IJBPAS, January, 2023, 12(1): 305-341

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

KELOIDS: AN OVERVIEW ON AETIOLOGY, PREVENTION AND TREATMENT

KOPPURAVURI NAGA PRASHANT[1*] AND SURABHI KS[2]

1: Department of Pharmaceutical Chemistry, Sri Adichunchanagiri College of Pharmacy, Karnataka, India

2: Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Karnataka, India

***Corresponding Author: Dr. Naga Prashant Koppuravuri: E Mail: knp.pharma@accp.co.in**

Received 26th March 2022; Revised 25th April 2022; Accepted 10th July 2022; Available online 1st Jan. 2023

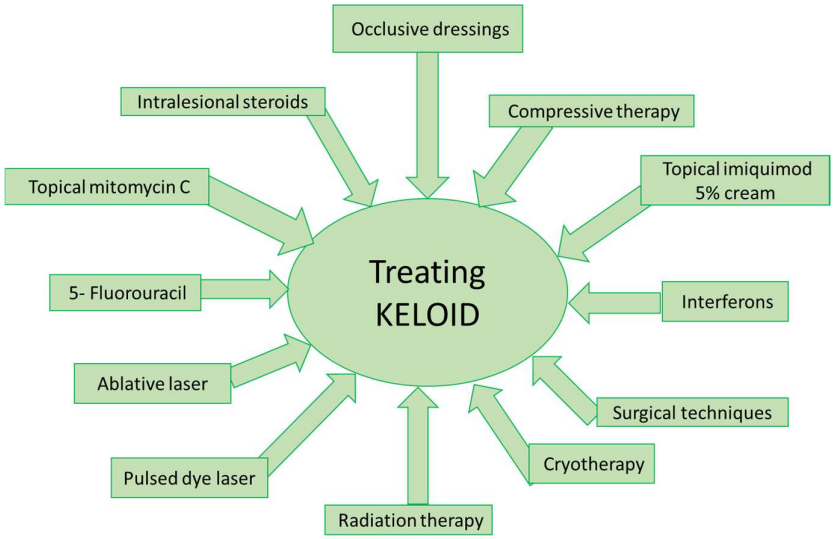
https://doi.org/10.31032/IJBPAS/2023/12.1.6772

ABSTRACT

Keloid or Che.loid, [kee-loid]

Keloid are abnormal scars that, if not treated appropriately, can cause substantial emotional and physical distress in patients. Scars are prone to recurrence and rarely regress. They are unpleasant, can cause pain, itching, discomfort, and can have a negative impact on one's quality of life. Keloid development is influenced by both hereditary and environmental factors. Predisposed individuals can develop a keloid after any level of skin trauma, such as surgery, piercing, tattooing, bugbites, burns, and so on. Rare genetic syndrome such as Rubinstein Taybi and Goeminne syndrome, can also improve the chance of development in dark skinned people. TGF-β1 may have a key role in the keloid formation. Many surgical and non-surgical therapy approaches have been researched and proven to be helpful; however, none have been proven to be totally satisfying or perfect for all keloid subtypes. Clinicians are up against a formidable obstacle as a result of this. When compared to monotherapy, a combinatorial therapeutic approach often appears to provide the best results with higher patient satisfaction. We examine the literature and sum up the general concepts behind the various treatment procedures in this study like use of corticosteroids, verapamil, silicone-based products, cryotherapy, imiquimod, 5-fluorouracil, laser therapy, mitomycin C, surgical excision, interferons, bleomycin, radiotherapy, etc. In this field, more knowledge and understanding are needed to give optimal therapeutic regimen for keloids.

Keywords: Keloid, TGF-β1, Rubinstein Taybi, Goeminne syndrome, Silicone, triamcinolone acetonide (TAC)



1. INTRODUCTION:

A keloid is a pink or red excrescence that is solid, irregularly formed, fibrous, and hyperpigmented. The growth usually arises as the result of cut, laceration or burn or less soften an acne pustule on the chest or upper back- and spreads beyond the limits of the original injury, often sending out claw-like (cheloid) prolongations.

The overlying epidermis is smooth, glossy, and thinned from pressure. The early, growing lesion is red and tender and has the consistency of rubber. It is often surrounded by an erythematous halo, and the keloid may be telangiectatic. Lesions may be tender, painful and pruritic and may rarely ulcerate or develop draining sinus tracts.

Keloids are often multiple. They may be tiny or large. Those that follow burns and scalds (to burn with hot liquid or steam) are large. Lesions are often linear, frequently having bulbous expansions at each end. The surface may be larger than the base, so that the edges are overhanging. The most common location is the sternal region, but keloids also occur frequently on the neck, ears, extremities, or trunk and rarely on the face, palms, or soles. The earlobes are often involved as a result of ear piercing, but involvement of the central face is rare. Keloids are much more common and grow to larger dimensions in black persons than others.

When certain individuals develop, keloids remain unsolved. Trauma is usually the immediate causative factor, but this induces keloids only in those with a predisposition for their development. There is also a regional predisposition.

Histologically, a keloid is a dense and sharply defined nodular growth of myofibroblasts and collagen with a whorl-

like arrangement resembling hypertrophic scar. Centrally, thick hyalinized bundles of collagen are present and distinguish keloids from hypertrophic scars.

Elastic tissue is scanty, as in a scar. Through pressure, the tumor causes thinning adjacent appendages, which it pushes aside. Mucopolysaccharides are increased, and often there are numerous mast cells **[1]**.

2. ETIOLOGY

Keloid is a benign skin tumor that develops as a result of improper wound healing. It results from an overabundance of extracellular matrix in the growing scar and it frequently extends beyond the primary skin lesion location **[2, 3]**. The disease's cause has yet to be determined. It refers to people who are predisposed to developing symptomatic, uncomfortable and disfiguring scars as a result of an injury or surgery.

Other people who are prone to keloid formation may develop them as a result of skin damage such as piercings, acne, tattooing, bug bites, burns, lacerations, abrasions, immunizations, and other procedures that cause cutaneous inflammation **[4, 5, 6]**.

The scars cause disfigurement or in extreme cases organ dysfunction. There is a genetic basis for keloid formation, as evidenced by the disease's more common prevalence in specific races, ethnic growth and in twins **[2, 7, 8]**.

Many receptors of keloid diseases linked with genetic defect related connective tissue such as Ehlers-Danlos syndrome, Goeminne syndrome, Rubinstein-Taybi syndrome or Dupuytren's contracture **[8-11]** can be found in the scientific literature.

In the genetic defect with mutations, one or several genes may be responsible for the formation of keloids. TGF -β1(transforming growth factor b1) a gene located on chromosome 19 which encodes the cytokine TGF-β1 is one of the most frequently mentioned among many genes that may have a key role in the formation of keloid **[8, 12, 13]**.

In the normal wound healing process, TGF-β1 improves angiogenic properties of endothelial progenitor cells to facilitate blood supply to the injured site **[14]** and stimulate contraction of fibroblasts to enable wound closure **[15]**. Keratinocyte migration is also promoted by TGF-β1 via regular cell migration associated with integrins, such as b1, a5, av, and b5 **[16]**. TGF-β1 is one the main collagen-stimulating factors, especially type I in fibroblasts. It also inhibits different MMPs, which further promotes the accumulation of collagen fibres **[17]**.

TGF β1 as one of the 3 isoforms of protein (TGF-β1, β2, β3) [12,13,8] has a key role

in the wound healing process **[18, 19]** and therefore all the irregulars of the cytokine resulting from gene polymorphism or mutation of TGF β1 may be direct cause of keloid disease development.

As per some research polymorphism c (509) T TGF β1 identified by PCR -RFLP (polymerase chain reaction restriction fragment length polymorphism) using specific primer pairs. The sense primer with the following sequence was used for amplification.

5'-CAG ACT CTA GAC TGT CAG-3'

And the antisense primer

5'-GTCACCAGAGAAAGAGGAC-3'

[20].

On basis of this analysis, it was found that the presence of allele T at position -509 of the gene TGF β1 is associated with a lower keloid formation **[20]**.

3. PREVENTION

A person has/had a keloid, or has an increased probability of obtaining another one/more parents, siblings, or offspring has/ had a keloid.

The good thing is that there are various means to decrease the chances of developing a full-blown keloid.

3.1 Ear piercing: Take good care of the ears after having a new piercing. If he/she notices his/her earlobe is thickening, he/she may be able to prevent a keloid if he/she acts soon. Remove the earring as soon as he/she notices it thickening and replace it with a pressure earring.

He/she must wear the pressure earring for at least 12-20 hours a day for 4-6 months to get the optimum benefits. In later stages, if he/she discontinues the usage of pressure, the earring pierce hole will likely close itself.

3.2 Tattoo, body piercing or cosmetic surgery: They can see how their skin will mend after getting a small amount of work done in a test location first, whether it's a tattoo, body piercing, or cosmetic surgery. if the skin in the test area thickens, they'll know it's possible to form a keloid.

A pressure garment can help prevent keloid formation in thickening skin. He/she should begin wearing a pressure garment as soon as he/she observes thickened skin in order to be effective. A dermatologist can fit the patient with a pressure garment, and other treatments may also work.

3.3 Surgery: If he /she has (or has/had) a keloid, inform the surgeon before the surgical procedure. The surgeon may be able to utilise a procedure to lessen the chances of developing a keloid after surgery. If he/she observes the surgical scar thickening, starting keloid therapy immediately may assist to prevent a keloid. A dermatologist can help a patient develop a keloid treatment strategy. 3.4 Injured skin: After the skin injury the right wound

healing can reduce the risk of developing a keloid.

If a person has/had a skin injury, following must be taken care.

a. Sunscreen with SPF 30, broad-spectrum protection, and water resistance.
b. Sterile petrolatum gauze.
c. Hydrogel wound dressing.
d. Silicone sheet or gel **[21]**.

a. Sunscreen with SPF 30, broad-spectrum protection, and water resistance: protect the injured skin from the sun. UV light from the sun has been shown in studies to enhance scarring and darken scars. They can avoid this by putting a bandage on the newly injured area and covering it with clothing.

It can take a long time for keloids to appear. Healed skin can darken and thicken as a result of exposure to UV rays from the sun. Wearing sunscreen after the wound has healed can prevent this. They must apply sunscreen to the wound if it is not covered by clothing or a silicon sheet.

