines to reach the keloids. Studies have found that lasers significantly down-regulates the expression of Connective Tissue Growth Factor (CTGF). The proliferation of keloid fibroblasts is thereby significantly inhibited resulting in improved aesthetic and symptomatic outcomes and decreased keloid recurrence.[74]

Keloids have been treated with several types of lasers including 585-nm pulsed dye laser (PDL), carbon dioxide ($CO_2$), argon, and neodymium: yttrium-aluminum-garnet (Nd:YAG) laser. The most popular laser used to treat the keloids is the 585-nm pulsed dye laser (PDL). The recommended energy is 6.0 to 7.5 J/cm$^2$ (7-mm spot) or 4.5 to 5.5 J/cm$^2$ (10-mm spot) and two to six sessions of treatment may be needed.[75-78]

The 1064-nm Nd:YAG laser is also popular for treating keloids. For this laser, the recommended energy is 14 J/cm2 (5-mm spot), to be repeated every three to four weeks. Fractional CO2 laser has also been found to be effective.[79]

Laser therapy is used as a monotherapy or else combined with other modalities like silicone gel sheeting and intralesional steroid injections.[80,81] Studies have been conducted to compare lasers with other modalities. Scrimali et al in their study conclude that in comparison to radiotherapy, the use of $CO_2$ laser after surgical excision of keloids has shown great results with no recurrence and without the risk of carcinogenesis.[82]

One of the most recent developments introduced into laser technology is the nonablative fractional laser (NAFL). Recently NAFL (1540/1550 nm) with a 15 mm handpiece have also been successfully used for the treatment of keloids. However, data regarding recurrence rates in a long-term follow-up is still lacking.[83]

Possible side effects of laser therapy include hypopigmentation, hyperpigmentation, blister formation and purpura. $CO_2$ lasers vaporize tissue, which can aerosolize infectious agents such as the hepatitis and HIV viruses and thereby potentially endanger health care personnel.

*Intralesional 5-Fluorouracil (5-FU)*

5-FU is a pyrimidine analogue, classified as an antineoplastic agent that reduces thymidylate synthase activity thereby inhibiting normal DNA and RNA synthesis. Studies have demonstrated ability of 5-FU to induce fibroblast apoptosis without necrosis and is known to inhibit TGF-β signaling in collagen I production.

Kontochristopoulos et al. in 2005 published the results of 20 patients treated with intralesional injections of 5-FU (50 mg/mL). The results revealed that 85% of the patients experienced greater than 50% improvement. Biopsy specimens taken after six injections exhibited a reduction in the amount of hyalinized collagen fibers, regression of the nodular concentric arrangement of the collagen fibers, less prominent vascularity and flattening of the dermal papillae without any signs of atrophy.[84]

Since then, further studies have been published proving the efficient role of 5-FU in the management of keloids though adverse effects have also been reported that include wound ulceration, hyperpigmentation, atrophy, erythema, tissue sloughing, swelling, pain, moulting, and telangiectasia. However, these complications quickly disappear. To minimize the side effects, studies have suggested lower dosages of the drug or usage in combination with other modalities.[85]

There is sufficient evidence to suggest that the combination of 5-FU and triamcinolone is superior to triamcinolone alone (15% vs. 40%), as reported by Davison et al.[86], Khan et al[87], Ren et al[88] and Darougheh et al.[89] Furthermore, it has been suggested that the triple combination of 5-FU, corticosteroids, and the pulsed-dye laser offer balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual drug. Fibroblast activity is suppressed by 5-FU, corticosteroids suppress inflammation and fibroblast activity, and the pulsed-dye laser suppresses angiogenesis and endothelial cells.[62,90]

*Bleomycin*

Bleomycin, derived from Streptomyces verticillus, induces fibroblast apoptosis and inhibits lysyl oxidase, a cross-linking enzyme involved in the maturation of collagen and TGF-β1, resulting in net reduction of collagen. Bleomycin blocks the cell cycle via the inhibition of DNA, RNA, and protein synthesis as well as the production of reactive oxygen species.[91]

Intralesional injection is the preferred method of drug administration. Several studies report the achievement of complete flattening in 54-73% of keloids with resolution of other symptoms like itching and pain.[92,93] Naeini et al. compared the efficacy of Bleomycin tattoo with that of cryotherapy combined with intralesional triamcinolone injection for the treatment of keloids and Bleomycin tattoo to be more effective.[94]

Manca et al reported use of Bleomycin in combination with electroporation and found it to be an effective treatment for patients affected by large keloid scars or patients who are non-responders to other treatments.[95]

Cutaneous side effects, including flagellate erythema (scratch dermatitis), hyperpigmentation, Raynaud's phenomenon, gangrene, fibrosis, eccrine hidradenitis, necrosis of keratinocytes, alopecia, edema, nail changes have been documented in literature. The most common adverse effects are minor ulceration that heal within few days and hyperpigmentation that may or may not resolve with time.[93,96]

