Long-Term Sequelae of Burn Injury: Current Understanding of Pathophysiology, Therapeutic, and Rehabilitative Options with an Emphasis on Hypertrophic Scarring and Laser Therapy

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1 Introduction

The chances of survival after a major burn injury have constantly increased over the past decades and further decreases in mortality rates seem to be out of reach [1]. Recent data shows that 96.8% of all patients treated in a US burn center survive [2]. However, many survivors suffer from disfiguring scarring, life-long physical disabilities, and adjustment difficulties. Focus has shifted more and more attempts to improve long-term outcomes with recent advances in discovering underlying mechanisms, treatment of scars, and early rehabilitation.

In addition to recent improvements in burn care, another important aspect is prevention of burn injuries, especially in high-risk groups and vulnerable populations such as young children and adolescents, disabled, or the elderly [3]. Given the fact that 73% of all burn injuries that require burn center treatment occur at home [2], education of the public and of specific groups could help decrease the overall number of burn victims, and decrease the number of patients with major disabilities that are unlikely to be reintegrated into society and economy due to devastating long-term sequelae.

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This chapter focuses on the long-term outcomes after a severe burn injury. We emphasize one of the most relevant topics in burn rehabilitation: hypertrophic scarring, its treatment with laser therapy including practical guidance, and place them in context of the current literature.

2 Hypermetabolic Response and Long-Term Sequelae of Burn Injury on Organ Systems

2.1 Hypermetabolic Response to Burn Injury and Its Long-Term Effect on Muscle, Bone, and Glucose Metabolism

Severe burn injury leads to a **pathophysiological response** that affects almost every physiological system within the body. Hallmarks of that response are hypermetabolic stress (increased metabolic rate) with skeletal muscle catabolism (burn-induced muscle cachexia), and insulin resistance (stress-induced diabetes). This **hypermetabolic state** affects skeletal muscle-, bone-, glucose-, and lipid metabolism as well as the cardiovascular- and immune system and has been shown to persist for up to 3 years [4].

Muscle loss, strength, and cardiopulmonary capacity: After severe burn injury, skeletal muscle (depot of lean body mass) is the main endogenous source for amino acids that are required for production of acute phase proteins and wound healing. As a result, loss of lean body mass occurs after a major burn injury and aggressive nutritional support can only attenuate it partially [5]. This also has functional relevance since lean mass correlates directly with skeletal muscle function [6]. Muscle strength and cardiopulmonary exercise capacity are typically impaired in burned children and in adults compared to non-burned individuals for many years after the injury. Also pulmonary function has been shown to be reduced for up to 7 years after burn [7].

Bone: Severely burned children can be at an increased risk for fractures than their non-burned peers [8]. The exact mechanism that leads to reduced trabecular bone mass for at least 2 years after burn is not yet fully understood. However, resorptive cytokines, elevated endogenous glucocorticoid levels, oxidative stress, and immobilization seem to play an important role in mediating reduction of bone formation and bone resorption, with the result of bone net loss. It is also unclear if this leads to early osteoporosis later on [9].

Insulin resistance and glucose intolerance, and as a consequence hyperglycemia in the acute phase after burn contribute to poor wound healing, skin graft failure, and respiratory tract infections. In severely burned individuals, endogenous glucose production of the liver (central insulin resistance) is increased. At the same time, the ability to store glucose in skeletal muscle is reduced (peripheral insulin resistance). As a result, patients have abnormal high blood glucose levels that can last for up to 3 years after burn [10]. This exacerbates loss of lean body mass and patients might be at risk for developing diabetes.

Long-term effects of temporary hyperglycemia in burn patients are currently unknown; however, glucose levels are usually targeted to be in the range of 90–140 [11]. Treatment modalities for glucose level control are discussed in Sect. 3.1.

2.2 Cardiovascular Response

After a major burn injury, the reaction of the cardiovascular system is complex. The cardiac response to the altered sympathomimetic response of the beta-adrenergic system is problematic and leads to an imbalance of oxygen demand and supply [12]. Contractility is reduced directly after burn due to increased release of antidiuretic hormone (ADH) [13]. Circulating pro-inflammatory cytokines such as TNF-α are impacting intracellular calcium currents and thus account for inducing cardiomyocyte apoptosis and further decreasing myocardial contractility [14]. Furthermore, massive plasma losses after major burn are likely to lead to hypovolemia with hypoperfusion and subsequent central organ ischemia, including acute myocardial and renal ischemia [15]. Elevated pulmonary artery resis-

tance caused by inhalation injury or pulmonary edema typically lead to right ventricular dysfunction [16]. Overall, these mechanisms lead to impaired relaxation, contractility, and reduced compliance of mainly the left ventricle [17, 18]. Compensation for the resulting reduced cardiac output occurs by increasing the heart rate, leading to increased demands of oxygen further leading to bilateral cardiac dysfunction [17, 19, 20].

Cardiac dysfunction is not only a problem during the acute phase, but persists at least for 2 years after burn [21]. A more recent study found that adolescents and young adults who were burned as children demonstrate cardiac abnormalities as long as 12 years after burn. In particular, they found myocardial fibrosis, systolic and diastolic dysfunction, and reduced exercise capacity compared to a non-burned control group. These findings indicate that burn injury leads to tissue remodeling in the heart [22]. Ongoing research aims in discovering underlying mechanisms.

2.3 Effects on the Pulmonary System

Inhalation injury contributes substantially to mortality in burn patients [23]. The pathophysiologic changes in the acute phase are well studied; however, only a few long-term studies exist. Furthermore, comparison of outcomes and measurements remains difficult because burn injury itself affects muscle mass and function, while scarring can lead to reduction of chest wall elasticity. Additionally, a consensual grading system for inhalation injury has not been developed [24].

Lung injury and subsequent long-term outcomes may be attributed to different mechanisms: inhalation injury and inhaled toxins, long-term mechanical ventilation, the systemic inflammatory response syndrome (SIRS), hypermetabolism, pneumonia, or sepsis [25].

For at least 6 months after smoke inhalation injury, airways are hyperactive and bronchospastic, causing patients to develop a productive cough. Elevated levels of inflammatory cytokines are typically found in serum, but elevated levels can also be seen in bronchioalveolar lavage [26]. Both, obstructive, and restrictive patterns, either alone or in combination, can occur after a burn injury, whereas it is more frequent in patients with concomitant inhalation injury [27]. Peak oxygen uptake (VO_2 peak) and time to fatigue is reduced in severely burned patients when tested by an incremental exercise test 5 years after burn and compared to healthy controls [28]. Studies in severely burned children have shown that although they can reach the same endurance levels as their healthy peers, their effort is greater and their respiratory system is more challenged [29]. In summary, pulmonary function and aerobic capacity are impaired for several years after burn, both in adults and children. However, burned children with inhalation injury have comparable long-term quality of life outcomes as burned children without inhalation injury [30]. The effect of exercise programs on cardiopulmonary function are discussed elsewhere in this chapter.

2.4 Long-Term Effects of Kidney Dysfunction

Acute kidney injury (AKI) is strongly associated with high mortality, in particular if it develops in the early postburn phase [31]. Patients who need an increased number of operations, receive nephrotoxic drugs, receive a high cumulative fluid balance early on and develop sepsis are at an increased risk for kidney injury [32].

The overall prevalence of acute kidney injury is approximately 25% with a median mortality of 35%. Renal replacement therapy is required in about 1–3% of burn patients with acute kidney injury. Unfortunately, these patients have a mortality rate of up to 80%. Furthermore, AKI is associated with the need for mechanical ventilation and a longer intensive care unit stay [33, 34].

AKI is thought to be a complex problem that affects the whole body on a metabolic, endocrine, and overall organ function of all organs that can persist even after renal recovery. The mechanisms of the so-called organ crosstalk include elevated vascular permeability, changes in gene

transcription, inflammatory cytokines, apoptosis, and cell recruitment [35, 36]. Preventing AKI therefore will not only reduce prevalence of chronic kidney dysfunction and its side effects but potentially has an effect on overall long-term outcomes.

