World Journal of Nutrition and Health, 2014, Vol. 2, No. 2, 28-32
Available online at http://pubs.sciepub.com/jnh/2/2/4

DOI:10.12691/jnh-2-2-4

Management of Keloids and Hypertrophic Scars: Role of Nutrition, Drugs, Cryotherapy and Phototherapy

Ibrahim A Maghrabi[1], Ahmed M Kabel[2,3,*]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
[3]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Taif University, Taif, Saudi Arabia
*Corresponding author: drakabel@gmail.com

Received August 17, 2014; Revised August 25, 2014; Accepted August 29, 2014

Abstract Keloids and hypertrophic scars are characterized by excessive deposition of dermal collagen with resultant scar tissue. This scar tissue is benign, non-contagious and sometimes accompanied by severe itching, sharp pains and changes in texture. In severe cases, it can affect movement of skin and may ulcerate. There are various lines of treatment of keloids and hypertrophic scars including nutritional therapy, drug therapy, radiation therapy, phototherapy cryotherapy and surgical excision.

Keywords: *management, keloids, hypertrophic scars*

Cite This Article: Ibrahim A Maghrabi, and Ahmed M Kabel, "Management of Keloids and Hypertrophic Scars: Role of Nutrition, Drugs, Cryotherapy and Phototherapy." *World Journal of Nutrition and Health*, vol. 2, no. 2 (2014): 28-32. doi: 10.12691/jnh-2-2-4.

1. Introduction

A keloid is a type of scar, which results from overgrowth of dense fibrous tissue that usually develops after healing of a skin injury. The tissue extends beyond the borders of the original wound, does not usually regress spontaneously and tends to recur after excision [1]. The first description of keloids concerned surgical techniques used in Egypt in 1700 BCE. Subsequently, in 1806, Alibert used the term cheloide, derived from the Greek chele, or crab's claw, to describe the lateral growth of tissue into unaffected skin [2].

Keloids are firm, rubbery lesions or shiny, fibrous nodules that vary from pink to flesh-coloured or red to dark brown in colour. A keloid scar is benign, non-contagious, and sometimes accompanied by severe itching and sharp pains and may affect movement of the skin [3]. Although they usually occur at the site of an injury, keloids can also arise spontaneously. They can occur as a result of severe acne or chicken pox scarring, infection at a wound site, repeated trauma to an area, excessive skin tension during wound closure or a foreign body in a wound [4].

Keloids should not be confused with hypertrophic scars, which are characterized by erythematous, pruritic, raised fibrous lesions that typically do not expand beyond the boundaries of the initial injury and may undergo partial spontaneous resolution. Hypertrophic scars are common after thermal injuries and other injuries that involve the deep dermis [2].

No single therapeutic modality is best for all keloids. The location, size and depth of the lesion; the age of the patient and the past response to treatment determine the type of therapy used [5]. Prevention is the key, but therapeutic treatment of hypertrophic scars and keloids includes occlusive dressings, compression therapy, intralesional corticosteroid injections, nutritional therapy, cryosurgery, excision, radiation therapy, laser therapy, interferon (IFN) therapy, 5-fluorouracil (5-FU) injection, doxorubicin injection, bleomycin injection, verapamil injection, topical retinoic acid, topical tacrolimus, botulinum toxin injection, and over-the-counter treatments. Other promising therapies include antiangiogenic factors, phototherapy, ultraviolet (UV) rays therapy, transforming growth factor beta3 (TGF-β3), tumor necrosis factor alpha (TNF-α) inhibitors and recombinant human interleukin which are directed at decreasing collagen synthesis [6].

2. Standard Treatments

These include occlusive dressings, compression therapy and intralesional corticosteroid injections [7].

2.1. Occlusive Dressings

They include silicone gel sheets and dressings, non-silicone occlusive sheets and cordran tape. These measures have been used with variable success. Their effects appear to result from a combination of occlusion and hydration, rather than from an effect of the silicone [3].