*Interferon (IFN)*

Interferon (IFN) α, β and γ are cytokines with antifibrotic, and antiproliferative properties with ability to decrease the synthesis of collagen I and III by inhibition of production of glycosaminoglycans (GAGs) in the fibroblasts, which form the scaffolding for the deposition of dermal collagen. IFN-α2 increases collagenase production whereas IFN-α2b inhibits cell proliferation and TGF-β1 expression. IFN-γ modulates a p53 apoptotic pathway by inducing apoptosis-related genes. IFN-γ inhibits TGF-β and therefore fibrosis, via initial activation of Jak1, which in turn stimulates the negative regulator of collagen YB-1 (Y-box protein-1), which activates Smad7, eventually leading to TGF-β1 suppression.[97]

Multiple recent studies have proven the efficacy of intralesional injection of interferon as a part of combination therapy. Lee et al. reported

about 85% decrease in depth and volume by treating 20 keloids with a combination of intralesional TAC and IFN alfa-2b compared with only a nonsignificant improvement obtained in 20 keloids treated with TAC alone.[98]

IFN injected into the suture line of keloid excision sites may be prophylactic for reducing recurrences and the use of IFN-α2b has showed 18% recurrence rate when applied to postsurgical excised keloids as compared to about 51% with only surgical excision.[99] Certain prospective studies , however have found interferon to be ineffective in the clinical management of keloids.[100]

Side effects may be systemic, including flu-like symptoms, fever, headache, arthralgia, fatigue, chills, confusion and other unfavorable reactions such as pain at the injection site, local erythema and edema.

*Verapamil*

Verapamil is a phenylalkylamine calcium channel antagonist that alters fibroblast shape from bipolar to spherical, induces procollagenase expression, inhibits the synthesis/secretion of extracellular matrix molecules (including collagen, glycosaminoglycan and fibronectin) and increases collagenase.[101]

Verapamil has also been observed to decrease IL-6 and vascular endothelial growth factor (VEGF) production in the keloid fibroblasts, which translates to decreased cell proliferation, increased apoptosis, and increased expression of decorin, which in turn inhibits fibroblast proliferation and migration.

Wang R et al. in a meta-analysis assessed the effectiveness of verapamil in preventing and treating keloid and the results showed that verapamil could improve keloid with few adverse effects and was not significantly different from conventional corticosteroid injections.[102]

Alexandrescu et al. found favorable results with 5-FU and verapamil combination in terms of symptomatic relief and decrease in height of the lesions whereas Margaret Shanthi et al. concluded that intralesional verapamil may be a suitable alternative to triamcinolone due to its safer profile.[103,104]

A recent study by Srivastava et al. revealed that fractional $CO_2$ laser and verapamil are as efficient as triamcinolone acetonide (TAC) for treating keloids, except it takes longer for laser and verapamil to act compared to TAC. The study suggested that Verapamil can be used as an alternative treatment modality that is cost-effective with minimal adverse effects.[105]

*Imiquimod*

Imiquimod is a synthetic imidazoquinolone amine, which has potent immunomodulating activity, when topically used. It induces release of interferon and cytokine at the site of skin application, specifically IFN-α, TNF-α, IL-1, IL-6, and IL-8 that act to decrease excessive collagen production by keloid fibroblasts. Besides, topical application of imiquimod tends to upregulate certain apoptosis-related genes in keloid fibroblasts.[106] In a study by Chuangsuwanich and Gunjittisomram, the investigators concluded that Imiquimod 5% cream could effectively prevent recurrence of the excised keloids, especially in the area that had less tension such as pinna. Martin-Garcia and Busquets also conducted a pilot study and the results suggest that imiquimod 5% cream may prove to be a reasonably effective adjuvant therapeutic alternative for the prevention of recurrences in excised earlobe keloids.[107,108]

Berman and Kaufman also reported that the recurrence rate of excised keloids treated with postoperative imiquimod 5% cream was lower than recurrence rates previously reported in the literature.[109]

Cacao et al. however suggest that imiquimod 5% cream is not effective in preventing recurrence of keloids over trunk after surgical excision and thereby strongly discourage using imiquimod 5% cream in the prevention of surgically excised trunk keloids.[110]

When formulated as a 5% cream, imiquimod is a safe and generally well-tolerated drug and the adverse effects include skin erosion, excoriation, flaking, and edema at the site of application.

**Future directions of treatment**

*Interleukin-10 (IL-10)*

IL-10 is a cytokine that is known to reduce inflammatory responses and its anti-inflammatory effects are mediated through activating AKT and STAT3 phosphorylation, downregulation of IL-10 receptor, and by facilitating crosstalk between the PI3K/AKT and STAT3 signal transduction pathways.[111-113] The absence of IL-10 is believed to lead to an amplified inflammatory response and abnormal collagen deposition.