2.5 Effects on the Liver

The liver is the major organ modulating the acute phase response via various pathways and thus affecting the inflammatory—and immune response, which has a great impact on recovery and mortality [37, 38].

Liver injury is correlated with the severity of the burn and is usually present to a variable extent in burn patients. Occurrence of liver and heart failure together is common and is associated with a longer hospital stay [39].

Fatty infiltration of the liver is a common finding in burn patients and is reversible [40]. Yet, in non-survivors fatty liver infiltration is associated with liver failure and sepsis, indicating an important role in the acute postburn phase [41].

Liver dysfunction is present immediately after burn, it typically peaks 2 weeks after burn and persists for 4–12 weeks. Mortality is also higher in patients who develop liver dysfunction than in those without [42]. In a study by Jeschke et al. [40], liver weight and size were massively elevated for up to 12 months postburn and hepatic protein synthesis was affected for up to 9 months. In particular, patients had reduced serum levels of albumin, pre-albumin and transferrin, and elevated acute phase protein levels. Serum AST and ALT levels, markers of hepatocyte damage, remained significantly elevated for up to 4 weeks after burn and returned to normal levels afterwards.

It is known that hepatocytes undergo both, necrosis and apoptosis. The mechanisms however have not been fully discovered yet. Hypoperfusion or ischemia-reperfusion and circulatory pro-inflammatory cytokines are considered leading to apoptosis and enzyme release. Hepatomegaly in burn patients is caused by two mechanisms: intrahepatic steatosis and edema. Fluid overload lasts for only about 1 week after resuscitation. Hence, over-resuscitation seems not to be the cause for edema formation [40, 43].

The liver also plays a central role in glucose metabolism postburn, as it releases more glucose than the body is able to utilize (central insulin resistance), as discussed above.

2.6 Mental Health and Pain

2.6.1 Acute- and Post-traumatic Stress Disorder

Preexisting psychiatric disorders are very common in burn patients and increase the risk for sustaining a burn either directly by leading to self-inflicting burns and suicide attempts, or indirectly increasing the risk (e.g., impulse control disorder, personality disorders, substance abuse including smoking, major depression). Those patients also have an increased risk to develop psychiatric problems after the burn [44]. The two most common psychiatric problems after a burn are Acute Stress Disorder (ASD) and Post-Traumatic Stress Disorder (PTSD). Both have many criteria in common, with the most important difference being time of occurrence. The cut-off point is 1 month after burn. Adults more frequently develop PTSD than children, with a prevalence ranging between 3% and 35% at 2 years postburn. That number decreases to 7–25% 3 years postburn [45] and is 2–19% in children [46, 47].

Patients that develop PTSD after a trauma are highly likely to develop psychological comorbidities such as anxiety, depression, substance abuse, and in particular suicidal behavior in adults [48, 49]. Especially children can develop issues in regard to mood and sleep as well as conduct, attention, and learning problems [50]. In addition, burn survivors in particular suffer frequently from adjustment difficulties and disturbed body image due to hypertrophic scars and disfigurement. Patients typically experience flashbacks or nightmares of the trauma, apart from various symptoms that can overlap with other psychiatric disorders [51]. Good relationships and social surroundings, participation in

leisure activities as well as positive expectations of the future are helpful in preventing PTSD [45]. Tools for assessment of PTSD can be found at https://www.ptsd.va.gov/professional/assessment/all_measures.asp.

Support groups are an important way to help burned individuals recover and often accompany them for life. They offer a variety of support for all age groups, and especially provide mental support. More detailed information can be found at the websites of The Phoenix Society and Burn Model Systems at https://www.phoenix-society.org and https://msktc.org/burn.

2.6.2 Pain

Burn patients often experience pain that can potentially be limiting and disabling. In fact, it is their number one complaint. An increase in the severity of pain and/or localizations correlate with depression and anxiety. But more interestingly, if symptoms of anxiety or depression are present, patients experience more severe pain [52]. Adequate pain control not only reduces pathophysiological stress responses with reduced production of cortisol and catecholamines, it also reduces the likelihood for the development of post-traumatic pain symptoms [53, 54]. Furthermore, reduced or abnormal sensibility does not only occur in the burned or grafted areas, but also in non-burned regions of the same patients. Thus, changes in the central nervous system are suggested [55].

2.6.3 Post-traumatic Growth

In modern trauma therapy, the focus is not only on reducing adverse effects, but also on supporting psychologic development from the traumatic event. Post-traumatic growth (PTG) is the "positive psychological change that results from a struggle through a life-altering experience" and in adult trauma survivors consists of "greater appreciation of life, improved interpersonal relationships, greater personal strength, recognition of new possibilities in one's life course, and spiritual or religious growth [56, 57]." To gain PTG, the trauma needs to be strong enough to significantly affect the patient's world view, but must not be so detrimental that the patient cannot recover. Notably, it is possible that PTG and distress are present at the same time, and studies have shown that distress is necessary initially for growth to happen later in the recovery phase [58]. Several factors have been identified as predictors for PTG; however, ultimately problem-focused coping and cognitive processing can be actively therapeutically addressed [59].

2.7 Long-Term Effects on the Skin: Hypertrophic Scarring

2.7.1 Pathophysiology of the Hypertrophic Burn Scar

Hypertrophic scarring (HTS) is currently one of the most challenging problems after burn injury, if not *the* most challenging. With a prevalence of approximately 70% [60], it is a massive burden to burn patients and affects them physically, functionally, and psychologically and is therefore the most important issue for reintegration into society.

Hypertrophic scars and keloids are the result of aberrant wound healing, with greatly enhanced fibroblast activity and deposition of collagen. HTS consist of thin collagen fibers that are typically organized in nodules with presence of α-smooth muscle actin (α-SMA), whereas in keloids collagen fibers are thickened and hyalinized [61]. Due to their different pathophysiologic mechanism, keloids grow over a long period of time and can occur without an obvious trigger. They grow beyond the border of the original wound and exhibit a high recurrence rate after surgical excision. HTS on the other hand develop within a few weeks after the skin injury, remain within the borders of the wound, tend to regress to a certain extent over time, and have typically low recurrence rates [62].

In this chapter, we focus on the current understanding of pathophysiology, development, characteristics, and current treatment options of the most relevant scar type developing after burn injury: the hypertrophic scar.

2.7.2 Key Aspects of Hypertrophic Scar Development

The deeper the burn wound, the longer it takes to heal [63]. As a result, deep burn wounds that take longer than 3 weeks to heal are significantly associated with higher risk for developing HTS [64, 65].

The composition and architecture of the extracellular matrix (ECM) is drastically changed, fibroblasts and keratinocytes display increased profibrotic properties and profibrotic cytokines are upregulated and expressed for a prolonged period of time. Collagen production and collagen degradation, both are impaired. In normal wound healing, immature type III collagen is gradually replaced by mature type I collagen, and collagen bundles are organized parallel to the skin surface. In HTS however, type III collagen is proportionally increased and the bundles are highly disorganized [66]. Elastin, important for skin elasticity, is not present in HTS for several years after burn [67].

Nodules, consisting of highly unorganized, immature collagen, small vasculature and large amounts of mucopolysaccharide are seen histologically. These pathognomonic nodules are sharply delineated from surrounding scar tissue, which are mostly composed of similar materials but demonstrate features of more mature scars (i.e., parallel orientation of collagen fibrils) [67].

