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Review Article

Updates on keloid scar pathogenesis, assessment and treatment modalities

Dermatology and Venereology

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ABSTRACT

Background: Keloids are disfiguring fibrous scars distressing patients emotionally. Keloids are yet considered as a challenge for doctors to treat due to their high ability of regrowth and extending. Prevention of keloid scar is considered as the first line of keloid management. Many theories were suggested to explain keloid formation. Imbalance between synthesis and degradation of collagen and extracellular matrix is the most realistic theory. Keloid scar assessment has been done clinically for years, though it hasn't shown all the aspects of scar. So, radiological assessment has been tried for a couple of years and proved to be efficient in keloid scar assessment combined to clinical assessment. Many treatments were tried in keloid therapy, where intra-lesional corticosteroids injection was stated as the first line treatment, later on other therapies as lasers, compression, cryosurgery, occlusive therapy, 5-fluorouracil, interferon, retinoid acids, vitamin D, surgical excision and radiation were tried either as a monotherapy or combined.

Objective: Detecting developments in the formation and treatment of keloids in order to help the doctor choose the optimal method of treatment according to each patient after its adequate clinical evaluation and by Doppler.

Conclusion: Keloids are a psychological burden for the patient and a challenge for doctors in treating it. Every day, new theories are being discovered about the formation and physiology of keloids, which helps to discover effective treatments. There is no specific method for evaluating keloids, so clinical scales are best used in conjunction with imaging. There is no specific treatment agreed upon, but the combined treatments have proven to be more effective than using each treatment alone.

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Key words: Keloid pathogenesis, keloid treatment, keloid monotherapeutic modalities, keloid combined therapeutic modalities.

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INTRODUCTION

Keloids are scars of fibrous tissue that grow beyond the wound borders which may be caused due to dermal injury or even spontaneous. Keloid formation is affected by many factors as environmental (inflammatory process), topological (keloid prone sites), and patient related factors (genetically) [1]. Keloid different causes are summarized in figure (1) [2].

Keloid worldwide prevalence varies according to ethnicity, for example it varies from 4.5% to 16% in Africans, Asians and Hispanics. Also incidence is higher during puberty and pregnancy [3]. Risk factors of keloids may also include people with blood group A which have an association with spontaneous keloids, hypertension as it has positive relation with keloid number and size, melanin pigment level in cells which is directly proportional with incidence of keloid formation. Age of onset, sex, delayed healing or healing by secondary intention, anatomical site of injury are also considered as risk factors for keloid formation [2].

Keloids are distressing and cosmetically disfiguring, also may cause functional problem as

contractures which significantly affect patient's life quality [4]. Keloid scars present in different consistencies e.g. soft, rubbery, doughy and hard. They may cause itching and may affect normal movement. Favorable sites to form keloids are the sites of increased tension (e.g. sternum, deltoid region, joints, upper trunk and back) but also may appear in sites with minimal tension as earlobe after piercing [2, 5].

Keloid treatment is challenging though intra-lesional corticosteroid injection is considered the first line of treatment [6,7]. Also, combined therapies with surgical excision or adjuvant therapies as cryosurgery, radiation, compression therapy, occlusive dressings, 5-fluorouracil, interferon, retinoic acid and others can be used [8]. Many factors affect the suitable type of keloid treatment as site, size and depth of keloid as well as patient related factors as age, race and previous treatments [2]. The main target of management of scars either caused unintended or iatrogenic is to regain the natural balanced wound healing and restore normal skin functions and integrity [9].

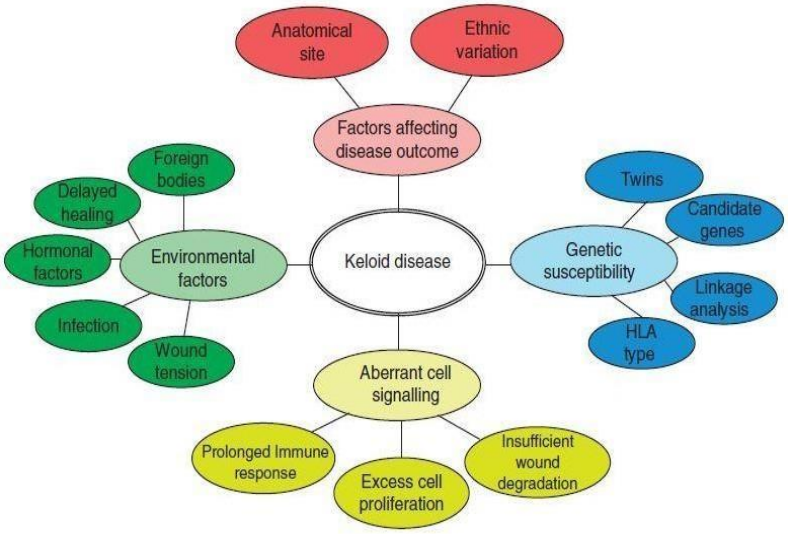

Figure (1): Possible causative factors in keloid pathogenesis [2].

