Keloids and Hypertrophic Scars

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Ivana Binic

Key Points

- Keloids and hypertrophic scars are benign, the localized proliferation of connective tissue of the skin, and result from abnormal wound healing.
- Hypertrophic scarring usually occurs within 4–8 weeks after some traumatic skin injury, has a rapid growth phase for up to 6 months, and then gradually regresses over a period of a few years. Keloids appear as firm, mildly tender tumors, pink or purple, with a shiny surface and sometimes telangiectasia.
- The most crucial factor in hypertrophic scar and keloid formation is prevention. Before any surgical procedure, patients should be asked if they have had previous problems with scarring.
- Multiple studies on hypertrophic scar and keloid formation have led to many therapeutic strategies to prevent or attenuate keloid and hypertrophic scar formation. The current arsenal of treatment methods includes surgical, medical, physical, and radiologic therapies, often used in combination. In the present, no existing single method is superior to others as an effective solution for all hypertrophic scars and keloids.

I. Binic (✉)
Clinic of Dermatovenerology, University Clinical Center Niš, University of Niš, Niš, Serbia

Definition

Keloids and hypertrophic scars are benign, the localized proliferation of connective tissue of the skin, and are the result of abnormal wound healing. Excessive scars may develop following the deep dermis injury, including burns, surgery, abrasion, piercings, vaccinations, and lacerations.

Hypertrophic scars are raised, but they stay within the boundaries of the original wound, and there is a possibility of spontaneous regression. Keloids are also raised but spread beyond the original wound boundaries, invading the surrounding skin. They may continue to grow over time and often recur following excision. Hypertrophic scars usually are more responsive to different treatment modalities than keloids (Vivas et al. 2012).

Basic Concepts of Pathogenesis

Despite the progress of science and various researches conducted continuously, the exact etiopathogenesis of the development of hypertrophic scars and keloids has not been explained to this day. The formation of such scars occurs when some of the phases of wound healing are disturbed. Wound healing itself is a complex process with phases that often overlap, including inflammatory response, the formation of granulation tissue with reepithelialization, and angiogenesis

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and matrix remodeling (Li et al. 2007). The inflammatory response that occurs immediately after the trauma, regardless of its origin, may play a significant role in determining the type of scar that will occur (Berman et al. 2017).

In both types of abnormal scars, there is a disbalance in the synthesis and degradation of the extracellular matrix, dysregulation of proinflammatory cytokines, persistent proliferation, and/or resistance to apoptosis in fibroblasts. All these abnormalities could alter the process of normal healing and result in abnormal scarring (Trace et al. 2016). Keloid fibroblasts show the most proliferative activity, but recent research does not rule out other epidermal cells' role and the immune system in keloidogenesis (Limandjaja et al. 2020).

In the normal maturation phase of wound healing, the connective tissue elements regress after the third week (English and Shenefelt 1999). In keloids, the collagen synthesis is about 20 times higher than that in normal skin and three times higher than that in hypertrophic scar (Rockwell et al. 1989). Also, it is shown that not only high collagen production matters but the ratio of type I to type III collagen is also high (Abergel et al. 1985). Along with decreased elastin, this abnormal collagen inside the dermis can explain these scars' firm clinical appearance (Almine et al. 2012).

Clinical Presentation

Hypertrophic scars are firm, raised formations that usually occur within 4–8 weeks after some traumatic skin injury (infection, wound closure with excess tension, burn), have a rapid growth phase for up to 6 months, and then gradually regress over a period of a few years (Gauglitz et al. 2011). If they occurred after surgery, the shape is linear, but after trauma or inflammatory lesion shape may be papular or nodular, but they do not exceed the limits of tissue damage.

Sometimes hypertrophic scars may finish like flat scars with no other symptoms.

In contrast, keloids may develop up to several years after minor injuries and extend beyond the site of injury. Sometimes they may form spontaneously in the absence of any known trauma, often on the midchest. They appear as firm, mildly tender tumors, pink or purple, with a shiny surface and sometimes telangiectasia. The borders of the tumor are well demarcated but irregular in outline. They persist, usually for long periods, and do not regress spontaneously (Murray 1994). Both types of scars are very often pruritic, but keloids may be the source of significant pain and hyperesthesia.