2.7.3 Proteoglycans and Glycoproteins

Another feature of HTS is elevated turgor and volume due to elevated glycosaminoglycan levels that lead to a hyperhydrated state. Decorin, a small leucine-rich proteoglycan (SLRP), responsible for collagen fibril organization, is significantly downregulated in HTS. It also controls profibrotic cytokines (TGF-β, PDGF) and several growth factors (epidermal growth factor EGF, insulin-like growth factor 1 IGF-1) by antagonistically binding and downregulation, what is disturbed in HTS [68].

2.7.4 Cellular Mechanism Involved in HTS

Deep dermal fibroblasts also play a role in HTS development. They are larger and exhibit the following features compared to superficial fibroblasts: increased collagen and decreased collagenase and decorin production, with increased production of inflammatory cytokines, namely transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) [69]. It is still unclear whether superficial fibroblasts are simply destroyed by injury and therefore cannot initiate the wound remodeling process or if cytokine stimulation leads to selective proliferation of deep dermal fibroblasts [70].

Myofibroblasts are responsible for wound contraction in the normal wound healing process. In HTS, they express large amounts of alpha α-smooth actin—similar to smooth muscle cells—and are the main factor responsible for the extensive contractions after burn injury [71]. Mechanical stress increases myofibroblast activity, prevents apoptosis of myofibroblasts [72], and leads to excessive accumulation of extracellular matrix. Yet, in burn patients HTS paradoxically occur also in areas minimally exposed to mechanical stress.

Hyperproliferative keratin phenotypes produced by activated keratinocytes have been identified in HTS tissue. These activated keratinocytes suggest disturbances at an epidermal-mesenchymal level [73] and may have negative impact on re-epithelialization.

2.7.5 Cytokines

Several cytokines play an important role in HTS development. TGF-β, for example, is a strong proliferative cytokine that interacts with many other cytokines and is highly upregulated in the serum and in wounds of burn patients. It plays an essential role in many wound healing processes. Of notice, one isoform, namely TGF- β_3, has antifibrotic properties and plays a role in the remodeling phase, which could be a potential therapeutic target [74].

2.7.6 Summary

Despite many theories to explain the mechanism of hypertrophic scar formation, it is still poorly understood and subject to extensive ongoing research.

3 Therapeutic Approaches of Long-Term Burn Sequelae

3.1 Pharmaceutical Treatment Options and Investigational Drugs

Recombinant growth hormone (rhGH) has been shown to lead to faster burn wound closure and donor site healing in children and adult burn victims [75]. At our center (Shriners Hospitals for Children and UTMB, Galveston), Branski and colleagues demonstrated numerous beneficial long-term effects (for up to 2 years) after a yearlong rhGH administration in severely burned children. Hypermetabolism was attenuated, lean body mass increased, body fat decreased, and cardiac output had decreased [76].

When administered acutely in critically ill adults, it led to increased morbidity and mortality [77]. Therefore, patients should be monitored closely for possible side effects, in particular hyperglycemia and hypercalcemia. Another disadvantage is the need for daily subcutaneous injections. The effects of long-term growth hormone administration (for 9 months after burn) on cardiac function, muscle strength, cardiopulmonary exercise function, after burn scarring, and overall safety in adult burn survivors are currently under investigation.

Oxandrolone, an orally administered anabolic steroid with a better side effect profile than rhGH, has been shown to attenuate hypermetabolism and lead to an increase in lean body mass, muscle strength, and growth in height in severely burned children, when administered for 1-year postburn [78], with even greater increases in bone density when administered for 2 years [79]. In adult burn victims, long-term data is lacking; however, beneficial effects have been documented for the early rehabilitative phase [80]. Although no liver failure has been reported, transaminases need to be monitored closely due to risk of abnormal liver function.

The non-selective β-adrenergic antagonist **propranolol** effectively and safely attenuates the hypermetabolic response and reduces heart rate and resting energy expenditure after burn [81, 82]. It has been shown that it not only blunts acute skeletal muscle loss [83], but more recently it also helps regain muscle mass in the early rehabilitation phase when administered for 1 year after burn [81].

The **combination of oxandrolone and propranolol** administered for 1 year after burn injury was shown to be safe and seems to have positive effects on hypertrophic scars and physical and psychological outcomes in children. Improvements could be shown 2 years after burn and therefore is suggested to be considered a treatment option in severely burned children [84].

Several therapies have been investigated to treat **bone loss**: Early intravenous administration of the bisphosphonate pamidronate successfully prevented loss of total body and spine bone mineral content (BMC) in the short term compared to placebo as well as 2 years postburn where BMC was still increased in the spine but no difference in whole body BMC was seen. Oxandrolone, given for 1 or 2 years has the potential to improve BMC as well as accelerate growth in height in burned children [79, 85]. Vitamin D substitution has not been shown to improve loss of BMC postburn to date, however improved serum Vitamin D levels in adults and reduced fracture incidence in children were seen [86, 87].

Several strategies exist for attaining **glucose control** to improve insulin sensitivity and to reduce skeletal muscle catabolism. With insulin therapy, glucose control can usually be maintained, however puts the patient at risk for hypoglycemia, and therefore has to be monitored closely [88].

An alternative treatment option is the oral biguanide **metformin**, with low risk for hypoglycemia [89]. **Fenofibrate**, a drug of the fibrate class, was shown to attenuate insulin resistance. However, data is too sparse yet to recommend it as standard treatment [88].

3.2 Physical Exercise Therapy

Positive effects on muscle strength, lean body mass, and peak cardiovascular exercise capacity during the rehabilitative phase after major burn injury in children [90, 91] and adults [92] have been shown after different exercise protocols. These effects seem to be even stronger if in addition if the growth hormone oxandrolone (0.1 mg/kg/day) is administered for 1-year postburn [93]. Also the combination of exercise with the non-selective β-adrenergic blocker propranolol (4–8 mg/kg/day, depending on resting-heart rate) appears to have beneficial effects on cardiovascular exercise capacity (VO_2 peak) in burned children [94]. More recently, the combination of the two drugs has been shown to add positively to exercise training to gain muscle strength and improve protein turnover during the early rehabilitative phase [95]. 12 weeks of a combined aerobic and resistance exercise training program was shown to be beneficial in severely burned children with improvements in peak oxygen uptake (VO_2 peak) and pulmonary function [96].

At our institution (Shriners Hospitals for Children and UTMB, Galveston), exercise protocols are in place as standard of care to help burn victims restore lean body mass, muscle function and to improve cardiopulmonary capacity. Future research should focus on objectively measurable exercise parameters to develop adequate exercise programs also for adult burn survivors since there is great inconsistency between burn centers and lack of awareness of the importance of such programs, as the survey of Diego and colleagues has shown [97]. It should be pointed out that no study has shown that beneficial effects of exercise training last beyond the rehabilitative phase. Nonetheless, as with the non-burn population, it is essential that physical exercise becomes an integral part in a burn survivor's life to be beneficial long term.

3.3 Scar Therapy

Apart from the stigma and unpleasant aesthetic appearance that accompanies hypertrophic burn scars, burn survivors suffer from severe pruritus, neuropathic pain, and contractures that often limit range of motion [98, 99]. The most important scar treatment is their prevention. Early excision, the avoidance of skin grafts—if possible, according to burn depth—and early pressure garment therapy are key. If a scar has formed despite preventive therapy, the most effective and important therapy is reconstructive surgery. This is discussed in detail elsewhere in this book.

A holistic approach is usually applied to prevent and treat hypertrophic scars, ranging from traditional conservative therapies, such as compression garments, silicone sheets or gels, physical therapy, intralesional injection of corticosteroids, or 5-fluorouracil. Effectiveness of these extensively used conservative methods has been proven empirically and are widely acknowledged legitimately as standard of care; however, to date little scientific evidence exists supporting their use due to the fact it is difficult to conduct adequately powered randomized clinical trials. Side effects can occur [62, 100–102], however in general they are quickly reversible once the treatment is stopped.