PATHOPHYSIOLOGY

Wound healing occurs in 3 stages; i) hemostasis and inflammatory phase: that begins just after the injury and continues for 4-6 days, ii) proliferative phase: starting from third day after injury and ends after 2-3 weeks and iii) maturation and remodeling phase: where scar maturation and reduction in scar size occurs at 42 days and completed fully after 1 year. Keloid pathogenesis is mainly due to abnormal healing of wounds either due to abnormal response to inflammation or prolonged proliferative phase [2].

Keloid formation has many theories, where the most approved one was the imbalance between collagen synthesis and degradation together with fibroblasts proliferation, apoptosis and inhibition [2, 9]. Increased collagen synthesis is related to keloid fibroblasts stimulation through inflammatory mediators mainly transforming growth factor beta-1 (TGF-beta 1). TGF-beta 1 isoforms are supposed to be responsible for collagen overproduction by fibroblasts in pathological scars [5]. As TGF-beta 1 and TGF-beta 2 are overexpressed, on the contrary TGF-beta 3 is less expressed which stimulates fibroblast activity and extracellular matrix collagen production. Another role of TGF-beta 1 in keloid formation is by increasing tissue inhibitors of metalloproteinases (TIMPs) and decreasing matrix metalloproteinases (MMPs) which are key mediators responsible for extracellular matrix degradation [9, 4, 5]. Another theory suggested that deficiency of active form of vitamin D together with less vitamin D receptors (VDR) in keloid scar tissue than normal skin has a role in keloid formation [10]. Other theories include:

1. Vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF) elevated levels help in keloid production. Also, some studies stated the imbalance between VEGF which is elevated and endostatin (collagen XVIII) which is downregulated in keloid patients and hence, they suggested using therapies based on endostatin in combination with other modalities [2, 11].
2. Periostin which is a protein secreted by extracellular matrix that is involved in angiogenesis. It was found that periostin levels are elevated in keloid tissue with higher blood vessel density compared to normal tissue [11].
3. Decorin is a proteoglycan component of connective tissue that has a role in inhibition of collagen and fibronectin synthesis and also has

an inhibitory action on angiogenesis. Studies found that decorin is downregulated in keloids [11].

4. Platelet-derived growth factor (PDGF) receptors together with insulin-like growth factor 1 (IGF-IR) receptors overexpression have a role in pathogenesis of keloid [2].
5. Loss of gap junctional intercellular communications may interfere with apoptosis and proliferation balance in fibroblasts [2].
6. Imbalance between collagen synthesis and degradation due to reduced fibroblasts apoptosis [2].
7. Abnormal signals sent by neighboring cells as keratinocytes, mast cells, T- helper 2 cells, IL 4, 5, 10 and 13 that induce fibrogenesis and enhance keloid formation [2].
8. Hypoxia; as oxygen is known to have a role in wound repair, so hypoxic environment is associated with keloid formation as proven by some studies that central area of keloid is severely ischemic compared to hypertrophic and normal scars, where the researchers found less vascular density together with great expression of hypoxia-induced factor-1 α (HIF-1 α) in the center of keloid rather than the keloid peripheral parts [11].
9. MicroRNAs which are small non-coding RNAs. They have a role in regulation of gene expression. Researchers have found that they are deregulated whether upregulated or downregulated in keloids [11].
10. Gene upregulation theory of fibroblasts; where these genes are upregulated in response to inflammatory response in the microenvironment [12].
11. Nutritional factors affecting keloid formation specially the role of lipid composition. Triglycerides were found to be 60% more in keloid tissue compared to normal skin, hence it is suggested that lipid metabolism has a role in stimulating inflammatory reaction in keloids [12].
12. Keloid is defined as benign tumor due to tumor-like behavior in some aspects as sustaining proliferative signaling, induction of angiogenesis, resisting cell death, invasion but with no metastasis and responsive to cancer treatments as chemotherapy, radiotherapy, 5-fluorouracil, bleomycin, mitomycin C, doxorubicin, tamoxifen and others [13].

DIFFERENTIAL DIAGNOSIS OF KELOIDS:

Differential diagnosis of keloids include hypertrophic scar, lobomycosis, benign skin tumors as xanthogranuloma, pseudolyphoma, leiomyoma, dermatofibroma and mixed tumor of the skin. Other malignant tumors that maybe similar to keloid include dermatofibrosarcoma protuberans, a melanotic malignant melanoma, trichilemmal carcinoma, keloidal basal cell carcinoma and cutaneous squamous cell carcinoma. If the lesion is suspected to be tumor whether benign or malignant, a biopsy must be taken in consideration before treatment [14].