In the majority of cases, hypertrophic scars develop over extensor joints and other areas of high tension (Berman et al. 2017). Keloids have a predilection for specific body areas: the anterior chest, earlobes, cheeks, upper arms, and shoulders (Trace et al. 2016). Less affected locations are the eyelids, cornea, mucous membranes, genitalia, palms, and soles, but both can occur at any anatomic location (Niessen et al. 1999). Risk factors for developing hypertrophic scars or keloids include trauma, mechanical forces (namely, increased wound tension or stretching), infection, inflammation, and foreign body reaction.

The incidence of keloids and hypertrophic scars is highest in the second to third decade of life, and their occurrence has equal sex distribution (Köse and Waseem 2008). Incidence rates of hypertrophic scarring vary from 40 to 70% following surgery to up to 91% following burn injury, depending on the depth of the wound (Deitch et al. 1983). Patients with keloids often report a positive family history, unlike patients suffering from hypertrophic scarring, and the concept of a genetic predisposition to keloids has long been suggested (Gauglitz et al. 2011). Keloid formation is seen in individuals of all races, except albinos, but dark-skinned individuals are more susceptible to keloid formation, with an incidence of 4.5 and 16% reported in the predominantly black and Hispanic population, respectively (Atiyeh et al. 2005).

Diagnosis and Differential Diagnosis

A clinical finding of flesh-colored to erythematous fibrotic plaque, together with a history of recent surgery or trauma, is sufficient to make the diagnosis. A biopsy is generally unnecessary and should certainly be avoided because of the possible worsening of scarring after it. It is needed only when the possibility of a malignant process should be ruled out with certainty (Ogawa et al. 2009). In the absence of supportive findings, malignant tumors, including dermatofibrosarcoma protuberans, and giant cell fibroblastoma, along with infections and sarcoidosis, should be considered in the differential diagnosis (Rabello et al. 2014).

In some cases, clinical differentiation between hypertrophic and keloid scars is of central importance before any treatment initiation because of a different course and prognosis.

Prevention

The most important factor in hypertrophic scar and keloid formation is prevention. Before any surgical procedure, patients should be asked if they have had previous problems with scarring. Before elective surgical procedures, all unnecessary wounds should be avoided in patients with a tendency to develop keloids (Wolfram et al. 2009). Risk factors that promote hypertrophic scars and keloids and physicians can limit attention to the early care of wounds, mechanical force (stretching tension) on the wound, wound infections, and foreign body reactions (Mutalik 2005).

Anything that accelerates wound healing and reduces skin tension (e.g., postsurgical taping for 12 weeks) will diminish the risk of abnormal scar formation. Surgical closure of an open wound should consider the wound's tension, incisions should not cross joint spaces, midchest incisions should be avoided, and incisions should follow skin creases whenever possible.

General Principles of Therapy

Multiple studies on hypertrophic scar and keloid formation have led to a plethora of therapeutic strategies to prevent or attenuate keloid and hypertrophic scar formation. The current arsenal of treatment methods includes surgical, medical, physical, and radiologic therapies, often used in combination. In the present, no existing single method is superior to others as an effective solution for all hypertrophic scars and keloids. Patients usually are treated with several treatment modalities combined depending on the patient's particular circumstances and the clinician's experience with each specific treatment method.

Hypertrophic scars and keloids are benign skin lesions, but very often they are associated with pain and/or pruritus with different degrees of discomfort; sometimes they cause functional problems (e.g., contraction/mechanical irritation due to elevation) and also cause cosmetic–esthetic concerns which may lead to psychological stress and functional disabilities that ultimately affect the patient's daily life (Vivas et al. 2012).

The most important goal of treating hypertrophic scars and keloids is to prevent function impairment and achieve a cosmetically acceptable appearance; therefore, treatment should include different therapeutic options appropriate for the patient.

The therapy goals must be set on an individual basis, respecting patient needs and complaints.