Pressure garments are in use for the prevention and treatment of HTS for over half a century and are still considered as standard basic treatment. They are worn for almost 24 h a day for at least 6 months after burn. The pressure achieved ranges between 15 and 40 mmHg [103, 104]. A recent animal study suggests starting pressure therapy immediately after skin graft take might be beneficial [105]. Even though in many cases it is difficult to attain sufficient pressure to the affected area and due to comfort issues, lack of compliance can occur, pressure garments are still to date considered standard treatment for burn scars.

Silicone sheets are usually worn for at least 12 h/day for several months, beginning therapy 2 weeks after wound healing. The mechanisms of action of silicone gel sheeting are occlusion and therefore increased skin hydration and electrical charge changes possibly due to the silicone molecule. To prevent maceration, sheets have to be removed intermittently to let the skin dry [101]. Side effects such as rash, pruritus, contact dermatitis, and dry skin can occur [106]. The combination of both, pressure garments and silicone

sheets, exhibits increased efficiency over one treatment alone [102].

The combination of intralesional injections with **Triamcinolone (TAC)** and **Fluorouracil (5-FU)** is the most effective regimen. It is more effective over each single treatment alone and has also less side effects, like skin atrophy or telangiectasia. As standard regimen 0.1 mL 40 mg/mL concentrated TAC mixed with 0.9 mL 50 mg/mL concentrated 5-FU is recommended. Scars should be treated weekly for at least 8 weeks. The dose administered should not exceed 2 mL in total per session or 0.5 mg/cm^2 [102].

Medical needling is indicated for large burn scar plates that cannot be treated with excision and flaps. A roller with 1–3-mm-long needles is typically rolled in vertical, horizontal, and diagonal directions over the scarred area. The small needles penetrate the papillary and reticular dermis causing mechanical micro injuries without thermal injury or necrosis as compared to other scar resurfacing methods. This induces new collagen and elastin formation and results in thinning of dermis, thickening of the epidermis, increase in non-inflammatory cytokines, and improvement of scar texture with a very low risk for hypo-/hyperpigmentation and scarring. The procedure can be performed under local- or short systemic anesthesia. Currently, there are fully automated devices on the market which are adjustable in speed and penetration depth; however, the principle remains the same. Noninvasive medical needling is also used for intralesional delivery of topical drugs, or can be used in combination with radiofrequency [107, 108]. Figure 1 shows pre- and post-interventional results.

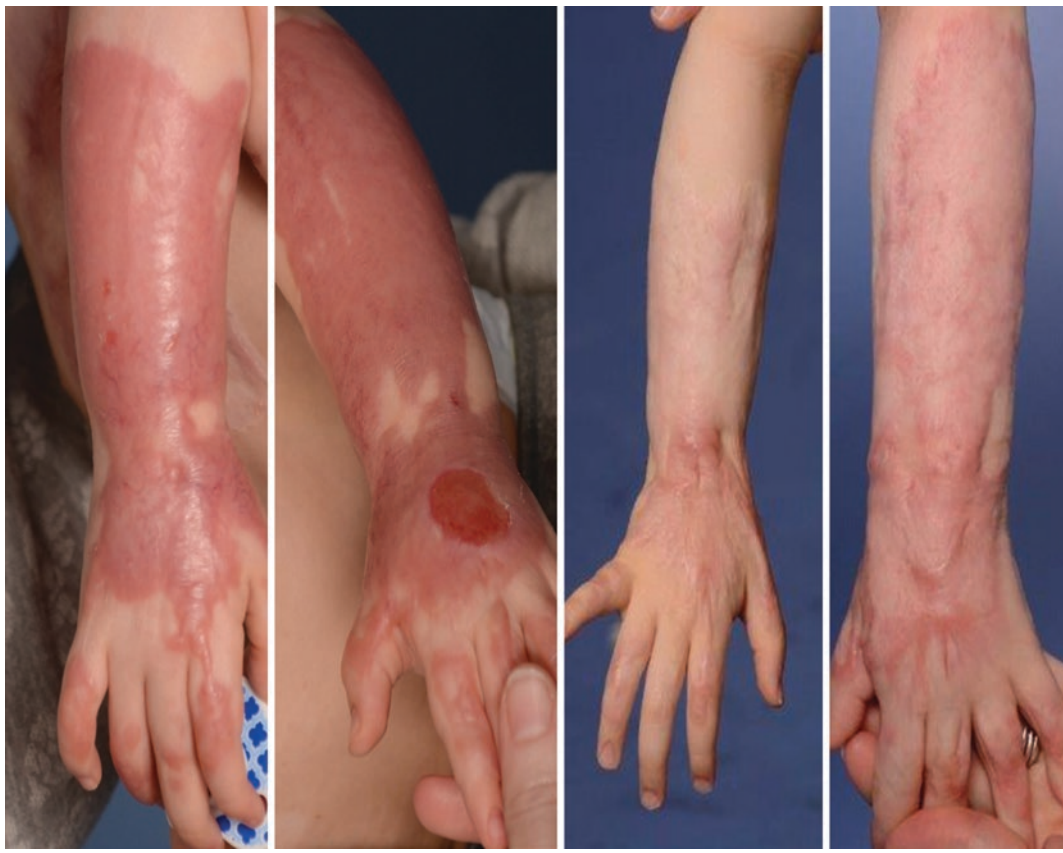

Fig. 1 Medical needling results. Left: Hypertrophic scar area localized on the right cheek and neck, preoperatively. Right: Result 3 months after medical needling. The scar texture has significantly improved without changes in pigmentation

Autologous fat grafting for reconstructive or aesthetic purposes became popular over the recent years. Basic science studies have shown that regeneration of all three layers of the skin is possible with autologous adipose-derived stem cells [109]. This seems to be of great benefit in particular for the treatment of burn wounds. Studies in burn patients have shown that it supports restructuring of collagen, improvement of pigment disorders and overall scar texture. Even though level of evidence is low and more clinical studies are required [110], autologous fat grafting is a promising therapeutic option for the treatment of burn scars, especially in combination with other therapies.

Laser therapy has become widely accepted as a major modality for the treatment of burn scars, especially with growing evidence of its effectiveness over the recent years [100, 111]. Attenuating the scar both aesthetically and functionally and to reduce pain and itching are the ultimate goals. Laser therapy can be used alone or in adjunct prior to surgery to soften the scar and improve outcomes.

3.3.1 Laser Types

Different types of lasers target a specific chemical entity known as a chromophore. Laser energy of a specific wavelength is absorbed by the three main chromophores melanin, hemoglobin, intra- and extracellular water. Penetration depth is dependent upon the amount of energy used [112].

Mechanistically, it has to be distinguished between ablative/non-ablative and fractional/non-fractional lasers. **Non-ablative lasers** use lower temperatures around 50–70 °C, which lead to coagulation of proteins and collagens, respectively. Whereas **ablative lasers** use temperatures greater than 100 °C, which cause tissue vaporization, surrounded by a thermal coagulation zone [113].

Fractional ablative laser therapy was developed to overcome side effects related to non-fractional ablative lasers and was first introduced in 2004 by Manstein and Anderson, who termed it fractional photothermolysis [114]. Fractional lasers split the laser beam into many microbeams, leading to hundreds to thousands of small micro injuries, called microthermal treatment zones (MTZ). Ultra-fast pulsed laser beams produce tissue ablation while significantly reducing heat deposition, and therefore causing less collateral damage. The spared surrounding tissue allows for a rapid wound healing response (re-epithelialization after 1-day post treatment), neocollagenesis, and tissue remodeling [115, 116].

Although a huge variety of different lasers have been studied for the treatment of hypertrophic burn scars, ablative fractionate lasers (AFLs) and pulsed dye laser therapy (PDL) seem to be the most beneficial.