PRE-TREATMENT EVALUATION SCORES FOR KELOID ASSESSMENT:

Fearmonti et al [15] developed semi quantitative methods using scales to make subjective methods more objective as illustrated in table (1).

- **Subjective scar assessment scales:** these scales were developed to evaluate treatment efficacy on the scar before and after treatment. Currently scales used are at least 5 that assess subjective parameters in an objective way [The Vancouver Scar Scale (VSS), Manchester Scar Scale (MSS), Patient and Observer Scar Assessment Scale (POSAS), Visual Analog Scale (VAS), and Stony Brook Scar Evaluation Scale (SBSES)]. These scales assess parameters as pliability, thickness or height, surface area, vascularity, pigmentation and texture [15].
- **Devices needed to objective scar assessment:** these devices should be non-invasive, easy to use, accurate, and reproducible to collect objective data easily with clinical utility. Available devices assess parameters as pneumatonometer and cutometer to assess pliability, chromameter to assess color, laser Doppler perfusion imaging for assessing perfusion, durometer to assess firmness, tissue ultrasound palpation system to assess thickness and 3-dimensional topography to assess characteristics of scar surface [15].
- **Color Doppler Ultrasonography:** color Doppler was originally developed in mid-1980s for cardiac investigation. It works by combining anatomical information of high resolution grey scale B-mode scanning with color-coded map that picture particular features of flow in two-dimensional region of interest which called color box. Color Doppler is tried in assessment of keloid to evaluate the keloid vascularity, thickness, volume, presence of blood flow showing type of vascularity, thickness of vessels, peak systolic velocity of the vessels. Also it detects any changes not evaluated by the scales as calcifications or fistula to determine which treatment is suitable for each case, moreover it is used to assess the response of keloid scars to different modalities [14, 16, 17].

Table (1): Comparison of scar assessment scales [15]

Scale	Scoring system	Attributes analyzed	Deficiencies	Advantages
Vancouver Scar Scale	0 to 13	Vascularity, height/thickness, pliability, and pigmentation	Lacks patient perception Pigmentation subscale less applicable to large, heterogeneous scars Operator-dependent errors Excludes pain and pruritis	Used widely in literature for outcome measure in burn studies
Visual Analog Scale with scar ranking	0 to 100 "excellent" to "poor"	Vascularity, pigmentation, acceptability, observer comfort *plus* contour and summing the individual scores	Photo-based scale does not include patient assessment	Simpler than VSS Assessments of intra- and interrater reliability easier to conduct
Patient and Observer Scar Assessment Scale	5 to 50	VSS *plus* surface area; patient assessments of pain, itching, color, stiffness, thickness, relief	Items represented may not adequately express patient's perceptions and concerns	Focuses on scar severity from clinician's and patient's points of view
Manchester Scar Scale	5 (*best*) to 18 (*worse*)	VAS *plus* scar color, skin texture, relationship to surrounding skin, texture, margins, size, multiplicity	Arbitrary assessment and weighting of items	Applicable to a wider range of scars Uses descriptors related to clinical significance instead of physical measurement alone
The Stony Brook Scar Evaluation Scale	0 (*worst*) to 5 (*best*)	VAS *plus* width, height, color, presence of suture/staple marks	Photo-based scale does not include patient assessment Not designed for long-term scar assessment	Specifically developed to assess short-term appearance of repaired lacerations

*VAS indicates Visual Analog Scale; VSS, Vancouver Scar Scale.
†None of the scar scales measure the following: 1). The amount of total body surface area that is scarred, 2). The functional disability caused by scar, 3). The effects of pain and pruritus in terms of activities of daily living.

PREVENTION OF KELOID SCAR

As keloid treatment is challenging and no cure is granted 100%, so, prevention is better than treatment and is the first step in therapy. Prevention is the responsibility of both patient and physician or surgeon equally [2].

❖ **Patients instructions:**

- Patients with past history or family history of keloid must avoid piercing or tattooing.
- Patients with acne especially males with acne keloidalis nuchae should have proper treatment.
- No need for non-emergency surgeries or aesthetic procedures.
- On need of surgeries , postoperative care is very important to avoid keloid formation as to wear proper clothes as surgical bra or silicone sheets over wounds, avoid wrong movements that may lead to widening sutures, avoid friction or rubbing wounds, keep the wound clean and aseptic.

❖ **Surgeons instructions:**

- Skin incisions should be done according to tension forces of skin.
- Use delicate instruments to avoid more skin trauma especially in black and dark skin.
- Suture edges must be taken with minimal tension forces as possible and avoid overuse of electrocautery.
- Avoid wound infection by removing any foreign bodies and giving suitable antibiotics.
- Use preventive therapeutic modalities as compressive, occlusive dressings, intra-lesional TAC, lasers to lessen keloid occurrence.
- Good follow up of the scars.