Depending on the chosen therapeutic option, improvement should be achieved after three to six treatments or after 3–6 months (e.g., volume reduction by 30–50%, symptom reduction >50%, and/or sufficient satisfaction of the patient) (Nast et al. 2012).

Treatment modalities for keloids and hypertrophic scars include pressure therapy, radiation, intralesional injections, cryotherapy, silicone-based products, surgical excision, lasers, and different combinations of two or more treatments.

Pressure Therapy

Pressure therapy has been the preferred conservative management for both the prophylaxis and treatment of hypertrophic scars and keloids since the 1970s, when physicians noted that pressure stockings used on lower extremity burns resulted in scars that matured more rapidly, with less erythema and thickness (Linares et al. 1993); pressure garments are predominantly used for the prophylaxis of hypertrophic burn scar formation, despite controversial data regarding their value in reducing excessive scarring and little scientific evidence supporting their use (Atiyeh 2007).

The compression phenomenon is not well understood, but possible mechanisms may include the following (Urioste et al. 1999): decrease in blood flow resulting in a decrease in a2-macroglobulin and a subsequent increase in collagenase-mediated collagen breakdown; hypoxia which leads to fibroblast and collagen degradation; lower levels of chondroitin 4-sulfate, with a subsequent increase in collagen degradation; and decreased scar hydration, mast cell stabilization, and a subsequent decrease in neovascularization.

Histologically, there is a partial restoration in extracellular matrix organization and disappearance of a-SMA-expressing myofibroblasts, probably by apoptosis (Wolfram et al. 2009).

Recommendations for the amount of adequate pressure and the duration of the therapy are based in general on empirical observations, and using continuous pressure of 15–40 mmHg for at least 8–24 h/daily is recommended for the first six months (Gauglitz et al. 2011). This type of therapy may be limited by patient discomfort, and the success rate depends largely on patient compliance.

Radiation Therapy

The first use of X-rays in the treatment of scars was at the beginning of the last century. Later evidence showed that radiation therapy used as monotherapy is inadequate for the treatment of keloids, and therefore, the use of radiation therapy was started as an adjunct to surgical excision (Wolfram et al. 2009).

Ionizing radiation has two effects on pathological scars: (1) an antiproliferative effect because of the inhibition of new cell formation by a delay of mitosis and (2) an anti-inflammatory effect because of lymphocyte apoptosis and induction of differentiation of fibroblasts/fibrocytes. As a result of these two processes, the tissue becomes hypoxic, less vascularized with less new fibroblast formation, decreased collagen production, and finally, keloid growth stops (Nast et al. 2012). An adequate dose of radiation does not influence the wound healing process.

Surgical excision in combination with radiotherapy is considered the most effective treatment available in severe keloids. Surgical excision as a sole treatment of keloids has a very high recurrence rate, between 45% and 100% (Berman and Bieley 1996).

Surgical excision followed by radiation therapy for keloid treatment provides the highest reported regression rates (Reish and Eriksson 2008).

Electron beam irradiation is usually started 24–48 h after keloid excision, and the total dose is limited to 15–20 Gy throughout several treatments (Slemp and Kirschner 2006). Response rates ranged from 65% to 99%, and recurrence rates ranged from 21% to 72%, with most occurring within 13 months of radiation treatment (Kovalic and Perez 1989). Risk factors for increased recurrence after adjuvant radiation therapy include a keloid with a diameter greater than 2 cm, prior treatment of the keloid, and male gender. Also, one of the advantages of radiation therapy is the amelioration of pruritus and tenderness often associated with keloid lesions (Vivas et al. 2012).

Chronic adverse effects include hypo- and hyperpigmentation, erythema, telangiectasia, ulcerations, and atrophy (Nast et al. 2012). Radiation-induced malignancies from scar treatments are rare. The total-body radiation dose from a superficial low-voltage radiotherapy technique is low, and it is difficult to definitively implicate this kind of treatment as the cause of neoplasm. There is concern regarding the use of

radiation in pregnant women and children as well as in regions of the body with high carcinogenic potential (i.e., breast, thyroid) (Vivas et al. 2012).