Use sunscreen with an SPF of 30 or higher, broad-spectrum protection, and water resistant to provide the protection they require.

b. Sterile petrolatum gauze: Petrolatum Gauze dressings are utilised in any hospital or clinical environments where wounds are dressed, such as the burn unit or emergency department, surgery-centres, nursing homes, doctors' office and industrial clinics. Non-adhering petrolatum clings and conforms to the wound without sticking. Hypoallergenic dressing that's both comfy and calming. Petrolatum also helps to protect the wound site from contamination by preventing the loss of bodily fluids. A single layer is sufficient to provide good coverage. Petrolatum can be utilized on any non-draining wound due to its physiological neutrality **[22]**.

c. Hydrogel wound dressing: hydrogels are a type of substance that is commonly employed in skin, blood vessels, muscle, and fat tissue engineering **[23]**. Hydrogels are three dimensional networks made up of hydrophilic polymers links that have been mechanically or chemically crosslinked. The insoluble hydrophilic structures have a remarkable ability to absorb wound exudates while also allowing oxygen diffusion to speed up healing **[24, 25]**. Importantly, hydrogels have a highly hydrated 3D polymeric network that can bind several times more water than their dry weight allowing the wound bed to maintain a high moisture level. Hydrogel networks can be produced in a variety of sizes and shapes due to their unique physical properties **[26, 27]**. As a result, hydrogel- based dressings are the best choice for covering skin wounds **[28]**.

Hydrogels also provide a substrate for loading cells, antibacterial agents, growth factors, and various supplemental and biomacromolecules **[29]**.

d. silicone gel sheet or gel: explained in 4.1

4. TREATMENT:

4.1 Occlusive dressings

Silicone gel sheeting (SGS) has been a popular occlusive dressing for the treatment of keloids and hypertrophic scars since the 1980. The SGS is made of a semi-occlusive silicone gel sheet and a long-lasting silicone membrane **[30]**. Though the precise mechanism of action of silicone products is unknown, it is thought that SGS works by hydrating the stratum corneum and creating an occlusive environment that prevents dehydration. Scar tissue has been shown to be susceptible to trans epidermal water loss, indicating that the stratum corneum water barrier function is compromised **[31]**. In a controlled study, SGS was also demonstrated to reduce the occurrence of hypertrophic scarring and scar volume **[32]**. SGS has been demonstrated to have minimal negative effects including irritation in the nearby area **[33]**. SGS has demonstrated benefits such as pain relief, pruritus relief and keloid flattening **[34]**. when the dressing is utilized as a preventive measure SGS has shown to be effective **[35]**. For at least 12 months, SGS should be worn upwards for 12 hours per day **[36]**. In hotter regions, the required continual application of SGS causes a quick increase in a level that favours the establishment of bacterial abscesses **[37]**. Studies have shown that utilising silicone gel sheeting can repair keloid scars by up to 90% while also lowering the occurrence rates of keloid after surgery **[38]**. Well-designed clinical trials are studies that are required to acquire a better knowledge of the usefulness of the silicon-based product in preventing and treating keloid.

4.2 Compressive therapy

Compression therapy which has been shown to shrink the skin, is typically used in conjunction with surgical excision to avoid recurrence of ear keloids **[39]**. compression therapy relies heavily on cellular mechano receptors **[40]**. The mechanism of pressure treatment includes cell death mediated by mechanoreceptors. Mechanoreceptors cause apoptosis of cells in the ECM and/or pressure-induced ischemia changes fibroblast activity and speeds up collagen degradation **[41, 42]**. There are a variety of compression treatments available, including button compression, pressure earrings, ACE bandages, compression wraps, elastic wrap bandages, custom pressure ear molds, earrings, and magnets **[41, 43]**. Ear keloids treated with compression therapy after

excision have a nonrecurrence rate of 70.5 to 95 percent, according to studies **[44, 45]**. Compression therapy, like occlusive therapy, works best when the pressure device is worn for at least 12 hrs per day for at least 6 months at a pressure of at least 24mmHg **[44, 45]**. The compression has the potential to cause tissue necrosis if the pressure exceeds 30mmHg **[43-45]**. Pressure earrings and pressure gradient garments consisting of lightweight porous Dacron, bobbinet fabric, zinc oxide adhesive plaster, spandex/elastane are among the pressure devices. In general, 60 percent of patients treated with these devices improved by 75 to 100 percent **[46]**.

4.3 Intralesional steroids.

Corticosteroids, particularly intralesional corticosteroids, are still used as a first line treatment **[36]**. During wound healing, corticosteroids reduce excessive scarring by lowering collagen synthesis, inflammatory mediator production, and fibroblast proliferation **[46]**. Triamcinolone acetonide (TAC), hydrocortisone acetate, dexamethasone and methylprednisolone are some of the corticosteroids that can be used to treat scars **[33]**. The corticosteroid TAC is the most since 1961 **[36, 47]**. TAC injections used intralesionally have been found to reduce scar volume and height, enhance scar pliability, and prevent recurrence **[48]**. Corticosteroids have been shown to minimise keloid scarring by inhibiting fibroblast development, attenuation of procollagen and glycosaminoglycan production, reducing endothelial budding, and promotion of collagen and fibroblast degeneration **[49]**. Inducing fibroblast hypoactivity by decreasing TGF -B expression and reducing fibroblast density by increasing fibroblast apoptosis are two mechanisms by which triamcinolone affects fibroblast growth **[50, 49]**. For facial keloids, TAC is injected at a dosage of 2.5 mg to 20 mg. Alternatively, 20mg to 40mg with a 25 to 27 gauge needle at 4-6 week intervals for non- facial keloids **[46, 36]**. TAC can be used as a stand-alone treatment or in conjunction with other therapies **[51, 48]**. TAC has been demonstrated to minimize scar volume and keloid recurrence by 50% after surgical excision when used as a monotherapy **[52, 47]**. Previous clinical investigations using TAC alone have shown efficacy and good clinical outcomes, including decreased keloid height, width, length-related pruritus and erythema and increased pliability **[53]**. When compared to TAC monotherapy, Intralesional TAC in combination with various treatment modalities, such as surgery, 5 FU, interferon (IFN) alpha 2b, pulsed dye laser (PLD), verapamil, all achieved significant

effect **[48, 54, 55, 72]**. The clinical benefits of adding 5- fluorouracil to a steroid injection for improved scar regression and lower recurrence have been described using molecular evidence. The activation of P53 and up regulation of p 21 may be linked to 5 FU induced G 2 cell cycle arrest and apoptosis **[56]**. Pain during injection, skin shrinkage, changes in skin colour, and the production of telangiectasias are all possible side effects of corticosteroid injection **[57]**.

4.4 Topical imiquimod 5% cream.

Imiquimod 1-[2-methylpropyl]-1H-imidazo[4,5-c] quinolin-4-amine) is a member of the imidazoquinolines family **[58]**. Imquimod 5% cream has been used to successfully treat basal cell carcinoma, actinic keratosis, and genital warts **[59]**. Imiquimod is a Toll-like receptor 7 agonist that inhibits collagen formation in fibroblasts by elevating local interferon alpha (IFN -alpha) concentrations **[41, 58]**. (IFN- alpha) has been demonstrated to reduce fibroblast activity, reduce glycosaminoglycan synthesis and increase collagenase levels in a dose- dependent manner **[60]**. Imiquimod 5% cream has shown potential as a post excisional treatment for keloids **[61]**. Due to the location of the keloid, studies have found inconsistent results regarding the efficacy of imiquimod 5% cream postoperatively following keloid excision **[62-64]**. The use of imiquimod caused mild discomfort in some individuals, who required a break from the drug. In some patients hyperpigmentation was also recognized **[58]**. The use of postoperative imiquimod 5% has been found in numerous studies to reduce the recurrence of earlobe keloids in patients **[62-64]**. In 2 investigations imiquimod 5% cream was given to earlobe keloids that had been shaved or completely removed. The recurrence rate on post shaved keloids was found to be 6% and after 12 months of follow-up, and after 24 weeks of parallel keloid excision it was shown to be 75% recurrence free. Although the existence of local adverse events had no effect on the treatment, it did need a resulting period **[65]**. Imiquimod 5% cream is commonly used as a topical therapy for 8 weeks after surgery in clinical practice. It is cost effective, easy to use and safe. Hyperpigmentation, erythema, irritation and secondary infections are all common imiquimod side effects that usually resolve upon suspending the therapy **[41, 62, 66]**. As a result of these factors, it is widely regarded as a useful adjuvant treatment option for the prevention of recurrence in excised keloids. Larger controlled research, on the other hand, is required for future investigation.

4.5 Topical Mitomycin C.

Mitomycin C (MMC) is a Streptomyces caespitosus antineoplastic compound. It's been employed as a chemotherapeutic drug and, more recently, in ophthalmologic and otorhinolaryngologic surgery as an anti-scarring agent **[67]**. MMC inhibits nucleic acid and protein synthesis, preventing cell proliferation **[68]**. MMC has been demonstrated to inhibit fibroblast proliferation in adult dermal fibroblasts in-vitro at dosages of 0.4 mh/ml and 0.1 mg/ml **[69]**. A one week continuous treatment to mitomycin C resulted in complete cell death, but a single five minute exposure resulted in cellular multiplication three weeks later **[69]**. MMC has been used to treat keloids topically and intralesionally, with different degrees of efficacy **[70]**. Clinical therapy regimens include soaking an absorbent material in 1 mg/ml mitomycin C for 3 to 5 minutes, then replying for three weeks, according to the literature **[68]**. In terms of keloid recurrence, one study discovered that treating keloid recurrence after surgery topically or in combination with intralesional TAC was successful in avoiding recurrence **[70]**. MMC has the potential to be employed in the treatment of keloids, according to the findings of these studies. Hypopigmentation and post - treatment pain have been associated with mitomycin C **[71]**.