The most frequently used laser for the treatment of hypertrophic burn scars are the ablative fractional CO_2 lasers and erbium:YAG (er:YAG). At our institution (Shriners Hospitals for Children and UTMB, Galveston), we use the fractional CO_2 laser, which we have extensive experience with. The CO_2 laser targets water in abnormal collagen up to 4 min below the surface. Figure 2 shows results of CO_2 laser therapy.

3.3.2 Laser Effects and Side Effects

The main effects that can be accomplished with CO_2 laser are a reduction of scar thickness, increased scar elasticity, improvement in surface texture and firmness, improvement in scar pigmentation (hyper- and hypopigmentation), dermal restructuring—reduction of TGF-β1 expression, increase of collagen Type I and III, thickening of epidermis, and last but not least a reduction of pain and pruritus [113, 117, 118].

Improvements in scar appearance have been shown to occur after only one single treatment [119], however usually several sessions with breaks of approximately 4 weeks to 3 months in between are required to attain a good result and can be combined with other treatment modalities like triamcinolone injections [120, 121].

Histologically, laser treatment leads to decrease in collagen bundle thickness and density in the upper dermis, and newly formed dermal papilla [122, 123]. Recent studies identified molecular effects on keratinocytes and fibroblasts [124].

Side effects/complications range from discrete to moderate erythema or edema (what usu-

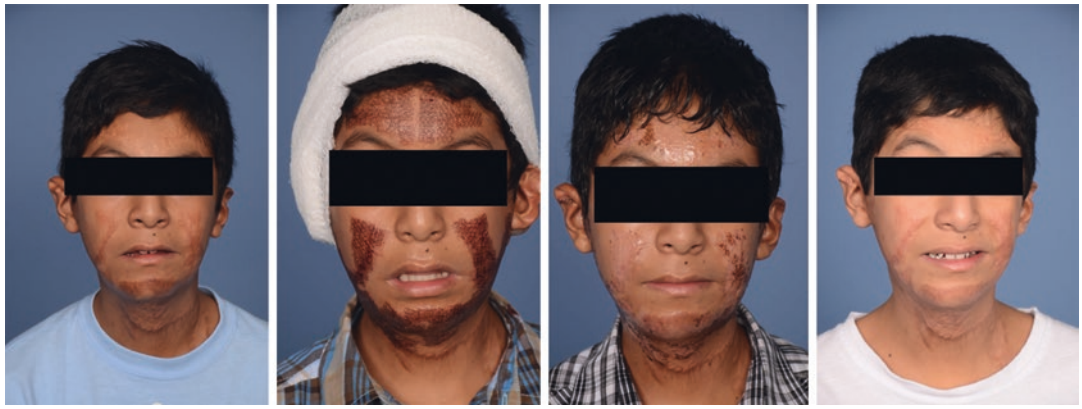

Fig. 2 CO_2 laser treatment. 11-Year-old male with hypertrophic scars with hypo- and hyperpigmented areas 2 years postburn. Left to right: Pre OP, 1 day post OP, 6 days post OP, 3 months post OP

ally resolves in 7–10 days), hyper- or hypopigmentation, post-inflammatory hyperpigmentation (PIH), pruritus or imprints from the laser-grid. Blistering is more common after PDL, whereas CO_2 lasers cause more often postprocedural pain, which can usually be treated sufficiently with non-opioid analgesics. Darker skin types are more likely to develop hypopigmentation or blistering. Overall, adverse events are rare and it can be considered a safe procedure if applied correctly [125, 126].

3.3.3 Laser Therapy: Practical Guidance

Treatment should not begin no less than 6 months after wound healing is complete and the scar has matured; however, expert's opinions vary widely. Successful results have also been accomplished with older burn scars of up to 7–23 years postburn [122, 127].

Laser selection is based on the following criteria: dyschromia (i.e., erythema, hypo- or hyperpigmentation), type of scar (hypertrophic, flat, atrophic), location (i.e., face, neck, trunk), and patient characteristics (i.e., skin type and comorbidities) [128].

We have found that the **CO_2 laser** is the most effective tool in almost all patients because it penetrates deep into tissues, necessary to treat thick hypertrophic scars. There are numerous commercially available fractional CO_2 laser units. At our institution (Shriners Hospitals for Children and UTMB, Galveston), we use the Lumenis Ultrapulse device (Lumenis, Santa Clara, CA) with various settings (ActiveFX®, DeepFX®, or SCAAR FX™). We tend to use the SCAAR FX setting for thick, hypertrophic scars, and the Deep FX setting for atrophic, papery scars. The ActiveFX is used to assist in surface changes and to treat hyperpigmentation. For immature hypertrophic burn scars, we use vascular laser settings. The underlying principle is to coagulate micro blood vessels, by targeting the chromophores hemoglobin and oxyhemoglobin, and thus eliminating the vascular supply to the scar. It also addresses localized pruritus, which can be a serious problem, especially in burned children. Historically, **pulsed dye laser** (PDL) has been used effectively for the treatment of burn scars [129]; however, it is slow and the endpoint required to see as indicator for an effective treatment is a purpuric response. At our institution, we use the Lumenis-M22 platform with different modules. One advantage of the 590 nm filter is that it has the benefits of the PDL but is faster and does not generate a purpuric response. For targeting any telangiectasia within the scar, we use the Nd:YAG handpiece. We often use the vascular laser and the CO_2 laser in the same session, with the vascular laser being used first as otherwise the effect of any vascular laser to a bleeding wound would be negligible. Figure 3 shows results of vascular laser treatment. Figure 4 summarizes frequently used laser settings.

Laser Type/Setting	Wave length	Energy	Indication	Endpoint
Ablative fractionated CO_2-Lumenis Ultrapulse	10.600nm			
SCAAR FX		60-100 mJ at 3% (100-150 mJ at 1%)	Thick, hypertrophic scars	Pinpoint bleeding
Deep FX		10-20 mJ at 10%	atrophic, papery scars	Pinpoint bleeding
Active FX		60-100 mJ at 3%, 125Hz, (5% if used alone)	Surface, hyperpigmentation	Full coverage of scar
PDL	585-595nm	7J/cm2	Erythema, pruritus	Purpuric response
M22 – Nd:YAG	1064nm		Teleangiectasia	
M22 – IPL + 590nm filter,	590nm	17J/cm2	Erythema, pruritus	

Fig. 3 Vascular laser treatment. 3-Year-old male with erythematous scars after a scald burn on both hands and forearms. Left: 7 months postburn, before treatment. Right: 16 months postburn, after two treatments with M22 laser. Additionally, the patient has been in compression garments since his wounds were closed

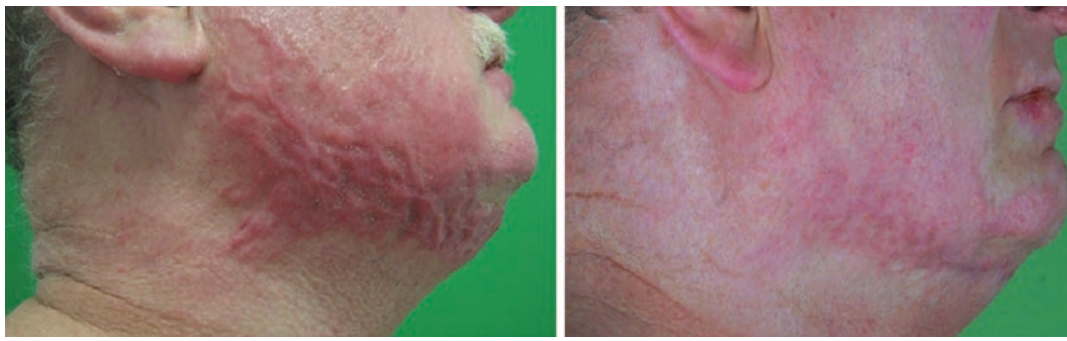

Fig. 4 Common laser/IPL Settings. *SCAAR* synergistic coagulation and ablation for advanced resurfacing, *PDL*, pulsed dye laser, *Nd:YAG* neodym YAG laser, *IPL* intense pulsed light

Pre- and aftercare: Perioperative antibiotic prophylaxis is indicated in patients with a history of infection or colonization with multi-resistant organisms. Patients with a history of herpes simplex virus undergoing ablative fractional laser treatment on the face should receive acyclovir for prophylaxis. Both are usually not necessary for non-ablative laser therapy. For patients who are likely to develop PIH, we advocate the use of Azelaic acid (15%) for its tyrosine kinase inhibitory action and have seen great results in most of our patients. Others use hydroquinone prior to laser therapy. For the actual treatment of PHI, a combination of a steroid, hydroquinone, and tretinoin can be used.