*Mesenchymal Stem Cell Therapy*

Mesenchymal stem cells (MSC) are multipotent stromal cells that can differentiate into a variety of cell types and display immunomodulatory and antifibrotic effects.[114]

The antifibrotic effects of MSC on various fibrotic diseases such as myocardial infarction, renal or liver cirrhosis have been investigated and reported in literature. On the similar lines, MSCs are being tried to prevent or attenuate excessive inflammatory processes that are characteristic of keloids. Fang et al. studied impact of Bone marrow derived mesenchymal stems (BMSCs) and found that BMSCs attenuate the proliferative and profibrotic phenotype associated with keloids and inhibit extracellular matrix synthesis through a paracrine signaling mechanism.[115]

Spikeman et al. found that the adipose tissue-derived stromal cells inhibit TGF-β1-induced differentiation and function of adult human dermal fibroblasts and TGF-β1-induced contraction in keloid scar-derived fibroblasts, in a paracrine fashion.[116]

Variable delivery methods and doses are being tried including via systemic injections, local injections (at the wound, intradermal or subcutaneously) or an engineered MSC-seeded tissue scaffold.[117-120]

The possible mechanisms underlying this mode of keloid treatment include:

i. Promotion of normal angiogenesis that aids in normal wound healing.
ii. Modulation and inhibition of proinflammatory cell activity
iii. Antifibrotic activity via downregulation of myofibroblast differentiation and collagen type I and III production.

More investigations and long-term preclinical studies are still required to apply this method in clinical practice.

*Fat Grafting*

Autologous fat grafting or lipotransfer, underneath or into the wound has been tried in severely-scarred lesions. These reports showed beneficial effects on excessive scar lesions, and

side effects were rarely reported. Statistical significant improvement of the scar appearance, skin characteristics, pain, and itch with restoration of volume and three-dimensional contour has been reported. The mechanism underlying fat injections is believed to be that transferred fat tissues deliver adipose-tissue derived MSCs to the wound.[121,122]

Future randomized controlled trials with a methodologically strong design are recommended to confirm the effects of autologous fat grafting on keloids.

*Transforming Growth Factor- β (TGF- β)*

TGF- β isoforms (TGF-β1,2,3) had long been a target of anti-keloid therapy. Multiple studies have shown that the ratio of TGF-β3, β1 and 2 is important in scar progression or remission. Various studies had been performed to investigate the effect of exogenous TGF-β1 and 2, neutralizing antibodies and exogenous TFG-β3 and had proven the impact of TGF-β isoforms. TGF-β1 and 2 have been found to increase fibrosis and TGF-β3 attenuates fibrosis.[123] Recombinant human TGF-β3 (avotermin) showed favorable results in phase I/II clinical trials though results in phase III clinical trials are still unsatisfactory.[124-126]

*Botulinum toxin type A (BoNT-A)*

Botulinum toxin is a potent neurotoxin produced by the bacterium Clostridium botulinum. Recent reports have suggested that botulinum toxin type A can minimize scar formation by reducing muscle tension during wound healing, modulation of collagen deposition , causing the fibroblast cell cycle to be paused in a non-proliferative state, G0 or G1, influencing TGF-β 1 expression and reducing transcription and expression of profibrotic cytokines in keloid-derived and hypertrophic scar-derived dermal fibroblasts.[127] BoNT-A may also upregulate S100A4 gene and downregulate GF-β1, VEGF, MMP-1, and PDGFA genes but there is a paucity of evidence regarding specific mechanisms of action.[128]

Intralesional injection has been used as the preferred delivery method, and treatment outcomes were generally favorable, and patient satisfaction was high in some studies. Improvement was also reported in pain, tenderness and itching sensation.[129] Some studies could not however confirm the suggested clinical efficiency of intralesional BTA for the therapy of keloids.[130]

**Prevention of keloids**

Prevention of keloids is undoubtedly an effective measure when there is a wide range of treatment options available but none can qualify to be called an ideal. Hence avoidance of all unnecessary wounds in patients prone to keloid remains an obvious though imperfect solution. Early recognition of keloid formation and prevention of recurrence is also integral in devising management strategy.[131]

Various measures mentioned in literature on the subject include:

*Tension-Free Primary Closure*

Wound epithelialization that is delayed beyond 10–14 days increases the risk of pathological scars, and quick primary closure to achieve rapid epithelialization is mandatory for avoiding inflammation and excess fibrosis. Good surgical technique is important and includes basic wound care steps like:

i. Debridement of dead or severely contaminated tissues.

ii. Adequate hemostasis to avoid hematoma, seroma or abscess formation.
iii. Tension free closure: The exact molecular mechanisms that govern the response of skin to physical tension remain uncertain.