The selection of radiation type, i.e., a conventional radiotherapy (RT), brachytherapy, or electron therapy, or fractionating, should be made individually by the treating radiation therapist. The current use of radiotherapy for keloids in routine practice is limited both because of the nonavailability of the modality in most centers and also a general understanding about its use. Treatment should preferentially be performed in specialized clinics with interdisciplinary consultation (dermatology, surgery, nuclear medicine). It may be an effective option for recalcitrant and large keloids not responding to other treatments.

Intralesional Therapy

Corticosteroids

Intralesional corticosteroid injections are one of the most common approaches in the therapy of hypertrophic scars and keloids. They often represent the first therapy used, either alone or in combination with some other treatment.

Most of the known effects of corticosteroids are thought to result primarily from their suppressive effects on the wound's inflammatory process. They reduce the scar's excessive growth by reducing collagen synthesis, altering the extracellular matrix components, such as glycosaminoglycans, and reducing proinflammatory mediators (Berman et al. 2017).

The most used corticosteroid is triamcinolone acetonide (TAC, 10–40 mg/mL, maximally 5 mg/cm 2), pure or diluted with 0.9% NaCl or lidocaine 1:2–1:4, injected strictly intralesional. The triamcinolone acetonide concentration depends on the size and site of the individual's lesion and age (Gupta and Sharma 2011). It is important to inject the steroid at a correct depth in the mid-dermis; otherwise, it may lead to irreversible atrophy. A blanching effect signals the endpoint of the infiltration (Nast et al. 2012). Further injections are performed as needed at 3–4-week intervals and usually, two or three sessions are sufficient. Occasionally, injections are continued for 6 months or more. The total number of injections depends on the response and possible side effects. Response rates have been highly variable, ranging from 50 to 100%, and a recurrence rate is reported to be 9–50% (Robles and Berg 2007).

When used alone, intralesional corticosteroid injections have the best effect on younger keloids, becoming completely flattened. In older hypertrophic scars and keloids, corticosteroids can soften and flatten the scars only to some degree and can provide symptomatic relief (Atiyeh 2007). Injections may be used alone or combined with other therapies, of which the combination with cryotherapy or surgery is the most widely used modality in clinical practice.

Side effects of intralesional steroid use include dermal atrophy, development of telangiectasias, and hypo-or hyperpigmentation. The injections can be painful, and pretreatment with local anesthetics or the addition of lidocaine may help (Kelly 2004). Intralesional steroids should be considered as the first-line treatment for early keloids and second-line treatment for early hypertrophic scars if other easier treatments have not been efficacious (Mustoe et al. 2002).

5-Fluorouracil (5-FU)

Recent data suggest that intralesional 5-FU injection is a safe, efficient tool in the ongoing battle against keloid scars. This treatment is increasingly becoming popular because of its good results. As a nucleotide analog (pyrimidine analog) incorporated into DNA in place of uracil, 5-fluorouracil (5-FU) inhibits DNA synthesis, especially in rapidly proliferating cells, and has been shown to inhibit fibroblast proliferation in vitro and in vivo. It also has an inhibitory effect on type I collagen gene expression in human fibroblasts by inhibiting TGF signaling (Reish and Eriksson 2008). Numerous studies have shown its effectiveness in treating hypertrophic scars and keloids, whether used alone or in combination with other therapeutic modalities, with

an average of 70% reduction in scar size after treatment termination (Ibrahim and Chalhoub 2018).

5-FU alone effectively treats keloids, but there are recommendations that for better results, it can be combined with surgical excision, as it prevents recurrence after excision in a majority of patients. Also, there is evidence that a combination of triamcinolone and 5-FU results in less skin atrophy and telangiectasia than triamcinolone alone. The treatment protocols vary from 50 mg/ml per session to 150 mg/ml per session, once a week, or every two weeks, with the longest treatment reaching ten months (Ibrahim and Chalhoub 2018). Further work to determine appropriate doses should be initiated. Adverse effects of 5-FU include transient hyperpigmentation, tissue sloughing, burning sensation, or pain at the injection site. To date, no studies have reported systemic complications (Reish and Eriksson 2008; Shah et al. 2016).