Prevention and treatment modalities of keloid are summarized in tables (2, 3) [4, 18].

Table (2): Current treatment strategies for hypertrophic scars and keloids [4]

Categories	Modalities	Suggested Mechanisms	Use
Prophylaxis	**Tension-free closure**	- Reduce inflammation by reducing mechanotransduction	- Debridement of inviable tissues, adequate hemostasis - Rapid tension free primary closure
	Taping or silicone sheeting	- Reduce inflammation by reducing mechanotransduction: occlusion and hydration	- Start 2 weeks after primary wound treatment - 12 hours a day for at least 2 months
	Flavonoids	- Induction of MMPs - Inhibition of SMADs expression	- Start 2 weeks after primary wound treatment - Generally twice daily for 4 to 6 months
	Pressure therapy	- Occlusion of blood vessels - Inducing apoptosis	- Pressure of 24 to 30 mmHg - More than 23 hours a day for at least 6 months
Treatment (current)	**Corticosteroids**	- Reducing inflammation and proliferation - Vasoconstriction	- Intra-lesional injection: triamcinolone 10 to 40 mg/mL - 1 to 2 sessions a month (2 to 3 sessions, but can be extended) - Tapes/plasters, ointments are available - Combination is common
	Scar revision	- Direct reduction of scar volume	- At least 1 year after primary wound treatment - Combination is recommended
	Cryotherapy	- Scar tissue necrosis	- Deliver liquid nitrogen using spray, contact or intra-lesional needle cryoprobe - 10 to 20 seconds freeze-thaw cycles - Combination is common
	Radiotherapy	- Anti-angiogenesis - Anti-inflammation	- Adjuvant after scar revision - 24–48 hours after scar revision surgery - Total of 40 Gray or less, over several divided sessions
	Laser therapy	- Vaporize blood vessel - Anti-inflammation	- 585-nm pulsed dye laser: 6.0–7.5 J/cm2 (7 mm spot) or 4.5–5.5 J/cm2 (10 mm spot) - 1064-nm Nd:YAG laser: 14 J/cm2 (5 mm spot) - 10,600 nm Ablative CO_2 laser (20-30 J/cm^2) - 2 to 6 sessions, every 3–4 weeks
	5-Fluorouracil	- Anti-angiogenesis - Anti-inflammation	- Intra-lesional injection: 50 mg/mL - Weekly for 12 weeks - Combination is common
Treatment (Emerging)	**MSC * therapy**	- Modulation of proinflammatory cell activity - Anti- fibrosis - Promote normal angiogenetic activity	- Modulation of proinflammatory cell activity
	Fat grafting	- Deliver adipose-tissue derived MSCs	- Fat injection or fat tissue grafting underneath or into the wound

	Interferon	- Downregulating TGF-β1 - Attenuates collagen synthesis and fibroblast proliferation	- Intra-lesional injection: 1.5 106 IU, twice daily over 4 days
	Human recombinant TGF-β3/TGF-β1 or β2 neutralizing antibody	- Adjust TGF-β3: TGF-β1 or β2 ratio	- Not available currently
	Botulinum toxin type A	- Reduce muscle tension during wound healing - Arrest cell cycle in non-proliferative stage - Influence TGF-β1 expression	- Intra-lesional injection: 70~140 U, 1 or 3 months interval, 3 sessions
	Bleomycin	- Decreasing collagen synthesis - Reduce lysyl-oxidase levels - Induce apoptosis	- Intra-lesional injection: 1.5 IU/mL, 2 to 6 sessions at monthly interval

* MSC: mesenchymal stem cell; MMPs: matrix metalloproteinase; TGF: transforming growth factor.

Table (3): Comparison of TAC and combination therapies [18]

Type	Treatment	Average recurrence rate (%)	Average follow- up (months)	Primary results	Benefits
Monotherapy	**TAC**	33%	12 months	- TAC injection shows 50-100% regression after treatment but has high recurrence rates	- Inexpensive - Easy to administer - Relatively safe
Surgical combination therapy	**Surgical Excision + Radiation**	23%	14 months	- Significant reduction in recurrence when compared to excision or radiation monotherapy	- Effective - quick symptom relief - Low recurrence - Fewer treatment sessions required
	Surgical Excision + TAC	15.4%	12-35 months	- Significant reduction in recurrence compared to excision or TAC monotherapy	- Ideal for auricular keloids - Effective and quick symptom relief - Low recurrence
	Surgical Excision + Pressure Therapy	10.6%	18 months	- Excellent results obtained for patients with auricular keloids	- Ideal first-line treatment for auricular keloids - Pressure therapy is a minimally invasive, inexpensive adjunct - Lower recurrence rates than Excision + TAC, or Excision + Cryotherapy for auricular keloids
	Surgical Excision + Cryotherapy	15%	43 months	- Excellent results obtained for patients with auricular keloids	- Ideal for large auricular keloids
	Surgical Excision + Mitomycin C	16.5%	6 months	- Similar efficacy to excision + TAC but with potential dose-dependent adverse effects	- Less efficacious when compared to excision + TAC - May be useful if TAC not available
	Surgical Excision + Imiquimod	24.7%	6 months	- Higher recurrence compared to excision + Mitomycin C but with less risk of	- Less efficacious when compared to excision + TAC - May be useful if TAC not

