PREVENTION AND CURATIVE MANAGEMENT OF HYPERTROPHIC SCAR FORMATION
ABSTRACT

Although hypertrophic scarring commonly occurs following burns, many aspects such as incidence of and optimal treatment for scar hypertrophy remain unclear. This review will focus on hypertrophic scar formation after burns in particular, exploring multiple treatment options and describing their properties as well as their effectiveness. To evaluate treatment efficacy and scar development, clinical scar assessment is of eminent importance. Recommendations regarding the classification of hypertrophy in the daily practice and in clinical trials are implemented in this review.
1. INTRODUCTION

Hypertrophic scarring following surgical procedures, trauma and especially burns is a great concern for patients and a challenging problem for clinicians. Peacock defined hypertrophic scarring as a scar raised above the skin level that stays within the confines of the original lesion. Hypertrophic scars may cause significant functional and cosmetic impairment, symptoms of pruritus and pain, which are all responsible for a decrease in quality of life. Hypertrophic scars result from general failure of normal wound healing processes. After burn injury they typically appear on the trunk and extremities. Frequently, hypertrophic scars are misdiagnosed as keloids. Their gross appearance is similar, although keloids proliferate or originate beyond wound margin. Furthermore, a hypertrophic scar typically decreases in size over time as opposed to keloid, which may have phases of reactivation and enlargement. The occurrence of keloid scars after burns is less common.

In the developed world four million patients acquire scars as a result of burns each year and the incidence is even greater in the developing world. Previous studies reported diverging incidences of hypertrophic scarring. Incidence rates vary from 40% to 94% following surgery and from 30% up to 91% following burns. Explanations for the wide spread in incidence are numerous, but an inadequate scar evaluation seems to be the most likely cause.

Hypertrophic scars usually develop within one to three months after injury, in contrast with keloid scars that may appear up to 12 months after injury. Many factors such as race, age, genetic factors, hormone levels, atopy and immunologic responses of the individual patient appear to play a role. The type of injury, wound size and depth, anatomic region and mechanical tension on the wound are important as well. Also, complicating factors such as bacterial colonization and infection of the wound seem to induce hypertrophic scarring. To predict the development of a hypertrophic scar in a burn wound, the time to heal is the most important factor and is closely related to depth and size of the wound. Unfortunately, in the majority of the published reports these factors are not defined accurately and only a few authors have used validated criteria or a classification to define hypertrophic scarring. Incidence percentages are shown in Tables 1 and 2, however the limitations discussed above should be taken into consideration.

2. SCAR EVALUATION

For the assessment of (hypertrophic) scars various tools are currently available. The Vancouver Scar Scale (VSS) (Figure 1) is a validated subjective scale scored by the provided. An important disadvantage of the VSS is that not all parameters are equal in weight; e.g. pliability has a 5-number score, whereas the others can value from 0 to 3. This means that the numbers cannot be simply added to calculate a total score. Another subjective and valid scale, the Patient and Observer Assessment
Table 1. Hypertrophic scarring rates after burn injury in adults.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gangemi et al.108 2008</td>
<td>703 Patients</td>
<td>Up to 12 years</td>
<td>72%</td>
<td>+ Treatment and patient characteristics described</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Classification for scar is used</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Race not documented</td>
</tr>
<tr>
<td>Bombaro et al.17 2003</td>
<td>30 Patients</td>
<td>1-2 Years</td>
<td>0%</td>
<td>- Race, depth and definition of hypertrophic scar not described</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Time of healing and follow-up period, treatment not mentioned</td>
</tr>
<tr>
<td>Bombaro et al.17 2003</td>
<td>73 Adults</td>
<td>-</td>
<td>75% In non-white</td>
<td>+ Race documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Depth, time of healing and follow-up period, treatment not mentioned</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63% In white</td>
<td>- Race documented</td>
</tr>
<tr>
<td>Lewis et al.12 1990</td>
<td>58 Chinese patients</td>
<td>3-9 Months</td>
<td>91,4%</td>
<td>+ Scale is used for definition of hypertrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Only Chinese patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Depth, age and treatment not mentioned</td>
</tr>
<tr>
<td>McDonald and Deitch187</td>
<td>113 Burn sites in adults</td>
<td>1 Year</td>
<td>25% In black</td>
<td>+ Only grafted wounds included</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Race, age and time of healing are described</td>
</tr>
<tr>
<td>Deitch et al.22 1983</td>
<td>121 Burn sites in 41 adults</td>
<td>9-24 Months</td>
<td>30% In black</td>
<td>+ Only superficial or moderate partial thickness depth burns included,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>all not grafted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Treatment and time of healing are well described</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16% In white</td>
<td>- No exclusion of keloids</td>
</tr>
</tbody>
</table>