Bleomycin

Bleomycin is an anti-neoplastic polypeptide antibiotic isolated from a strain of Streptomyces verticillus with antitumor, antibacterial, and antiviral properties (Vivas et al. 2012). In addition to the blocking effect on the cell cycle, bleomycin directly inhibits collagen synthesis via decreased stimulation transforming growth factor β1 and induces fibroblast apoptosis. It was first investigated in the mid-1990s as a scar-reducing agent.

Only a few relevant studies have investigated the efficacy of bleomycin in treating hypertrophic scars and keloids. Different administration routes were described: intralesional injection, multiple puncture deposits, Dermojet injection, and tattooing, without evidence of the superiority of any method (Trace et al. 2016). A recent technique for delivering bleomycin to these lesions is called bleomycin tattooing in which multiple punctures are made on the keloid or hypertrophic scar with a 25-gauge needle and bleomycin (2 ml/cm^2) is dripped onto the lesion (Naeini et al. 2006). In one randomized controlled trial, the relative mean resolution score in the bleomycin tattoo group was approximately 88%, with a complete response observed in 47% of patients (Vivas et al. 2012).

Locally applied bleomycin results in minimal side effects, well-tolerated, transient hyperpigmentation, and mild to moderate local pain among the most common (Perdanasari et al. 2014). Systemic toxic effects of intralesionally administered bleomycin seem to be uncommon. Bleomycin may thus be a promising agent for keloid therapy and hypertrophic scars; however, further investigation and efficacy trials are needed before this agent is included in future treatment protocols.

Interferons (IFNs)

Interferons are cytokines secreted by T-helper cells that, apart from other properties, interfere with collagen synthesis and fibroblast proliferation, increase collagenase levels, and inhibit overproduction of collagen and glycosaminoglycans by fibroblasts. All IFN isoforms (a, b, g) have been shown to have these effects, but most of them have been applied only experimentally and in small numbers of patients (Wolfram et al. 2009).

Specifically, IFN alfa-2b has been proposed to have antiproliferative properties, and it may improve the pathologic features of dermal fibrosis directly or by antagonizing the effects of TGF-β. It can be used as monotherapy or as adjunctive therapy. Conclusions from IFN trials as monotherapy have shown inconsistent results (Davison et al. 2006; al-Khawajah MM. 1996), but as postoperative therapy or in combination with other treatment methods, IFN seems to be more promising, with lower recurrence rates and better outcomes. However, contradictory results have also been reported, so current evidence is insufficient to recommend IFNs' routine use (Lee et al. 2008; Conejo-Mir et al. 1998). It may be used in selected cases, particularly when the other treatment modalities have failed. Adverse effects are common with the use of IFNs and include flu-like symptoms (fever, chills, night sweats, fatigue, myalgia, and headache) and pain on the site of injection (Vivas et al. 2012).

Cryotherapy

Cryotherapy has been used as monotherapy and in conjunction with other treatment forms for hypertrophic scars and keloids. The low temperature induced by cryogens creates ice crystals, which causes vascular damage leading to anoxia, thrombosis, and consecutive ischemic cell death (Rusciani et al. 2006). Individual cell types show different sensitivities to low temperatures, ranging from 24 to 27 °C for melanocytes and 230 to 235 °C for fibroblasts (Berman et al. 2017).

Cryotherapy delivery methods include contact, sprays, and intralesional needles. Response to cryosurgery has been reported as high as 80% (Rusciani et al. 2006), but newer keloids that are more vascular are more susceptible to this kind of therapy than chronic, older keloids. Also, there is a better response in smaller keloids. Success rates in studies in which contact or spray cryosurgery with liquid nitrogen was used varied between 32% and 74% after two or more sessions, with higher response rates of hypertrophic scars compared with keloids (Mustoe et al. 2002). Treatment recommendations include two 15- to 20-s thaw cycles performed on each visit every 3/4 weeks for a total of eight to ten visits (Kelly 2004). Recently, the intralesional-needle cryoprobe method has been assessed to treat hypertrophic scars and keloids and has been demonstrated to have successful results. Compared with that obtained with contact/spray probes, there is a shorter reepithelialization time, requiring fewer treatments to achieve results (Har-Shai et al. 2003). When using intralesional cryotherapy cold temperature is concentrated within the scar and sparing external skin. It can be performed through a 20 G injection needle, multiple 18 G injection needles, or an intralesional cryoprobe (Berman et al. 2017).

