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REVIEW OF LITERATURES

Keloids: Epidemiology, Histopathology, Mechanisms and Models of treatment

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ABSTRACT

Keloid is skin disorder of excess fibrous tissue deposition that usually follows a noxious insult to the skin. Irregular arrangement of connective tissue components together with exaggerated collagen deposition are noticed on histological examination of slides of keloid tissue. The definitive cause is not yet well-known.

Diverse array of risk factors including family history and black race are thought to share in the development process. Because of unaccepted cosmetic appearance and negative impact on patient's quality of life, keloid is widely investigated by many researchers. The treatment panel of keloid includes large number of treatment tools.

Many substances are available for direct intra-lesional injection such as triamcinolone acetate and botulinum toxin A. Cryotherapy of the keloid can result in occlusion of small vessels and reduce its size. Other modalities of treatment include laser therapy and radiotherapy. Modalities of laser treatment include fractional laser or pulsed dye laser. Laser assisted drug delivery is a recently developed modality. Surgical scar revision is often associated with recurrence

Keywords
Keloids, Triamcinolone acetonide, Laser

INTRODUCTION

Keloid is a dermal fibroproliferative disorder occurs due to abnormal wound healing and characterized by excessive deposition of collagen. It occurs due to skin injury as trauma, insect bite, burn, surgery, vaccination, skin piercing, acne, chicken pox, and herpes zoster infection which reach reticular dermis, but sometimes it may occur spontaneously **[1]**. Most of keloids develop within 3 months of skin injury, but some may develop after 1 year **[2].** Beside the cosmetic disfigurement, it may be associated with pain and pruritis which affects the quality of life in patients **[3]**

KELOID AND HYPERTROPHIC SCARS

Compared to hypertrophic scar, keloid develops slowly over months beyond the initial wound edges, while hypertrophic scar develops over weeks within the initial wound edges. Keloid consists of random organization of Type I and Type III collagen fibers, while hypertrophic scars consist of an organized parallel Type III collagen. The hypertrophic scar may heal spontaneously over years unlike keloids **[4].**

RISK FACTORS

Keloid may develop anywhere except in mucous membranes, but it develops more in ear lobes, sternum, deltoid region, and pubic area. The incidence is higher in second and third decade and during pregnancy due to sex hormones (androgen and estrogen) which cause vasodilatation that increase inflammation **[5].** Also, hypertension causes sever keloids by destruction of blood vessel and increase inflammation **[6].**

Racial factors include dark-skinned individuals of African, Asian, and Hispanic who have a higher incidence of keloid development compared to Caucasians. It ranges from 4.5% to 16% **[7].** In 5%–10% of cases have familial keloids due to autosomal dominant mode of transmission with

incomplete penetrance and variable expression on chromosome 2 and 7**[8].**

HISTOPATHOLOGY

Keloid is a clinical diagnosis so unusually sent for further analysis by the pathologist. The hallmark of a keloid is keloidal collagen which is a thickened eosinophilic hyalinized collagen bundles. Other findings include "Tongue-like" advancing edge below the papillary dermis, horizontal fibrous band in the upper reticular dermis and prominent fascia like a band in the deep dermis **[9]**.

PATHOGENESIS OF KELOID

The pathogenesis of keloid disease is still unknown. Many theories have been proposed but none of these theories have been proven. Keloid is considered to be the end product of an abnormal wound healing process **[4].**

Phases of wound healing:

A) Inflammatory phase:

It follows the onset of trauma. Homeostasis is achieved by blood vessel vasoconstriction and formation of platelet plug. Local mast cells release chemical factors to attract polymorphonuclear leukocytes and macrophages **[10]**

B) Proliferative phase:

It starts after 2-3 days and lasts for 3-6 weeks. The homeostatic plug is replaced by granulation tissue. The granulation tissue is formed of fibroblasts, macrophages, procollagen, elastin, proteoglycans, and hyaluronic acid. Macrophages release growth factors as transforming growth factor-β (TGFβ), platelet derived growth factor (PDGF), connective tissue growth factor (CTGF), epidermal growth factor (EDGF), and vascular endothelial growth factors (VEGF). PDGF and TGF-β activate fibroblasts and stimulate collagen type III and extracellular matrix (ECM) formation. VEGF induce angiogenesis resulting in formation of immature blood vessels **[11]**