2.2. Compression Therapy

It involves pressure, which has thinning effects on skin. Reduction in the cohesiveness of collagen fibers in

pressure-treated hypertrophic scars has been demonstrated by electron microscopy. Compression treatments include button compression, elastic adhesive bandages, compression wraps, spandex or elastane bandages, and supportive bandages [5].

2.3. Intralesional Corticosteroid Injections

They have been the corner stone of treatment. Corticosteroids reduce excessive scarring by reducing collagen synthesis, altering glucosaminoglycan synthesis and reducing production of inflammatory mediators and fibroblast proliferation during wound healing. The most commonly used corticosteroid is triamcinolone acetonide (TAC) [4]. Fitzpatrick [8] was the first to report experience with TAC + 5-FU. He mixed 1 mg/mL TAC with 5-FU (by adding 0.1 mL of 10 mg/ mL TAC to 0.9 mL of 50 mg/ mL 5-FU). Intralesional steroid therapy as a single modality and as an adjunct to excision has been shown to be efficacious in various studies with response rates from 50-100%. Complications of repeated corticosteroid injections include atrophy, telangiectasia formation and pigmentation [9].

3. Recent Lines of Treatment

3.1. IFN therapy has been demonstrated in invitro studies to reduce keloidal fibroblast production of collagen types I, III, and VI mRNA. IFN-α and IFN-β also reduce fibroblast production of glycosaminoglycans, which form the scaffolding for the deposition of dermal collagen. IFN-α, IFN-β, and IFN-γ have been shown to increase collagenase activity. Studies have shown that IFN-γ modulates p53 apoptotic pathway by inducing apoptosis-related genes. P53 was reported to be a potent suppressor of interleukin 6 (IL-6), a cytokine implicated in the hyperproliferative and fibrotic conditions [10].

3.2. 5-FU, a pyrimidine analogue with antimetabolite activity, inhibits fibroblastic proliferation in tissue culture and is believed to reduce postoperative scarring by decreasing fibroblast proliferation. Its efficacy and safety have been reported when used as a monotherapy or when used in combination with other drugs (e.g. TAC) for treatment of other fibrosing conditions, including infantile digital fibromatosis, knuckle pads, rheumatoid nodules and adverse foreign body reaction. Some data suggest that 5-FU is effective in treatment of hypertrophic scars and is somewhat effective in small keloids [11]. The combination of 5-FU with other therapies such as TAC or flashlamp-pumped pulsed-dye laser (PDL) significantly increases the efficacy over single modalities [12,13].

3.3. Intralesional doxorubicin (Adriamycin): Doxorubicin is a commonly used chemotherapeutic agent that irreversibly inactivates prolyl 4-hydroxylase in human skin fibroblasts and has been shown to inhibit collagen alpha-chain assembly [14]. Another mechanism of doxorubicin-induced inhibition of collagen synthesis includes the inhibition of the enzyme prolidase, which is the key enzyme in the process of collagen resynthesis [15]. Other agents such as doxycycline, daunorubicin, gentamicin, netilmicin and anthracycline are also capable of inhibiting prolidase in cultured human skin fibroblasts [16].

3.4. Bleomycin: Bleomycin injections cause necrosis of keratinocytes with a mixed inflammatory infiltrate. Several studies have demonstrated that bleomycin can be used effectively to treat keloids and hypertrophic scars. Bleomycin given at a concentration of 1.5 IU/mL to 13 patients using the multiple-puncture method produced complete flattening was in 6 patients, highly significant flattening in 6 patients and significant flattening in a single patient. Two patients presented a recurrence as a small nodule 10 and 12 months after the last infiltration [17]. Another study obtained complete flattening in 73.3%, highly significant flattening in 6.7%, and moderate flattening in 6.7% of lesions after the administration of jet intralesional injections of bleomycin in 15 patients with keloids and hypertrophic scars [14].