				adverse side effect	available
Medical combination therapy	**TAC + Laser Therapy**	15%	6 months	- Superior results than laser or TAC monotherapy	- Ideal for large difficult keloids
	TAC + 5-Fluoruracil	17.5%	3 months	- Superior results and less recurrence compared to TAC monotherapy	- Decreased side effects compared to TAC or 5-FU monotherapy
	TAC + Intra-lesional Cryotherapy	12%	6 months	- Intra-lesional cryotherapy performed prior to TAC injection showed superior results, decreased side effects, and a lower recurrence rate than TAC monotherapy	- Cost-effective - Useful for most anatomic locations - Widely available

TAC: triamcinolone acetonide corticosteroid.

TREATMENT MODALITIES OF KELOID

- **Medical therapies:**

1) **Intra-lesional corticosteroids:** it is considered the first line of treatment and prevention in keloids. It acts through suppression of fibroblast production by decreasing TGF-beta expression and collagen synthesis also it suppresses inflammation and mitosis [9, 12]. Triamcinolone acetonide (TAC) is widely used in keloid injection in concentration of 10 to 40 mg/ml at 4 to 6 weeks intervals to avoid adrenal suppression. On using TAC as monotherapy, mean recurrence rates are 33% and 50% at 1 and 5 year follow up respectively. Common side effects of corticosteroids injections are pain, atrophy and hypopigmentation. Combined intra-lesional TAC and cryotherapy are now considered the first line treatment of non-auricular keloids [18].
2) **Cryotherapy:** It acts in media as liquid nitrogen that affects microvasculature leading to cell damage and tissue anoxia. It has been used widely in treatment of keloids combined to intra-lesional corticosteroids. To obtain satisfying results 1, 2, or 3, freeze thaw cycles, each lasting 10-30 seconds is applied. Sessions may be needed every 3 weeks to a month interval. Success rates are 30- 75% either by spray or contact with liquid nitrogen. Its main side effects are permanent hypopigmentation and pain. Less number of sessions is recommended for better wound healing. New approach in cryotherapy is by application of liquid nitrogen using lumbar puncture needle through the long axis of keloid to deliver liquid nitrogen through intravenous drip set for 2 freeze thaw cycles of 20-30 seconds each, sessions needed to be repeated 5-10 times. Improvement by 75% occurs through keloid flattening [2, 14].
3) **Lasers:** Many lasers are used in treatment of keloids as non-ablative pulsed-dye laser (585 nm) especially in keloids with high vascularity, ablative lasers as erbium doped yttrium aluminum garnet (Er: YAG) laser (1064 nm), argon laser (488 nm) and ablative carbon dioxide lasers (CO_2). Ablative CO_2 laser emits rays with wavelength 10,600 nm with chromophore to water. Fractionated beam creates channels through vaporization. These channels called Microthermal Zones that have role in tissue regeneration. Multiple sessions are needed to improve the keloid scar with interval of a month at least, however high recurrence rates occur at one year. Main side effects of laser are pain, erythema and hypopigmentation [18, 9]. Fractional CO_2 is efficient as TAC but it needs many sessions and longer period to give the effect compared to it. Also laser gives better results when used on early scars of less than 2 years duration [19].
4) **Occlusive dressing:** they are used to avoid excessive scarring. Silicone gel sheeting (SGS) is the most used occlusive dressing. It acts through wound occlusion and hydration that eventually decrease the fibroblast activation and so collagen production. It is more effective as preventive method rather than treatment but needs restrict application for at least 12 hours a day for 12 months [9].
5) **Compressive therapy:** is primarily used after surgical excision to prevent keloid recurrence especially in ear keloids. It acts through mechanoreceptor induced apoptosis of cells in extracellular matrix where pressure induced ischemia stimulates collagen degradation. Compression therapies include elastic wrap, pressure molds, earrings, bandages and magnets. It is the best option for ear keloids where recurrence rates are less by 70-95% but also need strict application 12 hours per day for 6 month at least at a pressure of 24 mmHg, otherwise it may cause necrosis if pressure is more than 30 mmHg [9]. Surgical therapy followed by compressive therapy

is now considered as first line treatment of auricular keloids [18].