Directly after the procedure, we cool the wounds with ice packs. Lasered areas should be left open to air and kept elevated until swelling subsides. We recommend to wash treated areas twice daily with antimicrobial skin cleanser and application of hydrophilic ointment several times a day to prevent dryness and crustiness, until areas are fully epithelialized. By then, compression garments can be worn again. If pruritus occurs, hydrocortisone cream (1%) is applied locally. Sun should be avoided and at least SPF30 sunscreen lotion should be applied daily for a year when exposed after wounds have healed to support preventing PIH.

3.3.4 Conclusion

Despite its clear benefits, laser is certainly not a panacea for all burn scars. Surgical release and rearrangement of tissue is still a mainstay. However, laser therapy is definitively an essential part of any burn reconstruction program and has now become part of the standard of care. Scar management with the ablative fractional CO_2 laser is most effective in facial scars, large scar plates of the trunk, and less severe scar bands over joint surfaces, and has replaced conventional surgery in many instances.

4 Summary

Burn injury is not limited to the acute phase. On the contrary, with prolonged hypermetabolism and hypercatabolism as drivers, almost every organ system is affected. Many pharmaceutical options exist, some of them seem to be beneficial for several postburn problems at once, like muscle wasting and scarring. For the most visible organ, the skin, laser therapy has huge potential. However, well-timed surgery and proper surgical techniques are key. In order to achieve the overall goal of reintegration into everyday life, society, work place, school, etc., an individual multidisciplinary treatment plan needs to be developed and constantly adapted for each patient.

References

1. Capek KD, Sousse LE, Hundeshagen G, Voigt CD, Suman OE, Finnerty CC et al (2018) Contemporary burn survival. J Am Coll Surg 226(4):453–463
2. Burn Incidence Fact Sheet—American Burn Association [Internet] (2019). https://ameriburn.org/who-we-are/media/burn-incidence-fact-sheet/. Accessed 11 Feb 2019
3. NFPA Report—Fire Loss in the United States [Internet] (2019). https://www.nfpa.org/News-and-Research/Data-research-and-tools/US-Fire-Problem/Fire-loss-in-the-United-States. Accessed 11 Feb 2019
4. Jeschke MG, Gauglitz GG, Kulp GA, Finnerty CC, Williams FN, Kraft R et al (2011) Long-term persistance of the pathophysiologic response to severe burn injury. Androulakis IP, editor. PLoS One 6(7):e21245
5. Porter C, Herndon DN, Sidossis LS, Børsheim E (2013) The impact of severe burns on skeletal muscle mitochondrial function. Burns 39(6):1039–1047
6. Tapking C, Armenta AM, Popp D, Herndon DN, Branski LK, Lee JO et al (2019) Relationship between lean body mass and isokinetic peak torque of knee extensors and flexors in severely burned children. Burns 45(1):114–119
7. Porter C, Hardee J, Herndon DN, Suman OE (2015) The role of exercise in the rehabilitation of patients with severe burns. Exerc Sport Sci Rev 43(1):34–40
8. Klein GL, Herndon DN, Langman CB, Rutan TC, Young WE, Pembleton G et al (1995) Long-term reduction in bone mass after severe burn injury in children. J Pediatr 126(2):252–256
9. Schryver E, Klein GL, Herndon DN, Suman OE, Branski LK, Sousse LE (2018) Bone metabolism in pediatric burned patients: a review. Burns 44(8):1863–1869
10. Clayton RP, Herndon DN, Abate N, Porter C (2018) The effect of burn trauma on lipid and glucose metabolism: implications for insulin sensitivity. J Burn Care Res 39(5):713–723
11. Kamolz L-P, Pieber T, Smolle-Jüttner FM, Lumenta DB (2013) Optimal blood glucose control in severely burned patients: a long way to go, but one step closer. Crit Care 17(5):1005
12. Kaufman TM, Horton JW (1992) Burn-induced alterations in cardiac beta-adrenergic receptors. Am J Phys 262(5 Pt 2):H1585–H1591
13. Demling RH (1987) Fluid replacement in burned patients. Surg Clin North Am 67(1):15–30
14. Bryant D, Becker L, Richardson J, Shelton J, Franco F, Peshock R et al (1998) Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. Circulation 97(14):1375–1381
15. Papp A, Uusaro A, Parviainen I, Hartikainen J, Ruokonen E (2003) Myocardial function and haemodynamics in extensive burn trauma: evaluation by clinical signs, invasive monitoring, echocardiography and cytokine concentrations. A prospective clinical study. Acta Anaesthesiol Scand 47(10):1257–1263
16. Miller JG, Bunting P, Burd DA, Edwards JD (1994) Early cardiorespiratory patterns in patients with major burns and pulmonary insufficiency. Burns 20(6):542–546
17. Adams HR, Baxter CR, Parker JL (1982) Contractile function of heart muscle from burned guinea pigs. Circ Shock 9(1):63–73
18. Adams HR, Baxter CR, Izenberg SD (1984) Decreased contractility and compliance of the left ventricle as complications of thermal trauma. Am Heart J 108(6):1477–1487
19. Abu-Sittah GS, Sarhane KA, Dibo SA, Ibrahim A (2012) Cardiovascular dysfunction in burns: review of the literature. Ann Burns Fire Disasters 25(1):26–37