Scale (POSAS) (Figure 2), consists of a patient and an observer part to evaluate the scar.28,29 Besides the use of an assessment scale to define hypertrophic scarring, we now believe that the area of elevation in a burn scar is also of significance. Particularly in clinical trials, it is of interest to document which percentage of the originally treated wound surface has become hypertrophic. Objective measurements for the analysis of hypertrophy are scarce. Reports have been published on the use of negative impressions of the scar, ultrasound images, laser Doppler flow, color measurements and three-dimensional systems for the analysis of hypertrophy.25,30,31

Although management of hypertrophic scars has advanced in the past years, the lesions remain difficult to prevent and treat. Thereby, hypertrophic scars after burns require a special approach as the scars are often not linear, but widespread.24 Extensive research has lead to an increase of knowledge in the pathophysiologic processes of wound healing and the formation of scars, but still there is no consensus regarding the best treatment to reduce or prevent hypertrophic scarring. Recurrences remain common and satisfaction of patients is variable.24 In this review various treatment methods to prevent and treat hypertrophic burn scars, will be reviewed.
Table 2. Hypertrophic scarring rates after burn injury in children.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubison et al.23 2006 retrospective</td>
<td>170 Children</td>
<td>4 Months</td>
<td>74% Wounds healed</td>
<td>+ Distinction grafted and spontaneous healed wounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>spontaneous</td>
<td>+ Time of healing and follow-up period documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57% Wounds</td>
<td>- Race and depth not mentioned</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>grafted</td>
<td></td>
</tr>
<tr>
<td>Bombaro et al.17 2003 retrospective</td>
<td>13 Children &lt;15</td>
<td>100% In</td>
<td>75% In non-white</td>
<td>+ Race documented</td>
</tr>
<tr>
<td></td>
<td>years of age</td>
<td>non-white</td>
<td></td>
<td>- Depth, follow-up period, time of healing and treatement not mentioned</td>
</tr>
<tr>
<td>Spurr and Shakespeare14 1990 retrospective</td>
<td>152 Children</td>
<td>51% In</td>
<td>63% In 1968</td>
<td>- No distinction spontaneous healed and grafted wounds</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 years of age</td>
<td>1968</td>
<td>1984</td>
<td>- Follow-up period and race not mentioned</td>
</tr>
<tr>
<td>McDonald et al.89 1987 prospective</td>
<td>60 Burn sites in</td>
<td>57% In</td>
<td>31% In white</td>
<td>+ Only grafted wounds included</td>
</tr>
<tr>
<td></td>
<td>? children &lt;14</td>
<td>black</td>
<td>white</td>
<td>+ Race, age and time of healing are described</td>
</tr>
<tr>
<td></td>
<td>years of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deitch et al.22 1983 retrospective</td>
<td>124 Burn sites</td>
<td>31% In</td>
<td>13% In white</td>
<td>+ Only superficial or moderate partial thickness depth burns included,</td>
</tr>
<tr>
<td></td>
<td>in 59 children</td>
<td>black</td>
<td>white</td>
<td>all not grafted</td>
</tr>
<tr>
<td></td>
<td>&lt; 14 years of</td>
<td></td>
<td></td>
<td>+ Treatment and time of healing are well described</td>
</tr>
<tr>
<td></td>
<td>age</td>
<td></td>
<td></td>
<td>- No exclusion of keloids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-24 Months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Vascularity
- Normal: 0
- Pink: 1
- Red: 2
- Purple: 3