4.6 Intralesional and topical 5-fluorouracil (5FU).

5-fluorouracil is a pyrimidine analogue that acts as an antimetabolite to inhibit nucleic acid formation and cell proliferation. It suppresses fibroblast proliferation, angiogenesis and TGF-B induced collagen type I expression while improving fibroblast apoptosis without necrosis **[51]**. In-vitro, 5-FU has been found to inhibit fibroblast apoptosis, and decreases TGF-B induced collagen synthesis **[72]**. When used as single therapy for keloids, 5-FU has been shown to have a 21- 35 percent risk of recurrence after 3 months and to sustain keloid volume reduction for at least 6 months after the final therapy session in 58-65 percent of patient **[39]**. In one trial, intralesional injections of 5-FU (50mg/ml) once a week for 12 weeks were found to be effective **[73]**. Studies have shown that 5-fluorouracil is a successful treatment for keloid scars that have failed at least one other treatment, with a 19-47 percent risk of recurrence after at least 6 months and a remission of painful and itchy scar symptoms **[39, 74]**. Other studies have found that combining intralesional 5- FU and TAC injections with a combination treatment approach enhanced clinical outcomes **[54]**. In a study conducted by Asilian *et al*, 69 patients with keloids and hypertrophic scars were treated with a

combination of 5-FU (50 mg/ml), TAC (40mg/ml) and a 585 nm flashlamp-pumped pulsed dye laser (PDL) at 5-7.5J/cm square, indicating that it was more efficient than the TAC and TAC plus 5-FU **[75]**. When compared to baseline, all groups had a statistically significant reduction in length, height, and width at week 12 (P<05) **[76]**. One study found that 96 percent of female patients with ear keloids after excision had at least a 75% scar volume reduction and a 3.57% recurrence rate **[39]**. Anemia, leukopenia, and thrombocytopenia are known systemic adverse effects of 5- FU, although none have been reported following intralesional injection **[57]**.

4.7 Interferons

Interferons (IFN) are a class of cytokines with immunoregulatory, antifibrotic, and antiproliferative capabilities that mediate complicated cellular interactions **[77]**. IFN-alpha, IFN-B, and IFN- gamma are 3 IFN isoforms that have been found to decrease collagen and ECM expression while boosting collagenase activity **[51, 78]**. Invitro and Invivo, IFN-gamma has been shown to have antiproliferative effects **[79]**. IFN-alpha and IFN-gamma have been demonstrated to help in keloid recurrence and regressions [80,81,82]. In fibroblasts, both IFN- alpha-2b and IFN - alpha have been shown to decrease collagen synthesis and scar contraction **[50, 60, 77]**. IFN-alpha-2b has been described as being injected into keloids at least twice, with doses ranging from 500,000 to 6 million units **[60, 81, 83-85]**. IFN- alpha-2b treatment was found to be ineffective as a post excisional adjuvant therapy for keloids in prospective controlled clinical research, with a 54% recurrence rate **[86]**. In comparison to placebo, there is limited evidence for the efficacy of either IFN - alpha-2b or IFN-gamma **[60, 81, 83, 84, 85]**. One study revealed 18.7% keloid recurrence after keloid excision with postoperative interferon after a mean follow-up of 7.9 months, whereas numerous others found no significant difference in scar volume recurrence rates when compared to placebo **[81, 83, 84, 85]**. For 3-10 weeks, evaluators administered either 0.1 mg or 0.01 mg at a frequency of 1-3 times per week **[86, 87, 88]**. Intralesional IFN injections of 1.5 million IU twice daily for four days are routinely used in the treatment of keloids **[89]**. Pain at the injection site, flu-like symptoms **[82]**, myalgia, **[78]**, local erythema, and edema are all possible side effects **[52]**. Acetaminophen has been successfully utilized as a prophylactic treatment for flu-like symptoms and myalgia **[81, 85, 87, 88]**.

4.8 Bleomycin

Bleomycin is a chemotherapeutic drug having antiviral and antibacterial activities that is derived from a glycopeptide isolate of streptomyces verticillus [90]. Bleomycin functions as a chemotherapeutic by cleaving single- stranded and double-stranded aDNA **[91]**, and has been demonstrated to reduce TGF-β1- induced collagen expression and enhance collagen production **[52, 92]**. Bleomysin has been demonstrated to inhibit collagen turnover and lower lysyl- oxidase levels, both of which are necessary for collagen maturation **[92, 93]**. It has been used to treat keloids and hypertrophic scars in recent decades. To avoid toxicity hazards, the suggested dose for intralesional bleomycin injections starts at 0.1ml (1.5 IU/ml) and can be increased to a maximum of 6 ml for 2-6 sessions per month **[52]**. Bleomycins effectiveness in reducing keloid load has been explored using a variety of procedures, including tattooing, dermoget intralesional injection, and intralesional injection plus or minus in combination with electroporation therapy. The bleomycin tattooing procedure is characterised as dropping a bleomycin solution onto the area, then puncturing the treated area using a 22-to-25 gauge needle **[94]**. Bleomycin concentrations 30U/ cm square and 61U/cm square were dropped on patient scars at 1.5 IU/ml, followed by 40 punctures per 1 cm square of 5cm square in studies **[94]**. With 66-77 % of patients receiving greater than 70% scar flattening, bleomycin tattooing for keloids has shown some success across all tattooing protocols **[94]**. Recurrence rates after bleomycin tattooing varied from 14-28.6% at 10-18 months after treatment **[94]**. In 69.4% of 36 patients with keloids and hypertrophic scars, Bodokh Bru reported full flattening **[95]**. After administering jet intralesional injections of bleomycin to 15 patients, Saray el at observed complete flattening in 73.3 percent, highly significant flattening in 6.7 percent, and moderate flattening in 6.7 percent of lesions **[96]**. Huu *et al* studied the effectiveness of bleomycin injections on 55 patients with an average of 4 injections.70.8 percent of scars were entirely flat, 8.3 percent were reasonably flat, 17.5 percent were comparably flat, 3.3 percent were averagely flat,3.3 percent were averagely flat, and there were scars that were poorly flat scars. However, up to 18 months after therapy, a substantial prevalence of recurrence was seen **[97]**. Bleomycin in conjunction with intralesional steroids like triamcinolone has consistently produced positive outcomes. Camacho martinez *et al*. designed a two-part investigation more recently. They applied 0.3751 U of bleomycin and 4 mg of

triamcinolone 1 acetonide to a 1 cm square and found that it was an effective treatment for keloid **[98]**. Manca *et al* used intralesional bleomycin injections combined with electroporation therapy to cure keloids. Electroporation therapy increases cellular permeability by passing a current through the keloid region **[99]**. At 12 months after treatment, Manca *et al* observed that 94% of patients had a greater than 50% reduction in erythema, pain, and pruritus, and 83% of patients had a reduction in erythema, pain, and pruritus **[99]**. Pain at the injection site, cutaneous problems, hyperpigmentations, ulceration, and dermal atrophy are all possible side effects of the medicine, despite its safety **[90]**.

4.9 Surgical techniques

Traditional keloids removal involves surgical excision **[100]**. Excision, on the other hand, causes a new wound and can result in a keloid that is identical to or greater than the original **[102]**. As a result, surgical excision is not suggested as a single treatment option **[103, 104]**. Because recurrence rates for surgical excision range from 45-100%, simple complete or razor excision of a keloid is rarely utilized as a monotherapy **[41, 101]**. Incomplete surgical margins have been postulated as a possible reason for high recurrence rates after excision **[105]**. Surgical excision is frequently combined with various forms of treatment, including as radiotherapy, pressure therapy, IVF injection, intralesional corticosteroid injections, cryotherapy, bleomycin, and silicone gel or sheeting, to improve postoperative surgical outcomes **[35, 44, 89]**. Gently tissue handling, prevention of wound bed tension, eversion of wound edges, through approximation of wound margins, the sufficient infection and bleeding control or all general guidelines for initial wound closure following full excision **[41,109]**. The use of dermal replacement and epidermal skin grafting with keloid excision has also been reported as a variable alternative to primary closure of full keloid excision **[106]**. At 6 months, ziccardi *et al* reported no recurrence after using a full thickness skin transplant from removed keloid skin a **[107]**. Burm *et al* **[108]** investigated the use of complete thickness of skin grafts in the treatment of helical rim keloids defects with exposed cartilage. After the wound bed had de-epithelialized 2-3mm beyond the actual keloid border, these skin grafts were inserted. Burm *et al* observed no recurrence with no extra medication for all patients over a 9-month to 6-year follow up period **[108]**. In a recent case series investigation, 141 patients with anterolateral chest wall keloids had treatment that comprised full

excision Z-plasty, post- operative adjuvant radiotherapy, and post operative wound self-management. The results were excellent, with an incidence rate of only 10.6% **[109]**. The usage of steroid tape and injections helped to prevent keloids from reappearing **[109]**. The surgical excision of keloids can be done in a variety of ways, depending on the anatomical position, skin type and patient age. Linear closure with flap covering, excision with grafting, Z-plasty and W-plasty are some of them **[111]**. The surgeon doing the excision should use tension - free wound closure to limit the chance of keloid **[112, 113]**. The end prognosis is frequently linked to the operating surgeon's skill and technique, as well as the patient's active involvement in their wound care **[110]**.

4.10 Verapamil

Verapamil is a calcium channel blocker that was initially proposed for keloid treatment because of its potential to suppress fibrosis in invitro tests **[114]**. This changes the morphology of fibroblasts, promotes TGF-B1 apoptosis, renders ECM synthesis and depolymerizes actin filament **[115]**. Intralesional verapamil is a safe drug that has been used to treat keloid scars **[116]**. However, the results of this treatment have been varied. Verapamil was found to be an appropriate treatment with a recurrence rate of 28.6% in a single arm research employing intralesional administration of the drug intra and post operatively (every 2 weeks for 1 month, then once per month for 3 more months) **[117]**. The use of verapamil in the treatment of scars after abdominoplasty and mammoplasty has been found to inhibit the development of keloids and hypertrophic scars **[116]**. Another study comparing efficacy of intralesional TAC and verapamil, recognised that postoperative sites injected monthly with 2.5mh/ml verapamil had a larger recurrence rate than those injected with 10 mg/ml triamcinolone (hazard ratio=8.44, p=0.01). Because of the study's intra-patient control, half of the scar was injected with verapamil and the other half with triamcinolone, the findings seem to be very significant **[114]**. Furthermore, recent randomised controlled research found that verapamil was not as effective as TAC in minimizing keloid recurrence following surgical excision **[114]**. Another study found no evidence of efficacy for intralesional verapamil treatment, which did not diminish non pigmentation height and had a modest reduction in pliability **[118]**. Verapamil has been proven effective when taken in conjunction with other medications such as pressure treatment **[119]**, PDL **[120]**, TAC **[121]**, nifedipine **[122]** and others. With a combination of verapamil and pressure

therapy, the pigmentation, vascularity, elevation, flexibility, and pruritis of keloid originating from burn injuries improve **[114]**. A recent study by Khattab *et al*, which used a combination of verapamil and PDL to treat keloids, indicated that the combined therapeutic technique was more effective than intralesional verapamil alone in terms of improving the height and length of the lesion **[120]**. Morelli *et al* also showed that using TAC and verapamil together was effective in treating keloid scars over time, but using TAC alone had a faster and more effective response but a higher complication rate than using verapamil alone **[48]**. These studies showed that when administered as part of a combinational therapy, intralesional verapamil, which is safe to use and has few side effects, is more successful and provides long term stable results.