3.5. Intralesional verapamil: Verapamil is a calcium channel blocker that blocks the synthesis and secretion of extracellular matrix molecules (eg, collagen, fibronectin) and increases fibrinase [18]. In a randomized clinical trial, intralesional injection of verapamil was compared to intralesional TAC for treatment of keloids and hypertrophic scars, reporting a reduction in vascularity, pliability, height, and width in both groups after 3 weeks of treatment. This result was maintained at 1 year after stopping the treatment [9].

3.6. Topical retinoids: retinoic acid decreases normal tonofilament and keratohyaline synthesis, increases the production of mucoid substances and the epidermal cell growth rate, and inhibits DNA synthesis in vitro. In vitro studies have demonstrated that retinoids can modulate collagen production and the proliferation of normal and keloidal fibroblasts. In vivo application of topical retinoic acid can lead to a reduction of hypertrophic scars in 50-100% of patients and of keloids in less than 20% of patients. The most common adverse effects reported have been photosensitivity, irritant contact dermatitis and skin atrophy [3].

3.7. Topical tacrolimus: Tacrolimus is an immunomodulator that inhibits TNF-α. Gli-1, an oncogene, has been found to be overexpressed in fibroblasts of keloids. Rapamycin, a close analogue of tacrolimus, was used in an in vitro study and was found to inhibit the gli-1 oncogene, thus giving a rationale to initiate clinical trials of topical tacrolimus and rapamycin [19].

3.8. Topical tamoxifen: Tamoxifen is a synthetic nonsteroidal antiestrogen used to treat breast cancer, has been shown to inhibit proliferation of keloid fibroblasts and their collagen synthesis in monolayer cultures. Tamoxifen was shown to produce a dose-dependent and reversible inhibition of contraction of adult human dermal fibroblast in vitro. Tamoxifen has also been shown to reduce TGF-α production by keloid fibroblasts in vitro [20].

3.9. Topical TGF-β: TGF-β and its isomers have been shown to play a central role in fibrotic disorders characterized by excessive accumulation of interstitial matrix material in the lung, kidney, liver and other organs. TGF-β1 and TGF-β2 have been shown to stimulate fibroblasts to produce collagen and have a direct and independent effect on the contraction of fibroblasts in vitro. However, TGF-β3 may prevent scarring. Exogenous addition of TGF-β3 was shown to reduce fibronectin and collagen deposition in the early stages of cutaneous wound healing and in overall wound scarring. Avotermin, which

is derived from human recombinant TGF-β3, has shown promise in clinical studies. Wounds treated with avotermin showed significant improvement in scar appearance, with a response rate of greater than 70% [21].

3.10. Intradermal Ilodecakin: Ilodecakin is a human recombinant IL-10 formulation. IL-10 regulates fibroblast differentiation and proliferation, and has been shown to induce scar less healing when overexpressed in adult mouse wounds. Application of Ilodecakin to the margins of acute incisional wounds by intradermal injection decreases subsequent scarring [22].

3.11. Onion extract, that is, extract of Allium cepa, and specifically its derivative quecertin, is a bioflavonoid with antibacterial, fibrinolytic, antihistamine-releasing, and antiproliferative effects on both normal and malignant cells that can be found in onions and apples, red wine, and black tea. It inhibits enzymes involved in the proliferation of signaling pathways and it causes cell cycle arrest and apoptosis [23]. In vitro studies have demonstrated that quecertin inhibited keloid fibroblast proliferation, collagen synthesis, basal expression and activation of several key proteins such as insulin-like growth factor (IGF)-1, which is a potent mitogen and inhibitor of apoptosis that stimulates fibroblast proliferation and enhances collagen synthesis [24]. For treatment of preexisting scars, the combination of onion extract with other agents seems to generate better results than onion extract alone [25].