C) Maturation phase:

It is called remodeling phase and may last for one year. In this phase, the collagen type 3 is replaced by stronger collagen type 1 which arranged in bundles in dermis not in basket wave as normal unsacred dermis. Immature blood vessels undergo regression. Contraction of the scar tissue is mediated by the action of myofibroblasts **[12]**

In keloid

A) Dermal injuries as burn or trauma trigger immune cells on aberrant wound healing.
B) Macrophages and other immune cells increase inflammation and promote scar formation.
C) Growth factors as VEGF and PDGF stimulate chemotaxis, angiogenesis and fibrosis.
D) Myofibroblasts increase collagen synthesis and retard cell migration, thus resulting in excessive scarring.
E) Keloidal fibroblasts have a higher proliferative activity and lower rates of apoptosis compared to normal fibroblast. This results in overproduction of collagen and cytokines. Collagen production in keloids is twenty times greater than that of normal skin and three times greater than a hypertrophic scar **[12].**

MANAGEMENT OF KELOID

Different modalities of keloid management had been discussed but achieving a satisfactory result is challenging and may require combinations of different modalities.

A. Injections

1-Intralesional corticosteroid:

Many injectable steroids are available in treatment of keloid including hydrocortisone acetate (25 mg/mL), dexamethasone (4 mg/mL) and methylprednisolone (4 mg/mL) but triamcinolone acetonide (TAC) (40 mg/mL) is the most commonly used either alone or in combination with other therapy **[13].**

TAC is a fluorinated derivative of prednisolone with four times as potency as hydrocortisone but with less solubility so remains active at site of injection for a longer time **[14]**. The rate of improvement ranges from 50% to 100% with a recurrence rate ranging from 33% to 50% after 1 to 5 years **[15]**.

The recommended dose for TAC in keloid is 10 to 40 mg/mL according to practitioners' protocol. Side effects of intralesional steroid include local side effects such as pain, telangiectasia, skin and subcutaneous lipoatrophy, leukoderma, post inflammatory hyperpigmentation, and ulcerations **[16]**.

Systemic side effects may include Cushing syndrome with adrenal insufficiency which is a rare and serious side effect that occurs in children after single session with 40 mg of TAC thus care must be taken during administration of TAC in children with multiple or large lesions **[17]**.

2-5-Flurouracil:

5-Flurouracil (5-FU) is a fluorinated pyrimidine analogue which inhibits nucleic acid synthesis by disrupting the conversion of uridine into thymidine by inhibiting thymidylate synthase enzyme. It has also antimetabolite activity which inhibit fibroblast proliferation and inhibit transforming growth factor-β (TGF-β) induced

expression of type I collagen gene **[18**]. The most common side effects of 5-FU injection include pain, purpura, transient hyperpigmentation, ulceration, burning sensation, and skin erythema **[19]**

3-Botulinum toxin type A (BTA):

Botulinum toxin is a potent biological toxin derived from *Clostridium botulinum*, a gram-positive anaerobic bacterium commonly found on plants, soil, water and the intestinal tracts of animals. In keloid, BTA inhibits fibroblast proliferation by decreasing transforming growth factor (TGF)-β1 and connective tissue growth factor (CTGF), Also causes downregulations of transforming growth factor (TGF)-β1 gene and upregulation of Matrix metalloproteinase-1 (MMP-1) gene and S100A4 **[20].** Combination of triamcinolone acetonide and BTA seems to be more effective and less side effects as skin atrophy when compared to each drug alone **[21]**

4-Bleomycin:

Bleomycin is a cytotoxic antibiotic derived from *Streptomyces verticillus*. It has antineoplastic, antibacterial and antiviral properties. It induces fibroblast apoptosis and inhibits lysyl oxidase enzyme and TGF-β1 resulting in collagen reduction. Intralesional bleomycin is given at a dose of 1.5 IU/ml and requires 3–5 sessions to achieve good results in keloid **[22].** The most common side effects include: pain, ulcer, hyperpigmentation and dermal atrophy **[23].**

B. Cryotherapy:

It causes microvascular damage of keloid tissue resulting in its necrosis **[24]**. Different modalities are used for cryotherapy include spray and contact probes, or intralesional-needle cryoprobe. The intralesional modality is considered superior to other types **[25]**. Cryotherapy is applied every 2–3 weeks and better result is achieved when combined with other modalities. Side effects include hypopigmentation, pain and blistering **[26].**

C. LASER:

Laser targets skin chromophores as hemoglobin, melanin and water using the principle of photothermolysis which cause no damage to the surrounding structures.