4.11 Cryotherapy

Cryotherapy is a low- temperature treatment that produces tissue necrosis by causing vascular injury **[123]**. It's been used to treat keloids as a monotherapy or in conjunction with other therapies including intralesional steroid injections **[124]**. Cryotherapy has rapidly gained popularity in the keloid literature; when used to treat keloids, cryotherapy reduces inflammation while also increasing collagen organisation **[125]**. Cryotherapy is the process of freezing keloids to minimize scar volume and recurrence **[126]**. Cryotherapy is commonly delivered using Spray and contact probes, however the intralesional needle cryoprobe has been shown to be the most effective in healing keloid scars **[127]**. The temperature of keloid scar is reduced to below- 22 degrees °C during cryotherapy **[126]**. Cell anoxia, cryo necrosis and coagulative necrosis have all been related to reduced temperature inducing vascular damage **[123, 127]**. hypopigmentation, blistering, discomfort, delayed healing and infection have all been reported as a side effect of external cryotherapy **[126]**. Intralesional cryotherapy was introduced to reduce side effects, and there are now a number of nitrogen-based cryo devices described for the treatment of keloid scars, including two commercially available: a liquid nitrogen-based device **[123]** and an argon gas-based device **[128]**. Intralesional cryotherapy involves inserting a needle with or without a cryoprobe into the long axis of the keloid scar to allow liquid nitrogen vapour to pass through and freeze the tissue **[129]**. External cryotherapy induced hypopigmentation in dark- skinned people, hence intralesional cryotherapy was proposed to overcome this **[127]**. This is accompanied by findings of another study which indicated that patients with

Fitzpatrick type 1-11 to experience hypopigmentation and recurrence after intralesional cryotherapy [130]. Intralesional cryotherapy destroys the keloid's core while leaving the superficial epithelial cells, including melanocytes, unharmed **[127]**. As a result, volume loss is enhanced while the risk of hypopigmentation and other surface responses is reduced **[126]**. According to research, intralesional cryotherapy can reduce keloid volume by 51.4-67.4% after 12 months following the last treatment, according to studies **[123, 127, 128, 130]**. While comparing intralesional and spray cryotherapy, the former appeared to be most effective, although both exhibited good outcomes **[125]**. The results of a smaller research involving spray cryotherapy by park *et al* confirmed the requirement for sessions every two weeks to sustain effects. Furthermore, they found that spray treatment was ineffective in a percentage of cases, particularly for thicker keloids, and recommended that it should not be used as a monotherapy **[131]**. In Conclusion, while Cryotherapy is known to be painful, intralesional cryotherapy, especially with younger lesions is effective **[125]**.

4.12 Radiation therapy

researchers have been evaluating several radiation treatments to determine the best protocols for treating keloids since the beginning of the 20th century **[132]**. Since then, it's been used less frequently as a monotherapy and more commonly as an effective adjuvant treatment following surgical excision **[134, 135, 136]** with effectiveness rates ranging from 67 to 98 percent and recurrence rates of approximately 22 percent. When compared to monotherapy radiation therapy has been demonstrated to be most successful as adjuvant therapy to surgical excision **[134, 137]**. Though the mechanism of action of radiation therapy is unknown, in-vitro studies have shown increased rates of premature cellular senescence and reduced proliferation of keloid fibroblasts in a dose dependent manner **[136,132]** and acts by strangling angiogenesis and obstructing fibroblast activity **[51]**. Reduced fibroblast proliferation, increased cell senescence and apoptosis, all of which leading to reduced collagen production and keloid suppression have also been described **[138]**. In order to avoid postoperative recurrence, Surgical excision followed by radiation has become a basis of keloid treatment **[139]**. After surgical excision, various radiotherapy methods, namely electron beam radiotherapy, have been used. with varied degrees of success, brachytherapy superficial, and orthovoltage radiation have been used **[140]**. Brachytherapy is a

modern radiation treatment that has mixed success. Following the use of perioperative high dosage brachytherapy in patients who had failed earlier therapies, researchers discovered a 6% recurrence rate. All previously afflicted patients their symptoms totally removed **[144]**. Low dose rate (LDR) or high dose rate (HDR) intralesional brachytherapy can be used **[141]**. HDR brachytherapy has been extensively explored in compression to LDR brachytherapy because LDR treatment times range from 20-72 hrs but HDR treatment varied from 5-10 minutes **[142, 143]**. In a study of 72 papers, Mankowski *et al* examined the clinical outcomes of various types of radiation treatment for the management of keloids **[137]**. When subjected to combinational therapy with post-surgery excision, radiation used as monotherapy resulted in greater rates of recurrence (37%) according to the meta-analysis (27%). When comparing the various radiation-based therapies, brachytherapy had the lowest recurrence rate (15%), followed by x-ray (23%) and electron beam (23%) **[135]**. Finally, due to the introduction of new in-office devices, superficial photon radiotherapy has gained popularity **[145]**. Acute skin reactions and late problems are 2 types of radiotherapy side effects that are generally linked to the dose of radiation employed. oedema, ulceration, erythema, necrosis, desquamation and pigmentary changes are the most typical acute reactions that occur as soon as 7 days post keloid treatment. changes in pigmentation atrophy are among the late consequences. A few weeks after radiation for telangiectasia **[146]**.

4.13 Botulinum Toxin Type A (BTA)

Botulinum toxin type A (BTA), is a potent neurotoxin derived from bacterium clostridium botulinum that produces local muscle flaccid paralysis and reduces skin tension. It has been shown to improve scar cosmesis by reducing stress on healing wound edges, **[147]**, aggregating fibroblasts in G0 and G1 Phases of the cell cycle **[148]** and decreasing TGF-β1 expression **[149]**. In a prospective, uncontrolled study, 12 patients with keloids were treated with translesional botulinum toxin type A injection at a concentration of 35 units/ml, with a dosage of 70-140 units per session, at 3month intervals for 3-9 months **[150]**. This resulted in successful therapy, great patient satisfaction, and no major side effects or symptoms of keloid recurrence **[150]**. Despite the fact that a subsequent study (n=4) demonstrated no clinical advantages from botulinum toxin therapy in keloids, following research has been broadly supportive of this therapeutic response **[151]**. In a case study, 12 patients

(n=01 chinese, n=10 whites, and n=01 south asian) with keloids in various areas of the body (n=9 presternal, n=3 neck, thigh, and face) treated between 20 and 100 units of BTA on each session over the past 5 years (no frequency specified). Eight individuals received alternating intradermal triamcinolone injections at the same time. After a range of 2-43 months of frequent injections, the keloids were completely flattened. Two of the twelve patients experienced recurrences near previously treated regions.1 patient's condition worsened, resulting in ulceration and recurrence **[151]**. Botulinum toxin has a number of advantages to triamcinolone, including less side effects and a more rapid relief in symptoms **[152]**.

4.14 Pulsed-dye laser (PDL)

The pulsed dye laser (PDL) was among the first laser treatments for keloids **[153]**. PDL is a type of non-ablative laser therapy which enhances scar appearance by targeting keloid microvasculature **[154]**. Because this laser degrades haemoglobin, it can be used to treat vascular keloids **[153]**. The PDL was originally designed to treat vascular lesions by changing the laser's wavelength from 585 - 600 nm and targeting oxyhaemoglobin and haemoglobin as chromatophores **[154]**. PDL (585 nm) was shown to cause keloid recurrence after earlier flattening in an early case report, however subsequent investigations have proven success in keloid treatment **[157]**. PDL therapy is commonly applied in surrounding non-overlapping laser pulses throughout the length of the scar that used a laser wavelength of 585 nm to 595 nm to achieve a therapeutic effect **[158, 156, 159, 76, 143]**. PDL therapy can last anywhere from 12 to 18 sessions, with 4 to 8 weeks between sessions **[154, 158, 160]**. TGF-β expression was reduced, fibroblast proliferation was reduced, and fibroblast death was elevated in keloid biopsies after PDL treatment, according to Kuo *et al* **[155]**. This backed up histological results from keloid samples treated with PDL that showed a decrease in fibroblasts and the development of looser, less coarse collagen fibres **[156]**. PDL treatment can last anywhere from 12 to 18 sessions, with 4 to 8 weeks each exercise **[154, 158, 160]**. After 4-6 sessions, Cannarozzo *et al* **[154]** showed a 75 percent improvement in overall scar colour, pliability, height and texture in 49 percent of patients with hypertrophic and keloid scars. After six treatments, Al- Mohamady *et al* **[159]** reported a 55 percent advancement in the Vancouver scar scale, with older scars showing less advancements **[76, 160]**. There is no recent data on how PDL treatment affects the recurrence of keloid

scars, while there is evidence that it can induce scar recurrence in rare situations **[161]**. Crusting, blistering, post-inflammatory pigmentary and temporary changes are some of the possible side effects of PDL treatment for scars **[154, 159, 76, 160]**.