Cryotherapy is often used in combination with intralesional corticosteroids, and this combination is superior to either treatment alone. Cryotherapy is used directly before administering intralesional corticosteroid injections because success rates seem to be increased with this sequence (Gauglitz et al. 2011). One study found that this combination therapy produced an 84% positive response rate (Ceilley and Babin 1979). Lesions treated with combination therapy require fewer procedures and have lower recurrence rates.

Immediate local complications associated with cryotherapy include pain, stinging sensation, edema, and bulla formation. Other adverse effects include atrophy, necrosis, and hypopigmentation and hyperpigmentation (Zimmerman and Crawford 2012).

The risk for pigment abnormalities is related to the duration of freezing and the number of sessions. A freeze/thaw time that exceeds 25 s may lead to the destruction of the cold-sensitive melanocytes, thereby causing hypopigmentation, and should be avoided to achieve cosmetically successful results (Kelly 2004).

Silicone-Based Products

Silicone therapy was first reported in the early 1980s, and since then, an effective and well-established therapy has become the noninvasive standard of care for scar management. The mechanism of action remains not completely determined. Presumed effects include hydration of the stratum corneum, increased skin surface temperature, development of a static electric field, reduction of evaporation, and oxygen transmission (Mustoe 2008). Also, silicone products likely act on the epidermis to initiate signaling cascades that affect dermal fibroblasts (Hanasono et al. 2004).

Silicone is available as a cream, gel sheet, strip, spray, and foam. To be effective, a silicone sheet must be used over the scar for 12–24 h per day for 2–3 months, with removal for routine hygiene. The sheets can be reused until they start to disintegrate. Silicone gel is better for consistent movement areas, where sheeting will not conform and should be applied twice daily. Also, it is suitable for use on visible areas as the face and hands. It is applied as a thin layer where it dries to form an adherent, transparent, flexible silicone sheet that is impermeable to fluids (Meaume et al. 2014).

Positive effects from silicone products that have been reported include reduction of erythema, pigmentation, and induration and an improved overall appearance (Trace et al. 2016). Silicone products may be beneficial in patients who cannot tolerate the pain associated with other treatment procedures.

Numerous randomized controlled trials demonstrate that silicone is safe and effective for treating hypertrophic scars and keloids with consistent treatment effects (Meaume et al. 2014). In the past years, more and more studies have supported the use of silicone gels for the prophylaxis of abnormal scarring. In a Cochrane Review, the benefit of silicone used in scar prevention in patients with a predisposition to developing keloids after surgery was confirmed (O'Brien and Jones 2013).

In patients known to have a predisposition to form hypertrophic scars, applying topical silicone gel sheets should begin as soon as reepithelialization is finished, and daily application for at least 12 h is recommended. It is unknown what the exact duration of treatment is needed for maximum benefit.

Silicone gel dressings' efficacy depends on the scar's location, early commencement, the grade of response, and patient compliance. Side effects are minimal and very rare; however, rashes, pruritus, maceration, and dryness of the skin have been reported (Meaume et al. 2014).

Surgical Excision

Surgical excision is traditional, practical treatment for keloid and hypertrophic scar removal. It is very important before starting any surgical intervention to differentiate the type of scar clearly.

In the case of hypertrophic scars, surgical intervention timing is an important consideration in the treatment protocol. This type of scar is formed during at least one year, and in that year, the scar can show decreased contractures along with flattening, softening, and repigmentation (Reish and Eriksson 2008). Thus, surgical excision might not be needed, even though postexcisional recurrence rates of the original hypertrophic scar are usually low (Leventhal et al. 2006).