20. Martyn JA, Snider MT, Szyfelbein SK, Burke JF, Laver MB (1980) Right ventricular dysfunction in acute thermal injury. Ann Surg 191(3):330–335
21. Williams FN, Herndon DN, Suman OE, Lee JO, Norbury WB, Branski LK et al (2011) Changes in cardiac physiology after severe burn injury. J Burn Care Res 32(2):269–274
22. Hundeshagen G, Herndon DN, Clayton RP, Wurzer P, McQuitty A, Jennings K et al (2017) Long-term effect of critical illness after severe paediatric burn injury on cardiac function in adolescent survivors: an observational study. Lancet Child Adolesc Health 1(4):293–301
23. Osler T, Glance LG, Hosmer DW (2010) Simplified estimates of the probability of death after burn injuries: extending and updating the baux score. J Trauma 68(3):690–697
24. Palmieri TL (2009) Long term outcomes after inhalation injury. J Burn Care Res 30(1):201–203
25. Woodson LC, Branski LK, Enkhbaatar P, Talon M (2018) Diagnosis and treatment of inhalation injury. In: Herndon DN (ed) Total burn care (Fifth Edition) [Internet]. Elsevier, Amsterdam, pp 184.e3–194.e3. http://www.sciencedirect.com/science/article/pii/B9780323476614000174
26. Park GY, Park JW, Jeong DH, Jeong SH (2003) Prolonged airway and systemic inflammatory reactions after smoke inhalation. Chest 123(2):475–480
27. Mlcak R, Desai MH, Robinson E, Nichols R, Herndon DN (1998) Lung function following thermal injury in children—an 8-year follow up. Burns 24(3):213–216
28. Willis CE, Grisbrook TL, Elliott CM, Wood FM, Wallman KE, Reid SL (2011) Pulmonary function, exercise capacity and physical activity participation in adults following burn. Burns 37(8):1326–1333
29. Desai MH, Mlcak RP, Robinson E, McCauley RL, Carp SS, Robson MC et al (1993) Does inhalation injury limit exercise endurance in children convalescing from thermal injury? J Burn Care Rehabil 14(1):12–16
30. Rosenberg M, Ramirez M, Epperson K, Richardson L, Holzer C, Andersen CR et al (2015) Comparison of long-term quality of life of pediatric burn survivors with and without inhalation injury. Burns 41(4):721–726
31. Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL et al (2010) Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. J Burn Care Res 31(1):83–92
32. Palmieri T, Lavrentieva A, Greenhalgh DG (2010) Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. Burns 36(2):205–211
33. Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EAJ (2010) Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. Intensive Care Med 36(6):915–925
34. Coca SG, Bauling P, Schifftner T, Howard CS, Teitelbaum I, Parikh CR (2007) Contribution of acute kidney injury toward morbidity and mortality in burns: a contemporary analysis. Am J Kidney Dis 49(4):517–523
35. Shiao C-C, Wu P-C, Huang T-M, Lai T-S, Yang W-S, Wu C-H et al (2015) Long-term remote organ consequences following acute kidney injury. Crit Care [Internet] 19:438. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699348/
36. Dépret F, Prud'homme M, Legrand M (2017) A role of remote organs effect in acute kidney injury outcome. Neftekhimi 137(4):273–276
37. Jeschke MG (2009) The hepatic response to thermal injury: is the liver important for postburn outcomes? Mol Med 15(9–10):337–351
38. Moshage H (1997) Cytokines and the hepatic acute phase response. J Pathol 181(3):257–266
39. Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG (2014) Occurrence of multi-organ dysfunction in pediatric burn patients—incidence and clinical outcome. Ann Surg 259(2):381–387
40. Jeschke MG, Micak RP, Finnerty CC, Herndon DN (2007) Changes in liver function and size after a severe thermal injury. Shock 28(2):172–177
41. Barret JP, Jeschke MG, Herndon DN (2001) Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. J Trauma 51(4):736–739
42. Gong Y, Long X, Xu H, Yang X, Guo Q (2018) The changes and prognostic value of liver function in young adults with severe burn. Medicine (Baltimore) 97(51):e13721. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6320172/
43. Barrow RE, Hawkins HK, Aarsland A, Cox R, Rosenblatt J, Barrow LN et al (2005) Identification of factors contributing to hepatomegaly in severely burned children. Shock 24(6):523–528
44. McKibben JBA, Ekselius L, Girasek DC, Gould NF, Holzer C, Rosenberg M et al (2009) Epidemiology of burn injuries II: psychiatric and behavioural perspectives. Int Rev Psychiatry 21(6):512–521
45. Giannoni-Pastor A, Eiroa-Orosa FJ, Fidel Kinori SG, Arguello JM, Casas M (2016) Prevalence and predictors of posttraumatic stress symptomatology among burn survivors: a systematic review and meta-analysis. J Burn Care Res 37(1):e79–e89
46. Landolt MA, Buehlmann C, Maag T, Schiestl C (2007) Brief report: Quality of life is impaired in pediatric burn survivors with posttraumatic stress disorder. J Pediatr Psychol 34(1):14–21
47. Thomas CR, Blakeney P, Holzer CE III, Meyer WJ III (2009) Psychiatric disorders in long-term adjustment of at-risk adolescent burn survivors. J Burn Care Res 30(3):458–463
48. Brady KT, Killeen TK, Brewerton T, Lucerini S (2000) Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry 61(Suppl 7):22–32

49. Nepon J, Belik S-L, Bolton J, Sareen J (2010) The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Depress Anxiety 27(9):791–798
50. Caffo E, Belaise C (2003) Psychological aspects of traumatic injury in children and adolescents. Child Adolesc Psychiatr Clin N Am 12(3):493–535
51. Sareen J (2014) Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. Can J Psychiatr 59(9):460–467
52. de Heer EW, Gerrits MMJG, Beekman ATF, Dekker J, van Marwijk HWJ, de Waal MWM et al (2014) The association of depression and anxiety with pain: a study from NESDA. PLoS One 9(10):e106907
53. Saxe G, Stoddard F, Courtney D, Cunningham K, Chawla N, Sheridan R et al (2001) Relationship between acute morphine and the course of PTSD in children with burns. J Am Acad Child Adolesc Psychiatry 40(8):915–921
54. Stoddard FJ Jr, Sorrentino EA, Ceranoglu TA, Saxe G, Murphy JM, Drake JE et al (2009) Preliminary evidence for the effects of morphine on posttraumatic stress disorder symptoms in one-to four-year-olds with burns. J Burn Care Res 30(5):836–843
55. Malenfant A, Forget R, Amsel R, Papillon J, Frigon J-Y, Choinière M (1998) Tactile, thermal and pain sensibility in burned patients with and without chronic pain and paresthesia problems. Pain 77(3):241–251
56. Picoraro JA, Womer JW, Kazak AE, Feudtner C (2014) Posttraumatic growth in parents and pediatric patients. J Palliat Med 17(2):209–218
57. Kilmer RP, Gil-Rivas V, Griese B, Hardy SJ, Hafstad GS, Alisic E (2014) Posttraumatic growth in children and youth: clinical implications of an emerging research literature. Am J Orthop 84(5):506–518
58. Linley PA, Joseph S (2004) Positive change following trauma and adversity: a review. J Trauma Stress 17(1):11–21
59. Askay SW, Magyar-Russell G (2009) Post-traumatic growth and spirituality in burn recovery. Int Rev Psychiatry 21(6):570–579
60. Bombaro KM, Engrav LH, Carrougher GJ, Wiechman SA, Faucher L, Costa BA et al (2003) What is the prevalence of hypertrophic scarring following burns? Burns 29(4):299–302
61. Huang C, Murphy GF, Akaishi S, Ogawa R (2013) Keloids and hypertrophic scars: update and future directions. Plast Reconstr Surg Glob Open 1(4):e25
62. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG (2011) Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. Mol Med 17(1–2):113–125
63. Dunkin CSJ, Pleat JM, Gillespie PH, Tyler MPH, Roberts AHN, McGrouther DA (2007) Scarring occurs at a critical depth of skin injury: precise measurement in a graduated dermal scratch in human volunteers. Plast Reconstr Surg 119(6):1722–1732
64. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J (1983) Hypertrophic burn scars: analysis of variables. J Trauma 23(10):895–898
65. Cubison TCS, Pape SA, Parkhouse N (2006) Evidence for the link between healing time and the development of hypertrophic scars (HTS) in paediatric burns due to scald injury. Burns 32(8):992–999
66. Oliveira GV, Hawkins HK, Chinkes D, Burke A, Tavares ALP, Ramos-e-Silva M et al (2009) Hypertrophic versus non hypertrophic scars compared by immunohistochemistry and laser confocal microscopy: type I and III collagens. Int Wound J 6(6):445–452
67. Hawkins HK, Jay J, Finnerty CC (2018) Chapter 46: Pathophysiology of the burn scar. In: Herndon DN (ed) Total burn care, 5th edn. Elsevier, Amsterdam, pp 466.e3–475.e3. http://www.sciencedirect.com/science/article/pii/B9780323476614000447
68. Kwan P, Desmoulière A, Tredget EE (2012) Chapter 45: Molecular and cellular basis of hypertrophic scarring. In: Herndon DN (ed) Total burn care, 5th edn. W.B. Saunders, London, pp 495.e5–505.e5. http://www.sciencedirect.com/science/article/pii/B978143772786900045X
69. Tredget EE, Levi B, Donelan MB (2014) Biology and principles of scar management and burn reconstruction. Surg Clin North Am 94(4):793–815
70. Kwan P, Hori K, Ding J, Tredget EE (2009) Scar and contracture: biological principles. Hand Clin 25(4):511–528
71. Chiang RS, Borovikova AA, King K, Banyard DA, Lalezari S, Toranto JD et al (2016) Current concepts related to hypertrophic scarring in burn injuries: hypertrophic scarring in burn injuries. Wound Repair Regen 24(3):466–477
72. Aarabi S, Bhatt KA, Shi Y, Paterno J, Chang EI, Loh SA et al (2007) Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. FASEB J 21(12):3250–3261
73. Machesney M, Tidman N, Waseem A, Kirby L, Leigh I (1998) Activated keratinocytes in the epidermis of hypertrophic scars. Am J Pathol 152(5):1133–1141
74. Tredget E, Shankowsky H, Pannu R, Nedelec B, Iwashina T, Ghahary A et al (1998) Transforming growth factor-β in thermally injured patients with hypertrophic scars: effects of interferon α-2b. Plast Reconstr Surg 102(5):1317–1328
75. Breederveld RS, Tuinebreijer WE (2014) Recombinant human growth hormone for treating burns and donor sites. Cochrane Database Syst Rev [Internet] 9:CD008990. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008990.pub3/abstract
76. Branski LK, Herndon DN, Barrow RE, Kulp GA, Klein GL, Suman OE et al (2009) Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. Ann Surg 250(4):514–523