4.15 Ablative laser.

Keloids and hypertrophic scars can be cut and cauterised with a carbon dioxide laser (10600 nm), resulting in a dry operation environment with minimal tissue stress. When used alone, the carbon dioxide laser was connected to recurrence rates of 39-92%, and when combined with postoperative injectable steroids, recurrence rates were 25-74 % **[161]**. All though ablative carbon dioxide (CO_2) and erbium doped yttrium aluminium garnet (Er: YAG) lasers have long been used to heal scars, there is no evidence that they can be used to cure keloids. CO_2 and Er: YAG lasers target water molecules, producing collagen remodelling, increased levels of basic fibroblast growth factor, and lower levels of TGF -β in nearby tissue **[162]**. 30 patients with hypertrophic scars were treated with a combination of 3 different therapy modalities: In a korean study 10600 nm ablative CO_2(AFL), copper bromide laser (CBL) and intralesional TAC. CBL had improved vascularity and pigmentation outcomes at the end of the research. In terms of thickness and pliability, AFL and AFL plus TAC were very beneficial. Epidermal resurfacing was the outcome of collagen remodelling. CBL plus TAC did not worsen vascularity or pigmentation, implying that CBL may compensate for TAC-induced erythema. Lastly, combining AFL, CBL, and intralesional TAC provides a cutting-edge treatment strategy for hypertrophic scars **[161]**. Edema, erythema and hyperpigmentation are some of the side effects of laser therapy for keloids that have been described in research **[162]**. A possible adverse effect of ablative CO_2 resurfacing has been identified as hypertrophic scarring, particularly on the neck **[163]**.

4.16 laser-assisted drug delivery (LADD)

Drug penetration beyond the stratum corneum has been aided by lasers to boost the bioavailability of topical scar treatment **[164]**. CO_2 and Er: YAG lasers, which are common ablative lasers, are used in LADD to form cylindrically shaped micro-ablation zones of the skin, allowing for topical medications to penetrate the dermis **[165]**. Though LADD has been used to study topical keloid-treating agents there is insufficient data on the utilization of LADD for keloid therapy compared to corticosteroids, 5FU, and imiquimod **[166]**. The use of Er: YAG laser was investigated

by Cavalie *et al* **[167]** every other week in conjunction with topical β methasone cream twice daily until keloids improved sufficiently. There was a median overall improvement of 50 percent after nine treatments, with acne induced keloids showing the greatest improvement **[167]**. within the first 2 months after finishing treatment, 22 percent of individuals had recurrence **[235]**. The efficacy of intralesional triamcinolone acetonide therapy and topical desoxymethasone Er: YAG LADD was then compared by Park *et al* **[168]**. To compare these two regimens, this group conducted a split scar trial, in which each LADD steroid therapy was given in four sessions at six-week intervals **[168]**. The scar halves showed significant improvement 12 weeks after the last session, while some degradation was seen at the conclusion of the study period **[168]**. Patients assessed their satisfaction with their treatment outcome as "moderately satisfied" at the conclusion of the study **[168]**. In murine and porcine skin models, the use of 5-FU and imiquimod in combination with LADD has been demonstrated to promote medication penetration and lower the dosage needed for maximum efficacy **[169]**. More research is needed to determine the efficacy of these topical LADD for keloid therapies.

4.17 Platelet-rich plasma (PRP)

PRP is a type of autologous plasma that has been concentrated to contain supra-physiologic quantities of platelets and alpha granules, as well as vascular endothelial growth factor, platelet derived growth factor, and TGFβ which is growth factors and cytokines **[170]**. PRP has become popular as a supplement to other treatments for a variety of dermatologic disorders, such as chronic wounds, alopecia, and scars **[171]**. PRP's effectiveness in modifying keloid pathophysiology has been the subject of recent research. In an in-vivo study involving cutaneous fibroblasts, PRP increased fibroblast proliferation, collagen expression, and matrix protein production **[172]**. Increased TGF-β levels in PRP have been linked to activation of the TGF-β signaling pathway **[173]**. PRP is Currently being researched as wound bed injection therapy after surgical excision. When PRP was used intraoperatively during surgical excision and postoperatively for three months in a monthly regimen, Hersant *et al* **[174]** observed a 29 percent keloid recurrence at 2 years. This research demonstrates that PRP may be useful in modifying abnormal healing of keloid wounds that are frequently found after surgical excision. According to Jones *et al* **[175]**, using PRP as an adjunct to surgical excision and X-ray

radiation therapy for ear keloids reduces the recurrence rate to six percent after two years **[175]** according to Jones *et al* **[175]**. When PRP was used in combination with surgical excision and cryotherapy, Azzam *et al* **[176]** reported a recurrence rate of 32 percent **[176]**.

CONCLUSION:

Keloid is an abnormal scar which leads to physical distress and emotional distress (depending on size and location). Generally, keloids are formed after surgery and rarely because of bug bite, tattooing, burns and piercing. Permanent removal of the formed keloids is of a great question among scientists but treatment is available for subsidising its symptoms like inflammation, pain, itching and discomfort. People with black pigmented skin are more prone for keloid development. TGF- β1 is the important factor which plays a major role in the development of keloids. Treating Keloids doesn't have a standard protocol but using various drugs like corticosteroids, mitomycin, Imiquimod, radiation therapy and cryotherapy are leading while surgical therapy is rarely recommended.

Conflict of Interest: None

REFERENCE

[1] Andrew's diseases of the skin-clinical dermatology; William D James, Timothy G. Berger, Dirk M Elston, Isaac M. Neuhaus-12th Edition -597-598.

[2] Shih B, Bayat A. Genetics of keloid scarring. Arch Dermatol Res. 2010;302:319-339.

[3] Chike-Obi CJ, Cole PD, Brissett AE. Keloids: pathogenesis, clinical feactures, and management. Semin Plast Surg. 2009;23:178-184.

[4] Robles DT, Berg D. Abnormal wound healing: keloids. Clin Dermatol. 2007 Jan-Feb;25(1):26-32.

[5] Palko JR, Arfeen S, Farooq AV, Reppa C, Harpcopos GJ. Corneal keloid presenting forty years after penetrating injury: Case report and literature review. Surv Ophthalmol.2019 Sep-Oct;64(5):700-706.

[6] Kang S, Hur JK,Kim D. Advances in diagnostic methods for keloids and biomarker-targeted fluorescent probes. Analyst. 2019 Mar 11;144(6):1866-1875.

[7] Tuan TL, Nichter LS. The molecular basis of keloid and hypertrophic scar formation. Mol Med Today. 1998;4:19-24.

[8] Pastuszak-Gabinowska M, Peregud-Pogorzelski J, Luksza K, Sznelewski P, Brodkiewicz A. Wybrane aspekty molekularnych

podstaw tworzenia sie bliznowcow. Roczniki Pomorskiej Akademii Medycznej w Szczecinie.2011;57:10-17.

[9] Brown JJ, Bayat A. Genetic susceptibility to rised dermal scarring. Br J Dermatol.2009;161:8-18.

[10] Char F. Ehlers-Danlos syndrome. Birth Defects Orig Artic Ser. 1971;7:300-302.

[11] Gonzalez-Martinez R, Marin-Bertolin S, Amorrortu- velayos J. Association between keloids and Dupuytren's disease: case report. Br J plast Surg.1995;48:47-48.

[12] Bayat A, Bock O, Mrowietz U, Ollier WE, Ferguson MW. Genetic susceptibility to keloid disease and hypertrophic scarring: transforming growth factor β 1 common polymorphisms and plasma levels. Plast reconstr surg. 2003;111:535-543.

[13] Bayat A, Walter JM, Bock O, Mrowietz U, Ollier WE, Ferguson MW. Genetic susceptibility to keloid disease mutation screening of the TGFβ3 gene. Br J Plast Surg. 2005;58;914-921.

[14] Evrard SM. d`Audigier C. MAauge L. Israel-Biet D. Guerin CL. Bieche I. Kovacic JC. Fischer AM. Gaussem P. Smadja DM. The profibrotic cytokine transforming growth factor β1 increases endothelial progenitor cell angiogenic properties. J Thromb Haemost.2012;10:670.

[15] Desmouliere A. Geinoz A. Gabbiani F Gabbiani G. Transforming growth factor β1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and groeting cultured fibroblasts J Cell Biol. 1993;122:103.

[16] Gailit J welch MP. Clark RA. TGF-β1 stimulates expreesion of keratinocyte integrins during re-epithelialization of cutaneous wounds. J Invest Dermatol.1994;103;221.

[17] White LA. Mitchell TI. Brinckerhoff CE. Transforming growth factor β inhibitory element in the rabbit matrix metalloproteinase-1(collagenase-1) gene functions as a repressor of constitutive transcription. Biochim Biophys Acta.2000;1490:259.

[18] Krzemien S, Knapczyk P. Akualne poglady dotyczace znaczenia transformujacego czynnika wzrostu (TGF -B) w patogenezie

niektorych stanow chorobowych. Wiad Lek. 2005;58:536-539.

[19] Stepien Wyrobiec O, Hrycek A, Wyrobiec G. Transformujacy czynnik wzrostu β (TGF-β) – budowa, mechanizmy oddzialywania oraz jego rola w patogenezie tocznia rumieniowatego ukladowego. Postepy Hig Med Dosw(online) 2008;62:688-693.

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4283882/

[21] https://www.aad.org/public/diseases/a-z/keloids-self-care

[22] http://www.integritymedical.com/petrolatum-gauze/

[23] Nicodemus GD., Bryant S.J. Cell encapsulation in biodegradable hydrogels for tissue engineering applications, Tissue Eng. Part B. 2008;14:149-165

[24] Boateng J.S., Matthews K.H., stevens H.N., Eccleston G.M. Wound healing dressings and drug delivery system: A review. J. Pharm. Sci. 2008;97:2892-2923. Doi:10.1002/jps.21210.

[25] Kumar A., Jaiswal M. Design and in vitro investigation of nanoparticles using green chemistry. J. Appl. Polym. Sci.2016;133 doi:10.1002/app.43260.

[26] Van Vlierberghe S., Dubruel P., Schacht E. Biopolymer-based hydrogels as scaffolds for tissue engineering application: A review. Biomacromolecules. 2011;12:1387-1408. Doi: 10.1021/bm200083n

[27] Bilici C., Can V., Noochel U., Behl M., Lendlein A., Okay O. Melt-processable shape-memory hydrogels with self-healing ability of high mechanical strength. Macromol. 2016;49:7442-7449.doi:10.1021/acs.macromol.6b01539.

[28] Koehler J., Brandl F.P., goepferich A.M. Hydrogel wound dressings for bioactive treatment of acute and chronic wounds. Eur. Polym.J.2018;100:1-11. Doi:10.1016/j.eurpolymj.2017.12.046.