2. Pigmentation
- Normal: 0
- Hypopigmentation: 1
- Mixed: 2
- Hyperpigmentation: 3

3. Pliability
- Normal: 0
- Supple: 1
- Yielding: 2
- Firm: 3
- Ropes: 4
- Contracture: 5

4. Height
- Flat: 0
- < 2 mm: 1
- 2-5 mm: 2
- > 5 mm: 3

Figure 1. Vancouver Scar Scale26 modified according to Baryza and Baryza27.
### Figure 2. Patient and Observer Scar Assessment Scale. A, The Observer scale. B, The Patient scale.
3. PREVENTIVE MANAGEMENT

Optimal treatment of the burn wound is of eminent importance for wound healing and the prevention of hypertrophic scar formation. Deitch et al. demonstrated that wound closure should be achieved within three weeks to reduce the risk for hypertrophic scar development\textsuperscript{22}. Timing of grafting is still under debate, both for survival of the patients as well as the quality of the outcome with respect to hypertrophy. Adequate topical wound treatment allows for wound healing with controlled inflammation and should be applied to obtain fast wound closure.

The autologous split thickness skin graft is still the mainstay of burn wound surgery. Although autologous split thickness skin graft may result in faster wound closure, it may not prevent hypertrophic scar formation in the operated area.

In the long term, mesh grafts frequently can be recognized by the former interstices of the mesh where generally more hypertrophy is observed. The use of sheet grafts or mesh grafts with a small expansion ratio is therefore advocated to obtain superior functional and cosmetic results\textsuperscript{32,33}. Thickness of the split thickness skin graft is still subject of discussion. Both very thin (0.008 inch) and very thick (0.025 inch) split thickness skin grafts are associated with hypertrophic scarring\textsuperscript{34}. In the last decades, the survival of the burn patient has increased significantly, necessitating further development of methods for skin resurfacing. This has lead to the development of skin substitutes. Initially, most attention was focused on the epidermal replacement by cultured autologous keratinocytes\textsuperscript{35}. Later, more and more attention was focused on the role of dermal substitutes in wound resurfacing, specifically with respect to improvement of the quality of the scar and with that scar hypertrophy. Nowadays, dermal substitutes are considered to play a more prominent role in burn surgery and have shown to minimize hypertrophic scarring, contractures and increase scar elasticity in acute burn wounds\textsuperscript{36-38}. More studies on tissue engineering and skin substitution may result in more evidence and support for long-term clinical effectiveness. Besides methods for wound closure, corticosteroids, silicone and pressure therapy can also play an important role in the prevention of hypertrophic burn scars and will now be described.

3.1 Silicone

In 1982 the use of silicone materials in the treatment of hypertrophic burn scars was first described by Perkins et al.\textsuperscript{39}. Since then, many authors reported silicone as the key in noninvasive scar management, because it improves the appearance and reduces complaints of the scars, it is easy to apply and painless\textsuperscript{9,24,40-42}. Silicone can be used as rubber, gel or fluid\textsuperscript{16}. Numerous types of silicone products have been produced, such as silicone gel sheeting or silicone-filled cushions. Currently, product development has been focused on silicone gel, because it is easier to apply, can be used on more areas of the body and gives a higher patient compliance\textsuperscript{43}. Several studies have shown the efficacy of silicone gel sheeting in the prevention of hypertrophic scars\textsuperscript{16,41,44}, although the contrary has been described as well\textsuperscript{45}. It appears that it is important that the application starts from the second week at least until the third month of the
postoperative period. The exact mechanism of action of silicone in the prevention and management of hypertrophic scars is unclear, although it is likely to influence the collagen remodeling phase of wound healing. Potential mechanisms are summarized in Table 3.

It is recommended to wear silicone sheeting 12–24 hours a day for at least 2–3 months. Daily cleaning of the material and underlying skin is necessary to prevent irritation and heat rash. Other side effects of silicone are skin maceration and itching.