However, various pathways potentially responsible for conversion of mechanical forces into biochemical responses have been investigated and reported the phenomenon called mechanotransduction.[132] Gurtner et al. studied the fibrotic effects of mechanical tension and described the preventive effect of offloading wound tension on scar formation.[133]

*Passive Mechanical Stabilization*

To prevent wound tension and the consequential mechanotransduction, application of prolonged passive mechanical wound stabilization using microporous paper tapes or silicone based products has been reported.

Paper tapes help alleviate scar formation, but silicone-based products continue to be the premier option for prevention because it avoids repeated epidermal avulsion.[134-136] Occlusion and hydration of scar surface are currently suggested as likely mechanisms of the therapeutic action of silicone gel sheeting rather than an inherent antifibrotic property of silicone.[137]

Silicone sheets are recommended to be worn for about 12 hours each day for at least 2 months starting from two weeks after primary wound treatment. For areas of consistent movement, where sheeting will not conform, silicone gel is favored and should be applied twice daily.

Recently Fabbrocini et al. assessed the combined efficacy of needling and the use of silicone gel in prevention of keloids and found the results to be favorable.[138] Kwon et al. compared the effect of topical silicone gel and topical tretinoin cream for the prevention of keloids and found both the modalities to be of help with no significant difference in outcomes of the two.[139]

*Flavonoids*

Flavonoids (or bioflavonoids) are naturally-derived substances from various plants. The efficacy studies testing the ultimate benefit of these flavonoid-containing topical scar creams have provided controversial data. However, quercetin, a dietary bioflavonoid has been recently shown to inhibit fibroblast proliferation, collagen production and contraction of keloid and hypertrophic scar-derived fibroblasts through inhibition of the TGF-beta/ Smad-signaling pathway.[140]

Flavonoids are available in the form of gel and application is started two weeks after primary wound treatment and applied twice daily for four to six months.

*Onion Extract (Extractum cepae) and Heparin Gel*

Onion extract is believed to have fibroblast-inhibiting ability that decreases fibro-proliferative activity and synthesis of extracellular matrix (ECM), and increases the expression of matrix metalloproteinase MMP-1.[141]

The exact mechanism by which onion extract reduces scar formation is still poorly understood though it is thought that flavonoids (Quercetin and Kaempferol) in an onion extract are the components that do the work. Hosnuter et al. in their study found that Onion extract improved keloids which was statistically ineffective in improving pruritus. The study suggested that onion extract therapy can be used in

combination with an occlusive silicon dressing.[142]

Heparin molecules have a strong tendency to interact with collagen molecules, resulting in the formation of thicker fibrils that and induce intermolecular bonding in collagen. In combination, heparin and onion extract have been found to decrease keloid formation through their inhibitory activity on inflammation, fibroblast proliferation, and the production capability of fibroblasts.[143] Koc et al. found that combination of intralesional TAC and onion extract appears to be superior to TAC alone in the treatment of keloids and hypertrophic scars.[144]

*Pressure Therapy*

Cutaneous wound compression has been used not only for prophylaxis but also for treatment of established keloids. Pressure therapy is reported to reduce the signs and symptoms of keloids but the scientific evidence supporting their use is little and their clinical efficacy is also controversial.

The suggested mechanisms underlying pressure therapy include occlusion of blood vessels thus limiting the delivery of inflammatory cytokines, nutrients and oxygen from blood vessels to scar tissue. Increasing apoptosis may be another mechanism of pressure therapy.[145] The magnitude of desired pressure and the duration of therapy that is used clinically rely on empirical reports as there are no comparative analyses available in literature. The usual recommendation is 15–40 mm Hg for more than 23 hours a day for at least six months while the scar is still active.

The limitations of pressure therapy on sites other than ear lobes is difficulty in adequately fitting the garment to the wounded area and reduced compliance caused by side effects such as maceration and odor in hot and humid climates.[146] Postoperative pressure applied with pressure earrings has been prove to reduce recurrence rates markedly after surgical repair of earlobe keloids.[147-149]

**Long-Term Monitoring**

Because of the high rate of recurrence, at least one year of close follow-up is necessary to fully evaluate the effectiveness of therapy and to initiate further management at the earliest sign of recurrence.

Preoperative evaluation and counseling is critical to assess a patient's motivation for treatment and to assess the ability to participate in long-term care and follow-up visits.

**Conclusions**

Keloid remains a challenging condition, with potential cosmetic and functional consequences to patients. Several therapies exist that function through different mechanisms but there is no universally accepted treatment that can be termed as an ideal. Understanding of the pathogenesis has improved in recent years and it is hoped that in coming years, newer and more targeted therapies would be available.

Before initiating treatment, the physician must educate and inform the patient adequately about the possible recurrence rate and the limitations of current options. Use of various treatment modalities in combination is recommended due to the more favorable outcomes.

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