[29] Gupta P., Vermani K., Garg s. hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov. Today. 2002;7:569-579. Doi:10.1016/S1359-6446(02)02255-9

[30] Monstrey S, Middelkoop E, Vranckx JJ, *et al*. Updated scar management practical guidelines:

non-invasive and invasive measures. J Plast Reconstr Aesthet Surg. 2014;67(8):1017–1025.

[31] Suetake T, Sasai S, Zhen YX, *et al*. Functional analyses of the stratum corneum in scars. Sequential studies after injury and comparison among keloids, hypertrophic scars, and atrophic scars. Arch Dermatol. 1996;132(12):1453– 1458.

[32] Tandara AA, Mustoe TA. The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. J Plast Reconstr Aesthet Surg. 2008;61(10):1219–1225.

[33] Ud-Din S and Bayat A. New insights on keloids, hypertrophic scar , and striae. Dermatol clin 2014; 32 (2):193-209.

[34] Katz BE. Silicone gel sheeting in scar therapy. Cutis 1995; 56(1) : 65-67.

[35] Berman B, Perez OA, Kinda S, *et al*. A review of the biologic effect, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. Dermatol Surg. 2007; 33(11): 1291-1302; discussion 302-303.

[36] Gold MH, McGuire M, Mustoe TA, *et al*. Updated international clinical recommendations on scar management: part 2—algorithms for scar prevention and treatment. Dermatol Surg. 2014;40(8):825–831.

[37] Tang HL, Lau KK, Sam R, Ing TS. Chest wall abscesses due to continuous application of silicone gel sheets for keloid management. BMJ Case Rep. 2015;2015. pii: bcr201420677.

[38] Mustoe TA , Cooter RD, Gold MH, *et al*. International clinical recommendation on scar management. Plast Reconstr Surg 2002; 110(2): 560-571.

[39] Al-Attar A, Mess S, Thomassen JM, *et al*. Keloid pathogenesis and treatment. Plast Reconstr Surg. 2006;117(1):286–300.

[40] Li Z, Dranoff JA, Chan EP, Uemura M, sevigny J, Wells RG. Transforming growth factor-β and substrate stiffness regulate portal fibroblast activation in culture. Hepatology. 2007 Oct .46(4): 1246-56.

[41] Berman B, Maderal A,Raphael B, Keloids and hypertrophic scars: pathophysiology, classification,

and treatment. Dermatol Surg.2017:43 Suppl 1:S3-S18.

[42] Reno F, Grazianetti P, Cannas M, Effects of mechanical compression on hypertrophic scars: prostaglandin E2 release. Burns. 2001;27(3) : 215-218.

[43] Park TH, Seo SW, Kim JK, Chang CH. Outcomes of surgical excision with pressure therapy using magnets and identification of risk factors for recurrent keloids. Plast Reconstr Surg. 2011;128(2):431–439.

[44] Park TH, Rah DK. Successful eradication of helical rim keloids with surgical excision followed by pressure therapy using a combination of magnets and silicone gel sheeting. Int Wound J. 2017;14(2):302–306.

[45] Tanaydin V, Beugels J, Piatkowski A, *et al*. Efficacy of custom-made pressure clips for ear keloid treatment after surgical excision. J Plast Reconstr Aesthet Surg.2016;69:115-121.

[46] Hayashi T, Furukawa H, Oyama A, *et al*. A new uniform protocol of combined corticosteroid injections and ointment application reduces recurrence rates after surgical keloid/hypertrophic scar excision. Dermatol Surg. 2012 Jun. 38(6):893-7.

[47] Muneuchi G, Suzuki S, Onodera M, *et al*. Long-term out-come of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. Scand J Plast Reconstr Surg Hand Surg 2006; 40(2): 111–116.

[48] Morelli Coppola M, Salzillo R, Segreto F, *et al*. Triamcinolone acetonide intralesional injection for the treatment of keloid scars: patient selection and perspectives. Clin Cosmet Investig Dermatol 2018; 11: 387–396.

[49] Hochman B, Locali RF, Matsuoka PK, *et al*. Intralesional triam-cinolone acetonide for keloid treatment: a systematic review. Aesthetic Plast Surg 2008; 32(4): 705–709.

[50] Xu SJ, Teng JY, Xie J, *et al*. [Comparison of the mechanisms of intralesional steroid, interferon or verapamil injection in the treatment of proliferative scars]. Zhonghua Zheng Xing Wai Ke Za Zhi. 2009;25(1):37–40. Article in Chines.

[51] Lee HJ and Jang YJ. Recent Understandings of Biology, Prophylaxis and Treatment Strategies for Hypertrophic Scars and Keloids. Int J Mol Sci 2018; 19(3): E711.

[52] Trisliana Perdanasari A, Lazzeri D, Su W, *et al*. Recent developments in the use of intralesional injections keloid treatment. Arch Plast Surg. 2014;41(6): 620–629.

[53] Darougheh A, Asilian A and Shariati F. Intralesional triamcinolone alone or in combination with 5-fluorouracil for the treatment of keloid and hypertrophic scars. Clin Exp Dermatol 2009; 34(2): 219–223.

[54] Donkor P. Head and neck keloid: treatment by core excision and delayed intralesional injection of steroid. J Oral Maxillofac Surg 2007; 65(7) : 1292-1296.

[55] Khalid FA, Mehrose MY, Saleem M, *et al*. Comparison of efficacy and safety of intralesional triamcinolone and combination of triamcinolone with 5-fluorouracil in the treatment of keloids and hypertrophic scars: Randomised control trial. Burns 2019; 45(1): 69–75.

[56] Huang L, Cai YJ, Lung I, Leung BC, Burd A. A study of the combination of triamcinolone and 5-fluorouracil in modulating keloid fibroblasts in vitro. J Plast Reconstr Aesthet Surg. 2013 Sep. 66(9):e251-259.

[57] Heppt MV, Breuninger H, Reinholz M, *et al*. current strategies in the treatment of scars and keloids. Facial Plast Surg. 2015;31(4):386-395.

[58] Berman B, Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. J Am Acad Dermatol. 2002 Oct. 47(4 Suppl):S209-11.

[59] Gauglitz GG, Korting HC, Pavicic T, *et al*. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med 2011; 17(1–2): 113–125.

[60] Berman B, Duncan MR. Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production in vitro. J

Am Acad Dermatol. 1989;21(4 Pt 1):694–702.

[61] Berman B. Imiquimod: a new immune response modifier for the treatment of external genital warts and other diseases in dermatology. Int J Dermatol. 2002;41 Suppl 1:7–11.

[62] Berman B and Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. J Am Acad Dermatol 2002; 47(4 Suppl): S209–211.

[63] Martin-Garcia RF and Busquets AC. Postsurgical use of imiquimod 5% cream in the prevention of earlobe keloid recurrences: results of an open-label, pilot study. Dermatol Surg 2005; 31(11 Pt 1): 1394–1398.

[64] Stashower ME. Successful treatment of earlobe keloids with imiquimod after tangential shave excision. Dermatol Surg 2006; 32(3): 380–386.

[65] Smith P, Mosiello G, Deluca L, Ko F, Maggi S, Robson MC. TGF-β2 activates proliferative scar fibroblasts. J Surg Res. 1999 Apr. 82(2):319-23.

[66] Patel PJ, Skinner RB, Jr. Experience with keloids after excision and application of 5% imiquimod cream. Dermatol Surg. 2006;32(3):462.

[67] Veen EJ and Dikkers FG. Topical use of MMC in the upper aerodigestive tract: a review on the side effects. Eur Arch Otorhinolaryngol 2010; 267(3): 327–334.

[68] Shin JY, Yun SK, Roh SG, et al. Efficacy of 2 Representative Topical Agents to Prevent Keloid Recurrence After Surgical Excision. J Oral Maxillofac Surg 2017; 75(2): 401.e1–401.e6.

[69] Chen T, Kunnavatana SS, Koch RJ. Effects of mitomycin-C on normal dermal fibroblasts. Laryngoscope.2006;116(4):514–517.

[70] Sanders KW, Gage-White L and Stucker FJ. Topical mitomycin C in the prevention of keloid scar recurrence. Arch Facial Plast Surg 2005; 7(3): 172–175.

[71] Seo SH and Sung HW. Treatment of keloids and hypertrophic scars using topical and intralesional mitomycin C. J Eur Acad Dermatol Venereol 2012; 26(5): 634–638.

[72] Huang L, Wong YP, Cai YJ, *et al*. Low-dose 5-fluorouracil induces

cell cycle G2 arrest and apoptosis in keloid fibroblasts. Br J Dermatol. 2010;163(6):1181–1195.

[73] Nanda S and Reddy BS. Intralesional 5-fluorouracil as a treatment modality of keloids. Dermatol Surg 2004; 30(1): 54–56.

[74] Goldan O, Weissman O, Regev E, *et al*. Treatment of postdermabrasion facial hypertrophic and keloid scars with intralesional 5-Fluorouracil injections. Aesthetic Plast Surg. 2008;32(2):389–392.

[75] Asilian A, Darougheh A and Shariati F. New Combination of Triamcinolone, 5-Fluorouracil, and pulsed-dye laser for treatment of keloid and hypertrophic scars. Dermatol Surg 2006; 32(7) :907-915.

[76] Manuskiatti W, Fitzpatrick RE, Goldman MP. Energy density and numbers of treatment affect response of keloidal and hypertrophic sternotomy scars to the 585-nm flashlamp-pumped pulsed-dye laser. J Am Acad Dermatol. 2001 Oct. 45(4):557-565.

[77] Granstein R, Flotte T, Amento E. Interferons and collagen production. J Invest Dermatol. 1990;95(6 Suppl):75S–80S.

[78] Berman B and Duncan MR. Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production in vitro. J Am Acad Dermatol 1989; 21(4 Pt 1): 694–702.

[79] Euler T, Valesky EM, Meissner M, et al. Normal and keloid fibroblasts are differentially influenced by IFN-gamma and triamcinolone as well as by their combination. Wound Repair Regen 2019; 17(10): 12722.

[80] Conejo-Mir JS, Corbi R and Linares M. Carbon dioxide laser ablation associated with interferon alfa-2b injections reduces the recurrence of keloids. J Am Acad Dermatol 1998; 39(6): 1039–1040.