### 3.2 Pressure therapy

Mechanical compressive force by pressure garments to treat hypertrophic scars in burn patients was already described in 1860. It was only until the 1960s that this treatment became standard in several burn centers to accelerate the remodeling process.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydration</strong></td>
<td>Hydration can be caused by the occlusion of the underlying skin. It decreases capillary activity and collagen production, through inhibition of the proliferation of fibroblasts.</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td>A rise in temperature increases collagenase activity and therefore silicone reduces hypertrophic scars by breaking down collagen.</td>
</tr>
<tr>
<td><strong>Polarization</strong></td>
<td>The negative charge within silicone causes polarization of the scar tissue, resulting in involution of the scar.</td>
</tr>
<tr>
<td><strong>Silicone oil</strong></td>
<td>PRO: The presence of silicone has been detected in the stratum corneum of skin exposed to silicone. CON: Other researchers suggest the effects are not likely to be due to silicone release, as other occlusive products without silicone have also shown good results.</td>
</tr>
<tr>
<td><strong>Oxygen tension</strong></td>
<td>PRO: After silicone treatment the hydrated stratum corneum is more permeable to oxygen and thus oxygen tension in the epidermis and upper dermis rises. Increased oxygen tension will inhibit the “hypoxia signal” from this tissue. Hypoxia is a stimulus to angiogenesis and tissue growth in wound healing, as a consequence removing the hypoxia stops new tissue growth. CON: The contrary has also been described.</td>
</tr>
<tr>
<td><strong>Mast cells</strong></td>
<td>PRO: Some reports have suggested that silicone has influence on the number of mast cells in hypertrophic scar tissue. A higher number of mast cells in hypertrophic scars compared to normal scars has been reported in several studies. An increased number of mast cells was found in keloid and hypertrophic scars treated with silicone and it was suggested that silicone results in an increase of mast cells in the cellular matrix of the scar with subsequent accelerated remodeling of the tissue. CON: Some studies have reported no difference of the number of mast cells in hypertrophic scars compared to normal scars.</td>
</tr>
<tr>
<td><strong>Blood flow and pressure effect</strong></td>
<td>Beneficial effects of silicone are not mediated by changes in blood flow or a pressure effect.</td>
</tr>
</tbody>
</table>
phase of wound healing. Prophylactic pressure is recommended in burn patients if spontaneous closure of the wound takes longer than 10–14 days or those requiring grafting.

Pressure therapy is thought to have an effect on the collagen remodeling phase of wound healing. Several mechanisms of action have been described and are shown in Table 4. As soon as the wounds are fully closed and able to tolerate pressure, patients are fitted with pressure garments. Garments must be worn for at least 23 h a day until the scar is mature. The required amount of pressure lies between 24 and 40 mmHg. A significant difference was reported regarding thickness of burn scars that were preventively treated with garments with a mean value of 15 mmHg pressure compared with a mean pressure of 10 mmHg. A shortcoming of pressure garments is the difficulty to use them for scars in anatomical flexures and areas of high movement. Moreover, treatment is expensive as garments are custom-made and must be replaced regularly. Furthermore, they can be uncomfortable to wear and they have a poor appearance, which brings low patient compliance.

Table 4. Possible mechanisms of action in pressure therapy.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration</td>
<td>PRO: Decreased scar hydration results in mast cell stabilization and a subsequent decrease in neovascularization and extracellular matrix production.</td>
</tr>
<tr>
<td></td>
<td>CON: This hypothesis is in contrast with a mechanism of action of silicon, in which an increase of mast cells causes scar maturation.</td>
</tr>
<tr>
<td>Blood flow</td>
<td>1. A decrease in blood flow causes a decrease in α2-macroglobulin and a subsequent increase in collagenase mediated collagen breakdown, normally inhibited by α2-macroglobulin.</td>
</tr>
<tr>
<td></td>
<td>2. A decrease in blood flow causes excessive hypoxia resulting in fibroblast degeneration and decreased levels of chondroitin-4-sulfate, with a subsequent increase in collagen degradation. Hypoxia would also loosen the collagen fibrils aligned to the skin surface.</td>
</tr>
<tr>
<td>Prostaglandine E2 release</td>
<td>Induction of prostaglandine E2 release, which can block fibroblast proliferation as well as collagen production.</td>
</tr>
</tbody>
</table>

3.3 Corticosteroids

Intraleosional injection of corticosteroids is a second-line prophylaxis for patients with severe burns. Prevention of hypertrophic scarring by the use of corticosteroids is not frequently used as there are often large surfaces to deal with and it is not known whether or not the scars will become hypertrophic.

Corticosteroids can reduce scar formation by affecting the collagen remodeling and inflammation phase of wound healing. Various explanations are described in Table 5. Steroid injections can be commenced at one month postoperative and can be repeated monthly with reassessments of the scar condition. Disadvantages of this treatment are the burning sensation caused by the injections (in spite of the use of
anesthesia), skin atrophy, depigmentation, telangiectasias and the required long-term follow-up.