3.12. Vitamin E (tocopherol) is a lipid-soluble antioxidant with multiple biological effects, including the reduction of reactive oxygen species, which hamper healing and cause damage to DNA molecule, cellular membranes and lipids. In addition, vitamin E alters collagen production and inhibits the spread of peroxidation of lipids in cellular membranes, thus acting as a membrane-stabilizing agent. When vitamin E has been used topically in combination with other treatments for scars, such as silicone gel sheets, it has been demonstrated to improve preexisting hypertrophic scars by 50% in 95% of patients, compared with 50% improvement in 75% of patients treated with silicon sheets alone after 2 months of treatment [3].

4. Radiation Therapy

The use of radiotherapy to treat keloids remains controversial. Although many studies have demonstrated efficacy and decreased recurrence rate, the safety of radiotherapy has been questioned. In a retrospective study of superficial x-ray therapy of 24 excised keloids, the author reported a recurrence rate of 53%. Use of iridium Ir^{192} interstitial irradiation after excisional surgery resulted in 21% recurrence rate after 1 year. Excisional surgery and preoperative hyaluronidase solution followed by external radiation had a 0% recurrence rate. Adjunctive high dose-rate brachytherapy (Ir^{192}) used after excision and closure resulted in a 12% recurrence rate after 26 months [26].

5. Cryotherapy

Cryosurgical media affects the microvasculature and causes cell damage leading to tissue anoxia. Generally, 1, 2, or 3 freeze-thaw cycles lasting 10-30 seconds each are used for the desired effect. Treatment may need to be repeated every 20-30 days. Cryotherapy can cause pain and permanent depigmentation in selected patients. As a single modality, cryosurgery led to total resolution with no recurrences in 51-74% of patients after 30 months of follow-up observation [3]. Cryotherapy may be combined with other lines of treatment such as intralesional TAC injection [27].

6. Excision

Apply basic soft tissue handling techniques at primary wound repair sites and carefully plan the closure with minimal tension. Use buried sutures, when necessary, for a layered closure and to reduce tension. Whenever feasible, apply pressure dressings during the immediate postoperative period to wounds in patients in whom hypertrophic scars and keloid formation occur [2]**.** For better results and less recurrence rate, excision should be combined with other postoperative modalities, such as radiotherapy, injected IFN, or corticosteroid therapy **[7]**.

7. Phototherapy

7.1. Carbon dioxide laser: Ablation of keloids and hypertrophic scars using a carbon dioxide laser can cut and cauterize the lesion, creating a dry surgical environment with minimal tissue trauma. When used as a single modality, carbon dioxide laser was associated with recurrence rates of 39-92%, and when it was combined with postoperative injected steroids, it was associated with less recurrence rate [2,28].

7.2. Argon laser: Similar to the carbon dioxide laser, the argon laser can induce collagen shrinkage via generation of excessive localized heat. The argon laser has demonstrated recurrence rates of 45-93% [2].

7.3. PDL (585 nm): The 585-nm PDL provides photothermolysis, resulting in microvascular thrombosis. It was noted that scars became less erythematous, more pliable, and less hypertrophic after treatment with the 585-nm PDL. The findings were confirmed using objective measurements such as reflectance spectrometry readings, scar height and pliability measurements. Because of its efficacy, safety, and relatively low cost, the PDL remains the laser treatment of choice for hypertrophic scars. Concomitant use of TAC reduced symptom scores by 70% compared with PDL alone [3].

7.4. Photodynamic therapy: In vitro effect of 5-amino levulinic acid (ALA) and 635-nm diode laser irradiation on keratinocyte-fibroblast co-culture (Raft model) was studied, determining that 5 J/cm^2 reduces tissue contraction and collagen synthesis and preserves fibroblast viability [29].

7.5. Ultraviolet A-1: UVA-1 has been reported as an effective treatment for systemic sclerosis through induction of collagenase I produced by fibroblasts. Some studies reported clinical improvement in one keloid in addition to the histological reappearance of normal collagen and elastic fibers, while other studies have not reported as good clinical results**.** Animal models have shown a significant decrease in dermal thickness and collagen content in scars irradiated postsurgically with

UVA-1. UVA-1 exposure to hypertropic scars in rabbits after epithelialization may lead to softening of the scar, thinning of the skin, and a decrease in collagen content. However, immediate irradiation with UVA-1 after wounding could not prevent the development of hypertrophic scarring in rabbits [4].