6) **5-Fluorouracil (5-FU):** It's an antineoplastic agent that has the ability to interfere with DNA synthesis and cell proliferation which in turn inhibits fibroblast proliferation and also enhances apoptosis of fibroblasts without tissue necrosis [20]. It's injected intra-lesionaly at a dose 50 mg/ml, weekly for 12 weeks [4]. To avoid 5-FU side effects as erythema and ulcerations, it is preferred to add small amount of TAC [20].
7) **Botulinum toxin A (BTX-A):** as keloid maybe caused over areas with high tension on scars especially during healing phase; hence the use of BTX-A was introduced as it inhibits acetyl choline exocytosis so blocks neuromuscular junction which causes muscle relaxation so relieves scar tension [7, 12]. Botulinum toxin A acts by decreasing fibroblasts proliferation through altering the cell cycle to G1 phase. Also, BTX-A is proved to be safe and efficient compared to intra-lesional corticosteroids [21]. It's injected intra-lesionaly at a dose 70-140 U, 1 or 3 months apart for 3 sessions [4].
8) **Heparin gel 12 and Onion extract (Flavonoids):** Heparin has inhibitory effect on inflammation and production of fibroblasts. Flavonoids as quercetin and kaempferol found in onion extract are believed to stimulate matrix metalloproteinase expression which stimulate type I collagen degradation [22, 11]. They should be used 2 weeks after primary wound treatment, twice daily for 4-6 months [4].
9) **Calcium channel blockers:** Verapamil has shown an effect on collagen synthesis as they decrease extracellular matrix production and increase fibrinase and procollagenase, also it inhibit interleukin-6 and VEGF, so it is used in keloid treatment at a dose 2.5 mg/ml [19, 23]. Different forms of verapamil as intra-lesional injection and topical are effective especially as a scar modulator. Compared to intra-lesional corticosteroids injections, intra-lesional verapamil is cost-effective and has lower incidence of adverse effects with improving keloid appearance but intra-lesional corticosteroids yield fast results in treatment [11, 23].
10) **Imiquimod 5% cream:** is used as prophylactic immune-mediator that stimulates interferon-α which increases collagen degradation so it is used after surgical excision with less recurrence rates. Side effects as irritation, superficial erosion and hypopigmentation (especially if used after surgical excision) may occur [2, 11].
11) **Tacrolimus:** is an immunomodulator agent. Keloid fibroblasts show overexpression of tumor necrosis factor- alpha Gli-1 (TNF- alpha Gli-1) which is an oncogene. Tacrloimus has an inhibitory effect on this oncogene that may normalize natural apoptosis of extracellular matrix proteins. It is applied at a dose 0.1% ointment twice daily for 12 weeks [2].
12) **Tricholoroacetic acid (TCA):** TCA is a chemical peeling agent that causes protein denaturation at different depths according to concentration applied where very superficial at 10-20 %, superficial at 25-30%, medium to papillary dermis at 35-50% and deep to reticular dermis at >50%. Adverse effects as scarring or post inflammatory hypo- or hyperpigmentation may occur with concentrations >35% [24]. However, TCA in high concentrations induces collagen synthesis and dermal thickening, also stimulates new epidermal growth hence may be used in keloid treatment. This may be due to interleukin-10 expression that regulates type I collagen metabolism [25].
13) **Ultraviolet therapy:** UV-A1 with wavelength (340-400 nm) was reported to stimulate collagenase enzyme that cause decrease in dermal thickening, so softening of the scar occur. Dosage used to treat a keloid is >2250J/cm^2, thicker keloids need higher doses. Serious side effect as malignant melanoma may occur [12].
14) **Vitamin D:** is a fat-soluble vitamin obtained from diet, exposure to sun or supplements. The active form of vitamin D was proved to inhibit keloid fibroblasts proliferation in a study carried by Damanik et al. [26], where they noted that severity of keloid is directly proportional to low serum levels of 25-hydroxyvitamin D. Vitamin D activity is dependent on its receptors (VDR), Hahn et al. [10] found that VDR is less localized in keloid scar than normal tissue. Vitamin D is found in many forms as oral supplements, topical creams and injectable vials of 200,000 IU that may be used locally or systemically. Since vitamin D hasn't been used widely in keloid treatment, so further studies are needed to determine efficacy and the best mode of administration.
15) **Retinoic acid (Vitamin A):** it acts by inhibiting DNA synthesis, decreasing normal keratohyalin and tonofilament synthesis yet promoting mucoid substance production and increase epidermal cell growth rate. It is recommended to be applied twice daily for 3 months to get good results [2].
16) **Tocopherol (Vitamin E):** is the most important lipid soluble membrane bound antioxidant in the body. It consists out of 8 antioxidants from which stereoisomers are formed, α- tocopherol is the most potent one. Vitamin E acts as anti-inflammatory agent which affects scar remodeling. It's used to decrease pruritis, accelerate wound healing and inhibit of hypertrophic scarring. It is used in form of topical cream or gel either monotherapy or combined with other modality like silicone sheets. Many dosages of vitamin E have been used as (320 IU/gm, 200 U/gm, 5% tocotrienol+ 71.7% deionized water and others) applied twice a day from 2weeks to 4 months. Vitamin E is used also as prophylactic treatment before surgeries twice a day for 15 days then after surgeries for at least 30

days. Side effects as contact dermatitis, itching and rash may occur [27].