[81] Berman B and Flores F. Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon alfa-2b injections. J

am Acad Dermatol 1997;37(5 pt 1): 755-757.

[82] Tredget EE, Shankowsky HA, Pannu R, *et al*. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. Plast Reconstr Surg 1998; 102(5): 1317–1328.

[83] Davison SP, Mess S, Kauffman LC, Al-Attar A. Ineffective treatment of keloids with interferon alpha-2b. Plast Reconstr Surg. 2006;117(1):247–252.

[84] Al-Khawajah MM. Failure of interferon-alpha 2b in the treatment of mature keloids. Int J Dermatol. 1996;35(7):515–517.

[85] Wong TW, Chiu HC, Yip KM. Intralesional interferon alpha- 2b has no effect in the treatment of keloids. Br J Dermatol. 1994;130(5):683–685.

[86] Broker BJ, Rosen D, Amsberry J, *et al*. Keloid excision and recurrence prophylaxis via intradermal interferon-gamma injections: a pilot study. Laryngoscope. 1996:106(12 pt 1): 1497-1501.

[87] Granstein RD, Rook A, Flotte TJ, *et al*. A controlled trial of intralesional recombinant interferon-gamma in the treatment of keloidal scarring. Clinical and histologic findings. Arch Dermatol. 1990;126(10):1295–1302.

[88] Larrabee WF, Jr., East CA, Jaffe HS, *et al*. Intralesional interferon gamma treatment for keloids and hypertrophic scars. Arch Otolaryngol Head Neck Surg. 1990;116(10):1159–1162.

[89] Arno AI. Gauglitz GG, Barret JP, *et al*. Up-to-date approach to manage keloids and hypertrophic scars: a useful guide. Burns 2014;40(7):1255-1266.132.

Yamamoto T. Bleomycin and the skin. Br J Dermatol. 2006;155(5):869–875.

[90] Suarez E, syed F, Alonso-rasgado T, Bayat A. identification of biomarkers involved in differential profiling of hypertrophic and keloid scars versus normal skin arch dermatol Res. 2015;307(2):115-133.

[91] Takeuchi T. Antitumor antibiotics discovered and studied at the Institute of Microbial Chemistry. J Cancer Res Clin Oncol. 1995;121(9–10):505–510.

[92] Hendricks T, Martens MF, Huyben CM, Wobbes T.

Inhibition of basal and TGF β-induced fibroblast collagen synthesis by antineoplastic agents. Implications for wound healing. Br J Cancer. 1993;67(3):545–550.

[93] Sterling KM, Jr., DiPetrillo TA, Kotch JP, Cutroneo KR. Bleomycin-induced increase of collagen turnover in IMR-90 fibroblasts: an in vitro model of connective tissue restructuring during lung fibrosis. Cancer Res. 1982;42(9):3502–3506.

[94] Aggarwal H, Saxena A, Lubana PS, *et al*. Treatment of keloids and hypertrophic scars using bleom. J Cosmet Dermatol. 2008;7(1):43–49.

[95] Bodokh I, Burn P. [Treatment of keloid with intralesional bleomycin}. 1996. 123(12) :791-804.

[96] Sandulache VC, Parekh A, Li-Korotky H, Dohar JE, Hebda PA. Prostaglandin E2 inhibition of keloid fibroblast migration, contraction, and transforming growth factor (TGF)-beta1-induced collagen synthesis. Wound Repair Regen. 2007 Jan-Feb. 15(1):122-133.

[97] Huu ND, Huu SN, Thi XL, *et al*. successful Treatment of intralesional Bleomycin in Keloids of vietnamese population. Open Access Maced J Med Sci 2019;7(2) :298-299.

[98] Boyadjiev C, Popchristova E, Mazgalova J. Histomorphologic changes in keloids treated with Kenacort. J Trauma 1995;38(2) : 1995;38(2):299-302.

[99] Manca G, Pandolfi P, Gregorelli C, *et al*. Treatment of keloids and hypertrophic scars with bleomycin and electroporation. Plast Reconstr Surg. 2013;132(4):621e–630e.

[100] Gonzalez AC, Costa TF, Andrade ZA, *et al*. Wound healing - A literature review. An Bras Dermatol 2016; 91(5): 614–620.

[101] Kim DY, Kim ES, Eo SR, *et al*. A surgical approach for earlobe keloid: keloid fillet flap. Plast Reconstr Surg. 2004;113(6):1668–1674.

[102] Gauglitz GG. Management of keloids and hypertrophic scars: current and emerging options. Clin Cosmet Investig Dermatol 2013; 6: 103–114.

[103] McGinty S and Siddiqui WJ. Keloid. Treasure Island, FL: StatPearls Publishing, 2019.

[104] McGoldrick RB, Theodorakopoulou E, Azzopardi EA, et al. Lasers and ancillary treatments for scar management Part 2: Keloid, hypertrophic, pigmented and acne scars. Scars Burn Heal 2017; 3: 2059513116689805.

[105] Tan KT, Shah N, Pritchard SA, *et al*. The influence of surgical excision margins on keloid prognosis. Ann Plast Surg. 2010;64(1):55–58.

[106] Nguyen KT, Shikowitz L, Kasabian AK, *et al*. A Novel Approach to Keloid Reconstruction with Bilaminar Dermal Substitute and Epidermal Skin Grafting. Plast Reconstr Surg 2016; 138(1): 235–239.

[107] Ziccardi VB, Lamphier J. Use of keloid skin as an autograft for earlobe reconstruction after excision. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;89(6):674–675.

[108] Burm JS, Hansen JE. Full-thickness skin grafting with marginal deepithelialization of the defect for reconstruction of helical rim keloids. Ann Plast Surg.2010;65(2):193–196.

[109] Arima J, Dohi T, Kuribayashi S, *et al*. Z-plasty and Postoperative Radiotherapy for Anterior Chest Wall Keloids: An Analysis of 141 Patients. Plast Reconstr Surg Glob Open 2019; 7(3): e2177.

[110] Son D and Harijan A. Overview of surgical scar prevention and management. J Korean Med Sci 2014; 29(6): 751–757.

[111] Reish RG and Eriksson E. Scar treatments: preclinical and clinical studies. J Am Coll Surg 2008; 206(4): 719–730.

[112] Ogawa R, Akaishi S, Huang C, *et al*. Clinical applications of basic research that shows reducing skin tension could prevent and treat abnormal scarring: the importance of fascial/subcu-taneous tensile reduction sutures and flap surgery for keloid and hypertrophic scar reconstruction. J Nippon Med Sch 2011; 78(2): 68–76.

[113] Ogawa R, Akaishi S, Kuribayashi S, et al. Keloids and Hypertrophic Scars Can Now Be Cured Completely: Recent Progress in Our Understanding of the Pathogenesis of Keloids and

Hypertrophic Scars and the Most Promising Current Therapeutic Strategy. J Nippon Med Sch 2016; 83(2): 46–53.

[114] Danielsen PL, Rea SM, Wood FM, *et al*. Verapamil is Less Effective than Triamcinolone for Prevention of Keloid ScarRecurrence After Excision in a Randomized Controlled Trial. Acta Derm Venereol 2016; 96(6): 774–778.

[115] Alexandrescu D, Fabi S, Yeh LC, *et al*. Comparative Results in Treatment of Keloids With Intralesional 5-FU/Kenalog, 5-FU/Verapamil, Enalapril Alone,Verapamil Alone, and Laser: A Case Report and Review of the Literature. J Drugs Dermatol2016; 15(11): 1442–1447.

[116] Boggio RF, Boggio LF, Galvao BL, *et al*. Topical verapamil as a scar modulator. Aesthetic Plast Surg 2014; 38(5): 968–975.

[117] El-Kamel MF, Selim MK, Alghobary MF. Keloid Ectomy with core fillet flap and intralesional verapamil injection for recurrent earlobe keloids. Indian J Dermatol Venereol Leprol. 2016;82(6):659–65.

[118] Abedini R, Sasani P, Mahmoudi HR, Nasimi M,Teymourpour A, Shadlou Z. Comparison of intralesional verapamil versus intralesional corticosteroids in treatment of keloids and hypertrophic scars: a randomized controlled trial. Burns.2018;44(6):1482–8.

[119] Ramos-Gallardo G, Miranda-Altamirano A, Valdes-Lopez R, *et al*. [Verapamil in conjunction with pressure therapy in the treatment of pathologic scar due burn injury]. Rev Med Inst Mex Seguro Soc 2016; 54(4): 454–457.

[120] Khattab FM, Nasr M, Khashaba SA, et al. Combination of pulsed dye laser and verapamil in comparison with verapamil alone in the treatment of keloid. J Dermatolog Treat 2020; 31: 186–190.

[121] Kant SB, van den Kerckhove E, Colla C, et al. A new treatment of hypertrophic and keloid scars with combined triamcinolone and verapamil: a retrospective study. Eur J Plast Surg 2018; 41(1): 69–80.

[122] Lee RC and Ping JA. Calcium antagonists retard extracellular

matrix production in connective tissue equivalent. J Surg Res 1990; 49(5): 463–466.

[123] Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. Plast Reconstr Surg. 2003;111(6):1841–1852.

[124] Har-Shai Y and Zouboulis CC. Intralesional Cryotherapy for the Treatment of Keloid Scars: A Prospective Study. Plast Reconstr Surg 2015; 136(3): 397e–398e.

[125] Diegelmann RF, Bryant CP and Cohen IK. Tissue alpha-globulins in keloid formation. Plast Reconstr Surg 1977; 59(3): 418–423.

[126] Van Leeuwen MC, Bulstra AE, Ket JC, *et al*. Intralesional Cryotherapy for the Treatment of Keloid Scars: Evaluating Effectiveness. Plast Reconstr Surg Glob Open 2015; 3(6): e437.

[127] Har-Shai Y, Sabo E, Rohde E, *et al*. Intralesional cryosurgery enhances the involution of recalcitrant auricular keloids: a new clinical approach supported by experimental studies. Wound Repair Regen.2006;14(1):18–27.

[128] Van Leeuwen MC, Bulstra AE, van Leeuwen PA, *et al*. A new argon gas-based device for the treatment of keloid scars with the use of intralesional cryotherapy. J Plast Reconstr Aesthet Surg2014; 67(12): 1703–1710.