In contrast, recurrence rates of keloids after excision range between 45 and 100%, and surgical removal is not recommended as monotherapy (Mustoe et al. 2002). Excising the abnormal keloid tissue creates a new wound where new collagen forms; unfortunately, a larger and more aggressive keloid can recur in its place (Robles and Berg 2007).

Surgical excision of keloid should be avoided. Sometimes surgery can be used to treat keloids in order to reduce keloid mass (remove infected regions and provide symptomatic improvement) (Ogawa 2010).

The recurrence rate is lower than other treatment modalities between 8% and 50% (Butler et al. 2008). Adjuvant therapy for surgical intervention for keloids can be the preoperative and/or postoperative use of intralesional corticosteroids, pressure therapy, IFN injections, and radiation therapy; these combinations all have shown promising results (Vivas et al. 2012).

Lasers

Lasers were first used to treat hypertrophic scars and keloids in the mid-1980s (Apfelberg et al. 1984), and various lasers have been evaluated with varied success. Current data are difficult to compare due to different laser systems, too small case numbers, too short follow-up periods, lack of information on the scars' age and activity, and lack of differentiation between hypertrophic scar and keloids.

The first lasers used were ablative (i.e., causing tissue vaporization), nonselective lasers and comprised the carbon dioxide (CO^2) or erbium:yttrium-aluminium-garnet (Er:YAG) laser. CO^2 lasers emit light at a wavelength of 10,600 nm, which is strongly absorbed by water in the tissue, producing vaporization (Vivas et al. 2012). In hypertrophic scars and keloids, the CO^2 laser causes focal necrosis, which leads to collagen remodeling and lesion contraction (Lee et al. 2005). The CO^2 laser may be used as monotherapy, but a recurrence rate as high as 90% has been

reported (Apfelberg et al. 1989). Optimal treatment occurs when used in combination with intralesional corticosteroids (Garg et al. 2011). Adverse events associated with the CO^2 laser not only include erythema, reversible hyperpigmentation, and permanent hypopigmentation, but they also can be significant, including major burns (Tziotzios et al. 2012).

The Er:YAG laser emits infrared light at a wavelength of 2940 nm and is more strongly absorbed by water than the CO^2 laser (Vivas et al. 2012). A randomized clinical trial found the Er:YAG laser to be effective in improving the elevation and vascularity of hypertrophic scars, with fewer side effects than the CO^2 laser (Omranifard and Rasti 2007).

The use of the long-pulsed 1064-nm Nd:YAG laser, which selectively inhibits collagen production based on in vivo and in vitro studies, in the beginning demonstrated softening and flattening of keloids (Sherman and Rosenfeld 1988; Cho et al. 2010). Studies have shown that Nd:YAG laser treatments can significantly reduce the size, normalization in color, and improvements in scars' flexibility (Kumar et al. 2000; Koike et al. 2014). Results, however, were transient and scar recurrences were common. Side effects were mild and included a prickling sensation during treatment and post-treatment erythema (Cho et al. 2010). Nevertheless, more studies are necessary to elucidate the effect of an Nd:YAG laser to treat hypertrophic scars and keloids.

Until today, the most encouraging results have been obtained with the 585-nm pulsed dye laser (PDL), which has been recognized as an excellent and safe therapeutic option for the treatment of younger hypertrophic scars and primarily keloids (Alster and Handrick 2000). Research studies since the mid-1990s have shown evidence of improvement in scar erythema, texture, height, pliability, and associated symptoms using the flashlamp-pumped 585-nm PDL for treating both hypertrophic scars and keloids, with low recurrence rates and a low adverse effect profile. Several theories have been proposed on the mechanisms by which this laser achieves clinical effects. By causing tissue hypoxia via destroying blood vessels, the 585-nm PDL therapy is believed to induce neocollagenesis, collagen fiber heating with disruption of disulfide bonds, resulting in reorganization and realignment of collagen fibrils (Alster 2003; Alster and Williams 1995). Irradiation with the flashlamp-pumped 585-nm PDL may also affect collagen remodeling through cytokine stimulation and reduce extracellular matrix expression by reducing transforming growth factor β1. Adverse effects include transient hyper- or hypopigmentation and blistering. The PDL method carries a low risk of side effects when used at appropriate treatment parameters and time intervals (Lupton and Alster 2002). The most common adverse side effect of 585-nm PDL treatment is postoperative purpura, which can persist for 7–10 days (Gauglitz et al. 2011).