17) **Interferon (IFN) injection:** it decreases collagen I and III production. It is administrated intra-lesionaly at a dose 1.5*106 IU twice daily over 4 days, 50% reduction of keloid is achieved. Side effects as flu like symptoms and pain are common with treatment. It may be used as prophylactic treatment after surgeries and excision sites through injecting into suture line [2, 4].
18) **Mesenchymal Stem Cells (MSCs) therapy:** they are multipotent cells that have the ability to differentiate into various types of cells. They have immunomodulatory and antifibrotic effect by downregulation of myofibroblast differentiation and collagen type I and III. So they are tried to modulate the inflammatory process in keloids by inhibiting extracellular matrix synthesis, promoting normal angiogenesis that helps normal wound healing. Also adipose tissue derived stromal cells inhibit TGF-beta 1. They are applied either by systemic injection, local injection at the wound, intradermal or subcutaneously [11].
19) **Fat grafting:** it has been tried in severe keloid scars by autologous fat grafting or lipotransfer. It acts through delivering adipose tissue derived MSCs to scar. Improvement of pain, itching and scar appearance occurred. Rare side effects were reported [11].
20) **Bleomycin:** It is an anticancer agent that causes keratinocytes necrosis. It is helpful in patients with old scars that are resistant to intra-lesional corticosteroid injections where it is recommended to be given from 2 to 6 sessions 2 weeks or month apart according to the case severity [28]. To avoid side effects as pain, swelling, redness or haematoma, the doctor should start with a dose of 0.1 ml (1.5 IU/ml) up to 6 ml maximum [11].
21) **Mitomycin C:** It is an antibiotic agent that works as antiprolifertive and antineoplastic agent. It has the ability to decrease DNA synthesis and suppress proliferation of fibroblasts and so reduce scars formation. Mitomycin C has been tried as topical application through soaked gauze to wound bed or full wound thickness at a dose of 1 mg/ml for 3-5 minutes with reapplication after 3 weeks which showed that mitomycin C reduces rates of wound contraction. Intra-lesional injections caused wound ulceration. Adding mitomycin C as adjuvant therapy to surgical excision or shave-removed has less recurrence rate from 0-33%. Side effects include hypopigmentation, post-treatment pain and ulceration [9, 22, 29].
22) **Doxorubicin:** is an antibiotic which acts as a chemotherapeutic agent that inhibits collagen synthesis by inhibiting prolidase enzyme and alpha chain assembly [2]. Doxorubicin is available as injectable solution 2 mg/ml and powder for injection 10 and 50 mg. Adverse effects as poor wound healing as result of impaired collagen synthesis are associated with doxorubicin in cancer treatment. These adverse effects suggest the potential role in keloid treatment. No published studies on doxorubicin effect in keloid treatment, hence, further studies are needed to evaluate its efficacy and the best mode of administration [30].
23) **Tamoxifen:** is synthetic nonsteroidal antiestrogen used in breast cancer treatment. It has been noted that it has anti-keloidal effect by inhibition of keloid fibroblasts and collagen together with decreasing production of TGF-alpha when used at a dose 16 µmol/L [2].
24) **Radiotherapy:** It acts mainly by inhibiting fibroblasts but the most important that it inhibits angiogenesis by acting on endothelial cells thereby prevents dysfunctional blood vessels formation and so inhibits keloid formation that explains the improvement in color of keloids before flattening occurs [31]. Radiation therapy is nonspecific to keloid tissue and this may induce cancer especially with keloids over breast and thyroid, so it is not widely used [11].

- **Surgery and other Invasive therapies:**

  Surgical methods**:** better used as combined therapy with corticosteroids as recurrence rates are higher >50% when used as monotherapy**.** Several techniques are used in surgical removal of keloid as skin grafting after simple excision or intra-lesional cryosurgery that is used to target keloid tissue with minimal dermal injury, however, recurrence rate is up to 45-100%. Other postoperative combined modalities as radiotherapy, imiquimod 5% and interferon may be used [22, 11].

- **Combined Therapies:**

  Combined therapies are proved to be effective more than monotherapies and give better results in treatment of keloids with less recurrence rate.