7.6. Narrowband UVB: Studies on human skin fibroblasts have demonstrated that narrowband UVB reduces type I collagen synthesis by down-regulating TGF-beta1 expression at both the mRNA and protein levels and promoting the release of matrix metalloproteinase-1. Also, flattening of a hypertrophic scar after treating a patient with vitiligo with low-dose narrowband UVB once a week for 4 months was reported [30].

7.7. Broadband UVB: Broadband UVB at high doses has also improved fibrosing skin conditions including keloids, hypertrophic scars, scleroderma, old burn scars, and granuloma annulare through collagenase-mediated removal of excess dermal collagen via activation of matrix metalloproteinase-1 pathways [31].

7.8. Intense pulsed light (IPL): It was reported that IPL was effective in treating and improving inflamed hypertrophic scars [32]. Some studies have suggested that IPL is effective for improving the appearance of hypertrophic scars and keloids, regardless of their origin, and in reducing the height, redness and hardness of scars in the majority of the patients (92.5%). Improvement was excellent in 31.2%, good in 25.7%, moderate in 34% and minimal in 9.1% of patients [33].

8. Conclusion

There are various therapeutic options for treatment of keloids and hypertrophic scars including standard methods, drug therapy, excision, radiation therapy, cryotherapy and phototherapy. No single modality can be considered as the most suitable for treatment but the combination therapy seems to produce better results. The combination between bleomycin, triamcinolone acetonide and pulsed dye laser seems to be the best option for treatment of keloids and hypertrophic scars.

Competing Interests

The authors have no competing interests.

References

[1] Davison SP, Mess S, Kauffman LC, et al. (2006): Ineffective treatment of keloids with interferon alpha-2b. Plast Reconstr Surg., 117(1): 247-252.

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

[3] Alster TS, Tanzi EL (2003): Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol., 4(4): 235-243.

[4] Kakar AK, Shahzad M, Haroon TS (2006): Keloids: clinical features and management. J Pakis Assoc Dermatol., 16: 97-103.

[5] Butler PD, Longaker MT, Yang GP (2008): Current Progress in Keloid: Research and Treatment. J Amer College Surg., 206(4): 731-741.

[6] Mrowietz U, Seifert O (2009): Keloid Scarring: New Treatments Ahead. Actas Dermo-Sifiliográficas., 100 (2): 75-83.

[7] Berman B, Viera MH, Amini S, et al. (2008): Prevention and management of hypertrophic scars and keloids after burns in children. J Craniofac Surg.,19(4): 989-1006.

[8] Fitzpatrick RE (1999): Treatment of inflamed hypertrophic scars using intralesional 5-FU. Dermatol Surg., 25: 224-232.

[9] Margaret Shanthi FX, Ernest K, Dhanraj P (2008): Comparison of intralesional verapamil with intralesional triamcinolone in the treatment of hypertrophic scars and keloids. Indian J Dermatol Venereol Leprol., 74(4): 343-348.

[10] Lee JH, Kim SE and Lee AY (2008): Effects of interferon-alpha2b on keloid treatment with triamcinolone acetonide intralesional injection. Int J Dermatol., 47(2):183-186.

[11] Kontochristopoulos G, Stefanaki C, Panagiotopoulos A, et al. (2005): Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. J Am Acad Dermatol., 52(3): 474-479.

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

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

[14] Saray Y, Güleç AT (2005): Treatment of keloids and hypertrophic scars with dermojet injections of bleomycin: a preliminary study. Int J Dermatol., 44(9): 777-784.

[15] Muszynska A, Palka J, Gorodkiewicz E (2000): The mechanism of daunorubicin-induced inhibition of prolidase activity in human skin fibroblasts and its implication to impaired collagen biosynthesis. Exp Toxicol Pathol., 52(2): 149-155.