The recommended protocol for the treatment of hypertrophic scars and keloids with the 585-nm PDL is the use of nonoverlapping laser pulses at fluences ranging from 6.0 to 7.5 J/cm 2 (spot size 5–7 mm) or 4.5 to 5.5 J/cm 2 (spot size 10 mm) (Tanzi and Alster 2004). Lower fluences should be applied at initial treatment sessions, with upward adjustments. Two to six treatments may be necessary to improve scar resolution successfully (Alster and Handrick 2000).

Onion Extract

Onion extract is found and available in numerous over the counter scar treatment products. It is currently believed that the flavonoids (quercetin and kaempferol) in onion extract play the leading role in reducing scar formation (Gauglitz 2013). This "botanical" ingredient exhibited anti-inflammatory, bacteriostatic, and collagen down-regulatory properties in a rabbit ear model (Saulis et al. 2002), but the results are controversial in humans. Quercetin, a dietary bioflavonoid, has been recently shown to inhibit fibroblast proliferation, collagen production, and contraction of keloid and hypertrophic scar-derived fibroblasts (Gauglitz et al. 2011). Several studies compare the effect of onion extract with placebo or compare products with onion as adjuvant therapy, with different, often contradictory results (Koc

et al. 2008; Hosnuter et al. 2007). Onion extract's role remains questionable, but overall well tolerated and maybe most useful when used in combination with other therapies. In published German guidelines on scarring, this kind of creams with onion extract can be considered additional therapy for active hypertrophic scars and postsurgical prophylaxis (Nast et al. 2012).

Imiquimod

Imiquimod is a topical immune response modulator and is approved to treat basal cell carcinomas, actinic keratoses, and genital warts (Martin-García and Busquets 2005). Imiquimod stimulates IFN alfa, a proinflammatory cytokine, which increases collagen breakdown. Therefore, imiquimod 5% cream has been used after excision in an attempt to reduce keloid recurrence, and it was reported to have positive effects on the recurrence rate of keloids (Berman and Kaufman 2002). However, there are contradictory data in other studies (Cação et al. 2009), so additional investigations with larger sample size and longer follow-up are necessary to determine the role of imiquimod 5% cream in hypertrophic scar therapy (Shin et al. 2017).

Botulinum Toxin

Botulinum Toxin Type A (BoNT-A) is a potent neurotoxin that is produced by a gram-positive bacteria clostridium botulinum. In recent years, its use has grown in both esthetic and dermatological indications. The theory of using Botulinum toxin A for treating pathological scars was published in 2000 (Gassner et al. 2000). Until now, the exact mechanism of action is not yet understood, but it has been shown that Botulinum Toxin type A acts on wound tension, on collagen and fibroblasts (Lm et al. 2019). When injected locally, BoNT-A causes temporary paralysis on the wound edges, minimizing tension vectors on the edges until collagen could mature. Also, it acts by distributing fibroblasts into a less proliferative state (Berman et al. 2017).

There are many studies where intralesional botulinum is used to treat hypertrophic scars and keloids with different results (Shaarawy et al. 2015; Zhibo and Miaobo 2009; Xiao et al. 2009; Gauglitz et al. 2012).

Considering the cost of treatment, the absence of application protocols (dosage and rhythm), and the still unclear mechanism of action, this therapeutic modality cannot yet be included in the standard procedure for treating pathological scars.

Combination Therapy

Numerous therapeutic strategies have been described to prevent and reduce hypertrophic scars and keloids, but none of the treatments is effective in all patients. No universal consensus in the treatment regimen has been established, and there is limited evidence-based literature to guide the correct management. There is a great need for additional clinical studies, well-designed, double-blind, placebo-controlled, and randomized with the objective and standardized evaluative measures. A polytherapeutic approach to the treatment of abnormal scars has the best chance to help, and the right combination of treatments designed for each individual patient is the goal of every therapist.

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