[129] O'Boyle CP, Shayan-Arani H, Hamada MW. Intralesional cryotherapy for hypertrophic scars and keloids: a review. Scars Burn Heal. 2017;3:2059513117702162.

[130] Van Leeuwen MC, van der Wal MB, Bulstra AE, *et al*. Intralesional cryotherapy for treatment of keloid scars: a prospective study. Plast Reconstr Surg. 2015;135(2):580–589.

[131] Park TH, Cho H-J, Lee JW, *et al*. Could -79 Cspray-type cryotherapy be an effective monotherapy for the treatment of keloid? Int J Mol Sci. 2017;18(12):2536

[132] Xu J, Yang E, Yu NZ, Long X. Radiation therapy in keloids treatment: history, strategy, effectiveness, and complication. Chin Med J (Engl). 2017;130(14):1715– 1721.

[133] De Bearman R and Gourgerot H. Cheloides des maqueuses. Ann Dermatol Syphilol (Paris) 1906; 7: 151.

[134] Guix B, Henriquez I, Andres A, *et al*. Treatment of keloids by high-dose-rate brachytherapy: A seven-year study. Int J Radiat Oncol Biol Phys 2001; 50(1): 167–172.

[135] Love PB and Kundu RV. Keloids: an update on medical and surgical treatments. J Drugs Dermatol 2013; 12(4): 403–409.

[136] Ogawa R, Mitsuhashi K, Hyakusoku H, *et al*. Postoperative electron-beam irradiation therapy for keloids and hypertrophic scars: retrospective study of 147 cases followed for more than 18 months. Plast Reconstr Surg 2003; 111(2): 547–553.

[137] Mankowski P, Kanevsky J, Tomlinson J, et al. Optimizing Radiotherapy for Keloids: A Meta-Analysis Systematic Review Comparing Recurrence Rates Between Different Radiation Modalities. Ann Plast Surg 2017; 78(4): 403–411.

[138] Ji J, Tian Y, Zhu YQ, *et al*. Ionizing irradiation inhibits keloid fibroblast cell proliferation and induces premature cellular senescence. J Dermatol. 2015;42(1):56–63.

[139] Maarouf M, Schleicher U, Schmachtenberg A,Ammon J. Radiotherapy in the management of keloids. Clinical experience with electron beamirradiation and comparison with X-ray therapy.Strahlenther Onkol. 2002;178(6):330–5.

[140] Cheraghi N, Cognetta A, Jr and Goldberg D. RADIATION THERAPY for the Adjunctive Treatment of Surgically Excised Keloids: A Review. J Clin Aesthet Dermatol 2017; 10(8): 12–15.

[141] Van Leeuwen MC, Stokmans SC, Bulstra AE, *et al*. Surgical excision with adjuvant irradiation for treatment of keloid scars: a systematic review. Plast Reconstr Surg Glob Open. 2015;3(7):e440.

[142] Escarmant P, Zimmermann S, Amar A, *et al*. The treatment of 783 keloid scars by iridium 192 interstitial irradiation after surgical excision. Int J Radiat Oncol Biol Phys. 1993;26(2):245–251.

[143] Van Leeuwen MC, Stokmans SC, Bulstra AE, *et al*. High-dose-rate brachytherapy for the treatment of recalcitrant keloids: a unique, effective treatment protocol. Plast Reconstr Surg. 2014;134(3):527–534.

[144] Jiang P, Baumann R, Dunst J, *et al*. Perioperative interstitial high-dose-rate brachytherapy for the treatment of recurrent keloids: feasibility and early results. Int J Radiat Oncol Biol Phys. 2016;94(3):532–536.

[145] Jones ME, Hardy C, Ridgway J. Keloid management:a retrospective case review on a new approach using surgical excision, platelet-rich plasma, and in-office superficial photon x-ray radiation therapy. Adv Skin Wound Care. 2016;29(7):303–307.

[146] Zainib M and Amin NP. Radiation Therapy in The Treatment of Keloids. Treasure Island, FL: StatPearls Publishing, 2019.

[147] Gassner HG, Sherris DA and Otley CC. Treatment of facial wounds with botulinum toxin A improves cosmetic outcome in primates. Plast Reconstr Surg 2000; 105(6): 1948–1953.

[148] Zhibo X and Miaobo Z. Botulinum toxin type A affects cell cycle distribution of fibroblasts derived from hypertrophic scar. J Plast Reconstr Aesthet Surg 2008; 61(9): 1128–1129.

[149] Xiao Z, Zhang F, Lin W, *et al*. Effect of botulinum toxin type A on transforming growth factorβ1 in fibroblasts derived from hypertrophic scar: a preliminary report. Aesthetic Plast Surg 2010; 34(4): 424–427.

[150] Zhibo X and Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg 2009; 124(5): 275e–277e.

[151] Robinson AJ, Khadim MF, Khan K. Keloid scars and treatment with botulinum toxin type A: the Belfast experience. J Plast Reconstr Aesthet Surg. 2013;66(3):439–40.

[152] Shaarawy E, Hegazy RA, Abdel Hay RM. Intralesional botulinum toxin type A is equally effective and better tolerated than intralesional steroid in the

treatment of keloids: a randomized controlled trial. J Cosmet Dermatol. 2015;14(2):161–166.

[153] Srinivas CR, Kumaresan M. Lasers for vascular lesions: standard guidelines of care. Indian J Dermatol Venereol Leprol. 2011;77(3):349–368.

[154] Cannarozzo G, Sannino M, Tamburi F, *et al*. Flash lamp pulsed-dye laser treatment of keloids: results of an observational study. Photomed Laser Surg. 2015;33(5):274–277.

[155] Kuo YR, Jeng SF, Wang FS, *et al*. Flashlamp pulsed dye laser (PDL) suppression of keloid proliferation through down-regulation of TGF-β1 expression and extracellular matrix expression. Lasers Surg Med. 2004;34(2):104–108.

[156] Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. Lancet. 1995;345(8959): 1198–1200.

[157] Shih P-Y, Chen H-H, Chen C-H, Hong H-S, Yang C-H. Rapid recurrence of keloid after pulse dye laser treatment. Dermatol Surg. 2008;34(8):1124–1127.

[158] Stephanides S, Rai S, August P, *et al*. Treatment of refractory keloids with pulsed dye laser alone and with rotational pulsed dye laser and intralesional corticosteroids: a retrospective case series. Laser Ther.2011;20(4):279–286.

[159] Al-Mohamady Ael S, Ibrahim SM, Muhammad MM. Pulsed dye laser versus long-pulsed Nd:YAG laser in the treatment of hypertrophic scars and keloid: a comparative randomized split-scar trial. J Cosmet Laser Ther. 2016;18(4):208–212.

[160] Manuskiatti W, Wanitphakdeedecha R, Fitzpatrick RE. Effect of pulse width of a 595-nm flashlamp-pumped pulsed dye laser on the treatment response of keloidal and hypertrophic sternotomy scars. Dermatol Surg. 2007;33(2):152–161.

[161] Kim JH, Kim HJ, Kim YH, *et al*. The combination of copper bromide laser, a 10,600 nm ablative carbon dioxide laser and intralesional triamcinolone for the treatment of hypertrophic

thyroidectomy scars. J Eur Acad Dermatol Venereol. Jan/2012. 26(1):125-126.

[162] Nicoletti G, De Francesco F, Mele CM, *et al*. Clinical and histologic effects from CO_2 laser treatment of keloids. Lasers Med Sci. 2013;28(3):957–964.

[163] Avram MM, Tope WD, Yu T, Szachowicz E, Nelson JS. Hypertrophic scarring of the neck following ablative fractional carbon dioxide laser resurfacing. Laser Surg Med Laser Appl. 2011;26(1);10-15.

[164] Ali FR, Al-Niaimi F. Treatment of nonmelanoma skin cancers using laser-assisted drug delivery. Dermatol Surg. 2018;44(2);310

[165] Braun SA, Schrumpf H, Buhren BA, *et al*. Laser-assisted drug delivery: mode of action and use in daily clinical practice. J Dtsch Dermatol Ges. 2016;14(5):480–488.

[166] Zaleski-Larsen LA, Fabi SG. Laser-assisted drug delivery. Dermatol Surg. 2016;42(8):919–931.

[167] Cavalie M, Sillard L, Montaudie H, *et al*. Treatment of keloids with laser-assisted topical steroid delivery: a retrospective study of 23 cases. Dermatol Ther.2015;28(2):74–78.

[168] Park JH, Chun JY, Lee JH. Laser-assisted topical corticosteroid delivery for the treatment of keloids. Lasers Med Sci. 2017;32(3):601–608.

[169] Lee WR, Shen SC, Al-Suwayeh SA, *et al*. Laser-assisted topical drug delivery by using a low-fluence fractional laser: imiquimod and macromolecules. J Control Release.2011;153(3):240–248.

[170] Amable PR, Carias RB, Teixeira MV, *et al*. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther. 2013;4(3):67.

[171] Lynch MD, Bashir S. Applications of platelet-rich plasma in dermatology: a critical appraisal of the literature. J Dermatolog Treat. 2016;27(3):285–289.

[172] Cho JW, Kim SA, Lee KS. Platelet-rich plasma induces increased expression of G1 cell cycle regulators, type I collagen, and matrix metalloproteinase-1

in human skin fibroblasts. Int J Mol Med. 2012;29(1):32–36.

[173] Nam SM, Kim YB. The effects of platelet-rich plasma on hypertrophic scars fibroblasts. Int Wound J.2018;15(4):547–554.

[174] Hersant B, SidAhmed-Mezi M, Picard F, *et al*. Efficacy of autologous platelet concentrates as adjuvant therapy to surgical excision in the treatment of keloid scars refractory to conventional treatments: a pilot prospective study. Ann Plast Surg. 2018;81(2):170–175.

[175] Jones ME, McLane J, Adenegan R, *et al*. Advancing keloid treatment: a novel multimodal approach to ear keloids. Dermatol Surg. 2017;43(9):1164–1169.

[176] Azzam EZ, Omar SS. Treatment of auricular keloids by triple combination therapy: Surgical excision, platelet-rich plasma, and cryosurgery. J Cosmet Dermatol. 2018;17(3):502–510.