[16] Muszynska A, Wolczynski S, Palka J (2001): The mechanism for anthracycline-induced inhibition of collagen biosynthesis. Eur J Pharmacol., 411(1-2): 17-25.

[17] España A, Solano T, Quintanilla E (2001): Bleomycin in the treatment of keloids and hypertrophic scars by multiple needle punctures. Dermatol Surg., 27(1): 23-27.

[18] Copcu E, Sivrioglu N, Oztan Y (2004): Combination of surgery and intralesional verapamil injection in the treatment of the keloid. J Burn Care Rehabil., 25(1): 1-7.

[19] Kim A, DiCarlo J, Cohen C, et al. (2001): Are keloids really "gli-loids"?: High-level expression of gli-1 oncogene in keloids. J Am Acad Dermatol., 45(5): 707-711.

[20] Mikulec AA, Hanasono MM, Lum J, et al. (2001): Effect of tamoxifen on transforming growth factor beta1 production by keloid and fetal fibroblasts. Arch Facial Plast Surg., 3(2): 111-114.

[21] Saulis AS, Mogford JH, Mustoe TA (2002): Effect of Mederma on hypertrophic scarring in the rabbit ear model. Plast Reconstr Surg., 110(1): 177-183.

[22] Occleston NL, O'Kane S, Goldspink N, et al. (2008): New therapeutics for the prevention and reduction of scarring. Drug Discovery Today, 13(21): 973-981.

[23] Draelos ZD (2008): The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. J Cosmet Dermatol., 7(2):101-104.

[24] Koc E, Arca E, Surucu B, et al. (2008): An open, randomized, controlled, comparative study of the combined effect of intralesional triamcinolone acetonide and onion extract gel and intralesional triamcinolone acetonide alone in the treatment of hypertrophic scars and keloids. Dermatol Surg., 34(11): 1507-1514.

[25] Hosnuter M, Payasli C, Isikdemir A, et al. (2007): The effects of onion extract on hypertrophic and keloid scars. J Wound Care., 16(6): 251-254.

[26] Garg MK, Weiss P, Sharma AK, et al. (2004): Adjuvant high dose rate brachytherapy (Ir-192) in the management of keloids which have recurred after surgical excision and external radiation. Radiother Oncol., 73(2): 233-236.

[27] Bijlard E, Timman R, Verduijn GM, et al. (2013): Intralesional cryotherapy versus excision and corticosteroids or brachytherapy for keloid treatment: study protocol for a randomised controlled trial. Trials., 14:439.

[28] Martin MS, Collawn SS (2013): Combination treatment of CO2 fractional laser, pulsed dye laser, and triamcinolone acetonide injection for refractory keloid scars on the upper back. J Cosmet Laser Ther., 15(3): 166-70.

[29] Chiu LL, Sun CH, Yeh AT, et al. (2005): Photodynamic therapy on keloid fibroblasts in tissue-engineered keratinocyte-fibroblast co-culture. Lasers Surg Med., 37(3): 231-244.

[30] Oiso N, Kawara S and Kawada A (2008): The effectiveness of narrowband ultraviolet B on hypertrophic scar in a patient having

an isomorphic phenomenon and vitiligo. J Eur Acad Dermatol Venereol., 22 (12): 1527-1535.

[31] Taylor DK, Anstey AV, Coleman AJ, et al. (2002): Guidelines for dosimetry and calibration in ultraviolet radiation therapy: a report of a British photodermatology group workshop. BJD., 146 (5): 755-763.

[32] Shamsi Meymandi S, Rezazadeh A, Ekhlasi A (2014): Studying intense pulsed light method along with corticosteroid injection in treating keloid scars. Iran Red Crescent Med J., 16(2):e12464.

[33] Erol OO, Gurlek A, Agaoglu G, et al. (2008): Treatment of hypertrophic scars and keloids using intense pulsed light (IPL). Aesthetic Plast Surg., 32(6): 902-909.