4. CURATIVE MANAGEMENT

4.1 Silicone
Silicone can be used to prevent hypertrophic scar formation, but it is also a recognized therapy to treat these scars. Several clinical controlled and randomized studies have proven the effectiveness of silicone gel sheeting in hypertrophic scar management. However, not all clinical studies showed good results, possibly due to the fact that treatment and control areas were adjacent, the possible overlapping of the silicone sheet or the immaturity of the scars which could have improved with or without treatment. Recently, a comparative study was published in which the efficacy of silicone sheeting, silicone gel and a combination were evaluated and compared with an untreated control area in hypertrophic scars resulting from laser exfoliation. Only scars that were still in the erythematous and raised stage of healing, were included. Treated scars showed statistically significant improvement (elevation, erythema, pliability and symptoms of pain, burning and itching) compared with untreated control scars. Scars treated with silicone gel also showed less elevation compared with the scars following treatment with silicone sheeting. In a comparative study between the use of silicone gel filled cushions and silicone sheets or gel in the treatment of hypertrophic and keloid scars, improvement was found in both treatments. However, scars treated with silicone cushions obtained a superior and faster response in 100% of the scars. It is recommended to apply silicone gel twice daily or to wear silicone gel sheeting 12–24 hours per day for 6–12 months with temporary interruption when adverse effects appear.

4.2 Pressure therapy
At present, pressure therapy is a preferred method for conservative management of scars, especially in treating hypertrophic burn scars, to increase thinning and improve pliability of the scars. Clinical effectiveness has never been scientifically proven, although previous authors claim to have achieved success rates of 60–85%. Treatment is most effective when the scar is still active. Therefore, it loses some efficacy after

| Hypothesis                                                                 | 1. Decrease of fibroblast proliferation and therefore collagen synthesis. 
|                                                                          | 2. Vasoconstriction responsible for a reduction of oxygen and nutrient supply to the wound. 
|                                                                          | 3. Activation of endogenous collagenase. 
|                                                                          | 4. Suppression of inflammatory mediators such as TGF-β and the inhibition of leucocyte and monocyte migration as well as phagocytosis.
6 months\textsuperscript{51}. It is recommended to be worn for 18–24 hours a day with a pressure between 24 and 40 mmHg until the scar matures\textsuperscript{24,47-49}. Early release of the garments tends to be followed by rebound hypertrophy\textsuperscript{18}.

### 4.3 Corticosteroids

Intralesional corticosteroid injection is a possible approach to reduce hypertrophic scars. Rates of response vary from 50–100\% with a recurrence rate of 9–50\%\textsuperscript{18,56}. Injections may be used alone or in combination with other therapies\textsuperscript{57-59}. For instance, Mustoe et al. emphasize the combination of silicone gel sheeting and intralesional corticosteroids in the treatment of hypertrophic scars\textsuperscript{24}. A combination of intralesional corticosteroids with pulsed dye laser treatment (PDL) did not improve the hypertrophic scars\textsuperscript{59}.

Steroids, most commonly triamcinolone acetonide 10–40 mg/mL\textsuperscript{18,24,47,49}, can be injected intralesionally at 4–6 week intervals\textsuperscript{6}. The maximum dose is 1 mg (=0.1 mL of 10 mg/mL) per injection with at least 1 cm between injection sites. The maximum amount of injections is not known, although the authors of this review find the total dosage should not exceed 30–40 mg. This means the maximum treatable scar surface is approximately 40 cm\textsuperscript{2}. Therefore, one should realize that this therapy is not suitable for extensive burn scars. Steroids can also be administered topically, however, due to poor tissue absorption, it is likely to be effective in relatively superficial lesions only\textsuperscript{6,47}.