  1. **TAC combined to Lasers**: many laser were combined with TAC but the most used one is carbon dioxide laser that work synergistically to inhibit fibroblast production and so inhibits collagen. This combination shows low recurrence rate of 15.4% which is superior to each individually and is ideal for large keloids [18].
  2. **Laser-assisted drug delivery (LAAD):** where lasers are used as assisting method to deliver other drugs to deeper levels below stratum corneum than applying them topically. Lasers used in this technique are CO_2 laser and Er:YAG laser. Delivered drugs in LAAD technique are TAC, 5-FU and others which give better results than if used as monotherapy [9].
  3. **Infiltrated non cross-linked hyaluronic acid and cortisone therapy:** this combination is used in treatment of inflammatory tendons in

orthopedics. The role of cortisone in this combination is to decrease proliferation of fibroblasts while hyaluronic acid acts on prostaglandin 2 secretions that reduce the inflammation. According to this mechanism, the combination was used in treatment of keloid scar that resembles tendon in structure. Treatment sessions alternated every 15 days between cortisone and hyaluronic acid. Recurrence was nearly zero at 1 year follow up. This combination may be limited due to high price of hyaluronic acid injections [32].

4. **Surgical therapy followed by compressive therapy** is now considered as first line treatment of auricular keloids [18].

CONCLUSION

Keloid scar results in cosmetic and functional distress to patients and is considered as a challenge in assessment and treatment to physicians. Pathogenesis of keloid formation are updating every while that help in understanding keloid scar well. No accurate assessment for keloid scar is known, so clinical scores and radiological assessments have to be combined to cover whole aspects of keloid scar. Many therapeutic modalities have been tried in treatment of keloids though there is no ideal treatment is known to be the one of choice. Triamcinolone acetonide is considered the first line of treatment as monotherapy, but now combined modalities are believed to give better and efficient outcomes with low recurrence rates. Further researches may help in discovering more accurate assessment techniques and ideal therapies of keloid.

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الملخص العربي

مستجدات تكوين و تشخيص و علاج الجُدْرَة

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ملخص البحث

الخلفية: تعرف الجُدْرَة بانها ورم جلدي ليفي حميد و تكمن مشكلتها في تشويه الشكل الجمالي و الذي قد يسبب مشاكل نفسية للمريض، وعلاجها يعد تحدي للأطباء نظراً لقدرتها علي التمدد و النمو. الوقاية من تكوينها يعد اولي خطوات العلاج. تم اكتشاف العديد من نظريات تكوين الجُدْرَة و يعد اهم نظرية هي نتيجة عملية التئام غير طبيعية حيث تنتج الأَرومَةُ اللِيفِيَّة كميات كبيرة من الكولاجين السميك و المموج والذي يعطيها حجم بارز عن البشرة. يتم تقييم الجُدْرَة اكلينيكيا وهذا التقييم يعتبر غير كاف لجميع انواع و اشكال الجُدْرَة و لهذا تم استخدام الوسائل التصويرية كالدوبلر في تشخيص و تقييم الجُدْرَة. علاجات عديدة تم تجربتها و يعد حقن الكورتيزون الموضعي من اول خطوط العلاج، كما يوجد العديد من الطرق الحديثة في علاج الجُدْرَة بعضها فعال و آمن مثل ليزر ثاني اكسيد الكربون الجزئي، الكي بالتبريد، العلاج بالضغط او التغطية، الانترفيرون، فيتامين د، حمض التريكلوروسيتيك، الاستئصال الجراحي والاشعاع ، و غيرها الذين تم استخدامهم في العلاج اما منفردين او عن طريق دمج وسيليتين سوياً.

الهدف: الكشف عن مستجدات تكوين وعلاج الجُدْرَة حتي نساعد الطبيب علي اختيار الوسيلة المثلي للعلاج حسب كل مريض بعد تقيميها الوافي إكلينيكيا وعن طريق الدوبلر .

الاستنتاجات: تشكل الجُدْرَة عبئاً نفسياً للمريض و تحدي للأطباء في علاجها. يتم اكتشاف نظريات جديدة في كل يوم عن تكوين و فسيولوجية الجُدْرَة مما يساعد في اكتشاف العلاجات المؤثرة. ليس هناك طريقة محددة لتقييم الجُدْرَة، لذا من الافضل استخدام المقاييس الاكلينيكية مع الوسائل التصويرية. ليس هناك علاج محدد متفق عليه، و لكن العلاجات المدمجة اثبتت كفاءتها اكثر من استخدام كل علاج علي حده.

الكلمات المفتاحية:
تكوين الجُدْرَة، علاج الجُدْرَة، علاجات الجُدْرَة المفردة، علاجات الجُدْرَة مدمجة.

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