Common side effects of laser therapy in treatment of keloid include erythema, pain, edema, crusting, hyperpigmentation, hypopigmentation, burns and infection **[27]**

1-Pulsed dye lasers (PDLs):

The 585-nm PDL is the most popular laser used in treatment of keloids. It causes destruction of keloid's capillary leading to hypoxia that stimulates production of matrix metalloproteinase (MMP) as collagenase enzyme. It inhibits the expression of TGF-β1 **[28].** The recommended energy is from 6.0 to 7.5 J/cm2 (7-mm spot) or from 4.5 to 5.5 J/cm2 (10-mm spot) **[29]**

2- Fractional laser

Fractioned CO_2 (10 600 nm) and erbium:ytrium–aluminum–garnet (Er:YAG) (2940 nm) deliver energy through columns of microthermal zones (MTZs) that stimulates collagen remodeling and neocollagenesis. Also, they activate MMPs, TGF-β3, and myofibroblasts **[30]**

3- Long-pulsed 1064 nm Nd:YAG laser

The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser reduces keloid's vascularity that results in decreasing cytokine and growth factor so inhibits abnormal collagen deposition. The recommended energy is 14 J/cm2 (5-mm spot).

Fractional laser is better in firm scars while, the Nd:YAG laser is better in erythematous scars **[31]**

4- Laser-assisted drug delivery (LADD):

Ablative fractional laser promotes transdermal delivery of keloid adjuvant therapy through microthermal zones this allowing equal distribution of drug with fewer side effects **[32]**. Different modalities of LADD are available. Fractional CO_2 laser followed by topical application of triamcinolone acetonide 0.1% ointment is one of those modalities **[33].** Fractional CO_2 laser followed by topical application of triamcinolone acetonide suspension (20 mg/mL) or 5-fluorouracil solution (50 mg/mL) which resulted in reduction in keloid size with 23% with 5-fluorouracil and 27% with triamcinolone acetonide **[34].**

D. Scar revision surgery:

Surgical excision of keloid alone is associated with a high recurrence rate up to 100% **[35].** To improve the postoperative surgical outcomes, multimodal combination therapy such as postoperative intralesional injection of steroid, bleomycin, interferon or radiotherapy must be done **[36].** Most operation includes removal of keloid tissue then doing a Z-plasty or flap repair to relieve wound tension **[37].**

E. Radiotherapy*:*

It inhibits collagen synthesis by inhibition of angiogenesis and fibroblast activity thus results in cell apoptosis. It is used as adjuvant therapy 24-48h after surgical excision of keloid **[38]**. Different modalities are available including electron beam radiotherapy, brachytherapy and Xray **[39].** The recommended dose for keloids on the anterior chest wall is 20 Gray in four fractions

over 4 days; for earlobe keloids is 10 Gray in two fractions over 2 days, and for keloids at other sites is 15 Gray in three fractions over 3 days

Side effects of radiotherapy include early complication as acute skin reaction that occurs 7 days after radiation including pain, erythema, edema, ulceration and desquamations and late complication occurs several weeks after radiation including scarring, permanent pigmentation, depigmentation, atrophy and telangiectasis**.** Radiotherapy may cause cancer so it is not recommended for pregnant or radiosensitive sites as breast and genitalia **[40].**

CONCLUSION

Keloid remains a challenge to both patient and physician. To patients, keloids represent a chronic disfigurement with a high recurrence rate and economic burden. Also, it may be symptomatic and cause pain and itching that affects quality of life. Till now, no therapy has proven to be fully curative in management of keloid. So, new modalities and combination therapies are advisable for management of keloid.

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