### 4.4 Laser therapy

In scar management the use of lasers has become more important. When the first carbon dioxide and argon lasers were used in the treatment of hypertrophic scars, recurrence rates of 90\% and higher were seen\textsuperscript{18,24,60}. In combination with corticosteroid injections outcomes improved, although recurrence rates remained 16–74\%\textsuperscript{18,61}. In the past decade, improvement of postsurgical hypertrophic scars in 57–83\% of the cases has been described after treatment with flashlamp-pumped PDL, which targets oxyhemoglobin\textsuperscript{57,59,62}. Various authors have reported the effectiveness of PDL in the treatment of hypertrophic scarring, both post-surgically as post-burn\textsuperscript{63-65}, and in combination with intralesional corticosteroids\textsuperscript{57,59}. Not all results are positive though. Wittenberg et al. reported no difference in outcome of hypertrophic scars treated with the 595-nm PDL and the control sections in a single-blind randomized controlled study\textsuperscript{53}. In this study, patients received four laser treatments at 8 week intervals.

The mechanism by which laser achieves improved clinical outcome is still unclear. It probably influences the collagen remodeling phase and/or the angiogenesis (Table 6). One to six treatment sessions at 4–8-week intervals have been reported as most effective\textsuperscript{67,53,57,64}. Wavelength (optimally close to the oxyhemoglobin absorption peak 542 nm), fluence (range of 3.5–7.5 J/cm\textsuperscript{2}) and adjunctive therapies (e.g. corticosteroids, 5-fluorouracil) are parameters that affect outcome of this treatment\textsuperscript{66,67}. Minimal side effects and treatment discomfort have been reported\textsuperscript{59,63}. Temporary purpura, hypo- and hyperpigmentation are the most common adverse effects\textsuperscript{64,68}. 


Cryotherapy, freezing scar tissue, is used as a monotherapy for hypertrophic and keloid scars as well as in combination with other treatments, such as intralesional corticosteroids. A good response in 76% of the patients with hypertrophic scars without recurrence during 32 months of follow-up has been shown. Additionally, over 50% scar volume reduction was reported after one intralesional treatment in hypertrophic scars and keloids, without recurrence during 18 months of follow-up.

Cryotherapy is thought to influence the collagen remodeling phase of wound healing, which is further described in Table 6. For good results, up to 20 treatment sessions are needed. Cryotherapy may be less desirable to patients than other treatments, because of the resulting pain, skin atrophy and hypopigmentation, especially with the use of surface techniques (e.g. contact and spray probes) and because of the high frequency of treatment. Intralesional cryotherapy by use of a cryoprobe causes less damage of the epithelium and maximizes cell destruction deep in the lesion.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Hypothesis</th>
</tr>
</thead>
</table>
| Laser       | Light energy emitted from the majority of the lasers is absorbed by hemoglobin, generating heat and leading to damage of the microvasculature. This results in hypoxia which leads to 1. collagen fiber heating and subsequent alignment, and 2. histamine release which influences fibroblast activity, possibly due to mast cell activation. It was also reported that a 585-nm PD laser can decrease fibroblast proliferation and collagen type III deposition.
| Cryotherapy | The freezing of cryotherapy induces ischemic damage of the microcirculation. As a result the cellular destruction and anoxia promotes shrinkage of the hypertrophic scar tissue. A tendency to normalization of the collagen structure after treatment in hypertrophic burn scars suggests recovery of normal collagen synthesis.
| Interferon  | Interferon causes a decrease of the synthesis of collagen type I and III by fibroblasts and an increase of collagenase activity. Biopsies of hypertrophic burn scars treated with systemic interferon-alpha 2b showed a decreased number of fibroblasts compared to biopsies of immature burn scars and normotrophic scars. A reduction in serum transforming growth factor (TGF)-β concentration could also play a role in scar reduction. Thereby, it was suggested that improvement of hypertrophic scars after injection is associated with induction of myofibroblast apoptosis. Most recently, it was reported that improvement of hypertrophic burn scars after treatment with interferon-alpha 2b is associated with decreased numbers and activity of fibrocytes.
| 5-Fluorouracil | It inhibits rapidly proliferating cells, such as fibroblasts, by blocking DNA synthesis and transcription.

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4.6 Radiation

Radiation for the treatment of hypertrophic scars has not been described frequently, in contrast to the application in keloids in which especially brachytherapy is successful.
Most likely, this is due to lack of efficacy in hypertrophic scars and the serious adverse effects. Therefore, it will not be discussed in this review.

4.7 Surgery

Many aspects of surgery for hypertrophic scarring have been debated. The decision to operate on hypertrophic scars is based on many parameters such as age of the scar, location, surface area, cause, irresponsiveness to conservative treatments, opinion and expectations of the patient, as well as opinion and expertise of the surgeon. The scar should be critically evaluated for its appearance, as hypertrophic scars are frequently misdiagnosed as keloids. The recurrence rate of keloid scars that have been excised is high (45–100%)\textsuperscript{6,24,71}. Gentle handling of the tissue, removal of residual inflammatory tissue, and reorientation of scars within the lines of minimal tension should be considered as surgical dogmas\textsuperscript{6,18}.

Small hypertrophic scars can be excised and the defect should be closed primarily. Both intra- and extralesional excision of the scar has been advocated. In larger surface areas of hypertrophic scarring excision may be considered, but adequate closure of the defect should be provided. Healthy skin that surrounds the hypertrophic scar may be utilized to cover the defect. Surgery by means of tension releasing Z-plasties has proven to be effective in reducing scar hypertrophy, as one of the main effects of Z-plasty is to convert the direction of the scar from vertical to parallel to the lines of minimal tension\textsuperscript{56}. Tissue expansion and (local pedicled or free) flaps are also commonly applied solutions. The use of dermal substitutes in reconstructive surgery has increased the surgical armamentarium and has been shown to improve the outcome of wound healing. Improvement in scar quality (i.e. elasticity and hypertrophy) has been found with the use of dermal substitutes in reconstructive and acute burn wounds\textsuperscript{32,38,72,73}. The dermal replacement serves as a temporary matrix for the ingrowth of fibroblasts, macrophages, lymphocytes and endothelial cells\textsuperscript{38} and is thought to guide the cells to deposit collagen in a more randomized fashion, comparable with normal skin. Additionally, it is hypothesized that the substitute bridges the interstices of the autograft. It replaces the dermis of the graft which is otherwise lacking in the gaps and consequently prevents hypertrophy\textsuperscript{12}. Due to the high recurrence rate of hypertrophy after surgery, compression therapy, silicone application, intralesional corticosteroids or radiation is recommended following excision\textsuperscript{6,18,49}.

5. NEW DEVELOPMENTS

5.1 Interferon

Interferons are naturally occurring antifibrotic cytokines that are reported to have beneficial therapeutical effect in abnormal scars. Tredget et al. showed a significant improvement of hypertrophic burn scars in 78% of the patients after interferon therapy\textsuperscript{74}. Explanations for the effects of interferon are shown in Table 6. Adverse effects of interferon therapy include flu-like symptoms and pain on injection\textsuperscript{6,11}.
5.2 5-Fluorouracil

5-Fluorouracil is a pyrimidine analogue with antimetabolite activity\textsuperscript{75}, which has been used against many malignancies\textsuperscript{47}. The experience and several case reports of 5-fluorouracil in hypertrophic (burn) scars were described, as well as the therapy in combination with corticosteroid injections and PDL therapy\textsuperscript{58}. Rarely a hypertrophic scar did not respond favorable and recurrence did not occur. Furthermore, significant clinical improvement (scar height, erythema and pliability) was seen in the monotreatment of hypertrophic scars with 5-fluorouracil\textsuperscript{57}. 5-Fluorouracil probably affects the collagen remodeling phase (Table 6). Adverse effects of this treatment include pain, hyperpigmentation, wound ulceration, purpura at injection sites and tissue sloughing\textsuperscript{11,47,58}. An additional remark regarding 5-fluorouracil as well as interferon, is the utility for the treatment of extensive areas of burn scars, as systemic (side) effects may become more important.

5.3 Other therapies

Other experimental therapies include intralesional injection of bleomycin, onion extract/heparin gel, enalapril, basic fibroblast growth factor (FGF2) and the blockage of transforming growth factor (TGF-\textbeta{}).

Bleomycin is an antineoplastic agent and cytotoxic antibiotic that has been used successfully for many years in the treatment for recalcitrant plantar warts\textsuperscript{76}. The efficacy of intralesional bleomycin in the treatment of hypertrophic scars has been shown in several small studies; complete flattening of scars in 53.8–73.3\% of the patients was achieved, without recurrences\textsuperscript{76,77}. A possible hypothesis is the inhibition of collagen synthesis as a result of bleomycin\textsuperscript{77}.

Also onion extract/heparin gel has been used in the treatment of hypertrophic scars\textsuperscript{78,79}. In a comparative study of 107 patients, Ho et al. showed that scar development after surgery was less in onion extract/heparin gel treated scars than in untreated scars\textsuperscript{79}. The onion extract possesses fibroblast inhibiting properties, reducing fibroproliferative activity and the production of the extracellular matrix\textsuperscript{67}. Heparin may also play an important role as it interacts with collagen molecules\textsuperscript{78}. Unfortunately, heparin will also have systemic effects.

Iannello et al. described substantial improvement with the use of low-dose enalapril, an angiotensin-converting enzyme (ACE)-inhibitor, in two patients with postsurgical hypertrophic scars and keloids, within 1–6 months\textsuperscript{80}. It is suggested that the ACE is related to fibrous tissue formation and enalapril would therefore reduce scar mass\textsuperscript{80}.

FGF2 in burn wounds is suggested to be a mediator that is released from injury sites and plays an important role in early wound healing. In a comparative study, 20 patients with burn wounds were either treated with FGF2 solution or treated conservatively. Clinical evaluation of pigmentation, pliability, height and vascularity showed significant improved results in the FGF2 scars. The occurrence of hypertrophic scarring however, was not significantly less in patients receiving FGF2 treatment\textsuperscript{81}. In other reports, burn wounds treated with FGF2 were significantly less hard than burnwounds not treated with FGF2 and surgical wounds developed significantly less hypertrophy after the administration of FGF2\textsuperscript{82,83}.
During tissue remodeling TGF-β is expressed at high levels and significantly influences the formation of connective tissues. Especially TGF-β1 and 2, two of the three isotypes of TGF-β, have been identified as key players in hypertrophic scar formation\textsuperscript{84–86}. A new treatment option for hypertrophic scars is the blockade of TGF-β1 and 2 by use of anti-TGF-β1 and 2 monoclonal antibodies and/or administration of TGF-β3, which target the fibroblasts. The effects of the antibodies in rabbit wounds were studied and a reduction in scar hypertrophy was found when antibodies were injected one week after wounding\textsuperscript{87}. Another option is the inhibition of TGF-β receptor II-mediated signaling, which has been reported to reduce hypertrophic scars in a rabbit cutaneous model\textsuperscript{88}. Treatment options and recommendations are summarized in Figure 3.

6. CONCLUSION

Research into the biological nature of the scar has lead to an increased understanding of mechanisms in hypertrophic scar formation, resulting in the development of more specific therapeutic options. Unfortunately, hypertrophic scars remain difficult to treat. In this review, multiple therapies and studies have been discussed. A great deal of the published studies to determine incidence of hypertrophic scarring or to assess the efficacy of a treatment, have shortcomings. Additionally, the differences in study designs makes evaluating and comparing therapies difficult. It is of importance that a consensus concerning the definition of a hypertrophic scar, according to an assessment tool, will be developed and internationally used. Our recommendation regarding hypertrophic scarring in the daily practice is to classify and assess the scar by means of the VSS or POSAS, taking into account that the VSS is a more qualitative scale and the POSAS a more quantitative. Scars with a VSS height score of $>1$ or a POSAS thickness score of $\geq 3$, can be defined as hypertrophic. Regarding the assessment of scars in clinical trials, we recommend the use of the POSAS or VSS and additional documentation of the percentage of the original wound surface area that is involved. To determine the incidence of hypertrophic scarring or to assess treatment effectiveness, the following data should be taken into account: skin type, age, wound depth, time of healing, treatment, time of surgery, wound area and hypertrophic scar area (percentage of the original wound area with hypertrophy according to VSS and/or POSAS).

Additional research is required to determine best possible treatment. Since there is no optimum treatment option present-day, patient expectations, adverse effects and costs should be considered in order to determine the best treatment individually.
Figure 3. Treatment options and recommendations.

VSS, Vancouver Scar Scale; POSAS, Patient and Observer Scar Assessment Scale; TGB-β, transforming growth factor-β; FGF2, Basic fibroblast growth factor.
REFERENCES


101. Nedelec, B., Shankowsky, H., Scott, P.G., Ghahary, A. & Tredget, E.E. Myofibrob-