77. Takala J, Zandstra DF (1999) Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785–792
78. Porro LJ, Herndon DN, Rodriguez NA, Jennings K, Klein GL, Mlcak RP et al (2012) Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. J Am Coll Surg 214(4):489–504
79. Reeves PT, Herndon DN, Tanksley JD, Jennings K, Klein GL, Mlcak RP et al (2016) Five-year outcomes after long-term oxandrolone administration in severely burned children: a randomized clinical trial. Shock 45(4):367–374
80. Li H, Guo Y, Yang Z, Roy M, Guo Q (2016) The efficacy and safety of oxandrolone treatment for patients with severe burns: a systematic review and meta-analysis. Burns 42(4):717–727
81. Herndon DN, Rodriguez NA, Diaz EC, Hegde S, Jennings K, Mlcak RP et al (2012) Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. Ann Surg 256(3):402–411
82. Flores O, Stockton K, Roberts JA, Muller MJ, Paratz JD (2016) The efficacy and safety of adrenergic blockade after burn injury: a systematic review and meta-analysis. J Trauma Acute Care Surg 80(1):10
83. Herndon DN, Wolfe RR (2001) Reversal of catabolism by beta-blockade after severe burns. N Engl J Med 345:1223–1229
84. Herndon D, Capek KD, Ross E, Jay JW, Prasai A, Ayadi AE et al (2018) Reduced postburn hypertrophic scarring and improved physical recovery with yearlong administration of oxandrolone and propranolol. Ann Surg 268(3):431–441
85. Murphy KD, Thomas S, Mlcak RP, Chinkes DL, Klein GL, Herndon DN (2004) Effects of long-term oxandrolone administration in severely burned children. Surgery 136(2):219–224
86. Mayes T, Gottschlich MM, Khoury J, Kagan RJ (2015) Investigation of bone health subsequent to vitamin D supplementation in children following burn injury. Nutr Clin Pract 30(6):830–837
87. Al-Tarrah K, Hewison M, Moiemen N, Lord JM (2018) Vitamin D status and its influence on outcomes following major burn injury and critical illness. Burns Trauma [Internet] 6:11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5910591/
88. Porter C, Tompkins RG, Finnerty CC, Sidossis LS, Suman OE, Herndon DN (2016) The metabolic stress response to burn trauma: current understanding and therapies. Lancet 388(10052):1417–1426
89. Jeschke MG, Abdullahi A, Burnett M, Rehou S, Stanojcic M (2016) Glucose control in severely burned patients using metformin: an interim safety and efficacy analysis of a phase II randomized controlled trial. Ann Surg 264(3):518–527
90. Clayton RP, Wurzer P, Andersen CR, Mlcak RP, Herndon DN, Suman OE (2017) Effects of different duration exercise programs in children with severe burns. Burns 43(4):796–803
91. Peña R, Ramirez LL, Crandall CG, Wolf SE, Herndon DN, Suman OE (2016) Effects of community-based exercise in children with severe burns: a randomized trial. Burns 42(1):41–47
92. de Lateur BJ, Magyar-Russell G, Bresnick MG, Bernier FA, Ober MS, Krabak BJ et al (2007) Augmented exercise in the treatment of deconditioning from major burn injury. Arch Phys Med Rehabil 88(12):S18–S23
93. Przkora R, Herndon DN, Suman OE (2007) The effects of oxandrolone and exercise on muscle mass and function in children with severe burns. Pediatrics 119(1):e109–16
94. Porro LJ, Al-Mousawi AM, Williams F, Herndon DN, Mlcak RP, Suman OE (2013) Effects of propranolol and exercise training in children with severe burns. J Pediatr 162(4):799.e1–803.e1
95. Chao T, Porter C, Herndon DN, Siopi A, Ideker H, Mlcak RP et al (2018) Propranolol and oxandrolone therapy accelerated muscle recovery in burned children. Med Sci Sports Exerc 50(3):427–435
96. Suman OE, Mlcak RP, Herndon DN (2002) Effect of exercise training on pulmonary function in children with thermal injury. J Burn Care Rehabil 23(4):288–293
97. Diego AM, Serghiou M, Padmanabha A, Porro LJ, Herndon DN, Suman OE (2013) Exercise training after burn injury: a survey of practice. J Burn Care Res 34(6):e311–e317
98. Schneider JC, Holavanahalli R, Helm P, Goldstein R, Kowalske K (2006) Contractures in burn injury: defining the problem. J Burn Care Res 27(4): 508–514
99. Rumsey N, Clarke A, White P (2003) Exploring the psychosocial concerns of outpatients with disfiguring conditions. J Wound Care 12(7):247–252
100. McGoldrick RB, Sawyer A, Davis CR, Theodorakopoulou E, Murison M (2016) Lasers and ancillary treatments for scar management: personal experience over two decades and contextual review of the literature. Part I: Burn scars. Scars Burns Heal 2:205951311664209
101. Friedstat JS, Hultman CS (2014) Hypertrophic burn scar management: what does the evidence show? A systematic review of randomized controlled trials. Ann Plast Surg 72:S198–S201
102. Kafka M, Collins V, Kamolz L-P, Rappl T, Branski LK, Wurzer P (2017) Evidence of invasive and non-invasive treatment modalities for hypertrophic scars: a systematic review: evidence of treatment modalities for hypertrophic scars. Wound Repair Regen 25(1):139–144
103. Macintyre L, Baird M (2006) Pressure garments for use in the treatment of hypertrophic scars—a review of the problems associated with their use. Burns 32(1):10–15
104. Van den Kerckhove E, Stappaerts K, Fieuws S, Laperre J, Massage P, Flour M et al (2005) The assessment of erythema and thickness on burn related scars during pressure garment therapy as a

preventive measure for hypertrophic scarring. Burns 31(6):696–702
105. DeBruler DM, Baumann ME, Blackstone BN, Zbinden JC, McFarland KL, Bailey JK et al (2019) Role of early application of pressure garments following burn injury and autografting. Plast Reconstr Surg 143(2):310e–21e
106. Uslu A, Sürücü A, Korkmaz MA, Uygur F (2019) Acquired localized hypertrichosis following pressure garment and/or silicone therapy in burn patients. Ann Plast Surg 82(2):158–161
107. Aust MC, Knobloch K, Reimers K, Redeker J, Ipaktchi R, Altintas MA et al (2010) Percutaneous collagen induction therapy: an alternative treatment for burn scars. Burns 36(6):836–843
108. Ramaut L, Hoeksema H, Pirayesh A, Stillaert F, Monstrey S (2018) Microneedling: where do we stand now? A systematic review of the literature. J Plast Reconstr Aesthet Surg 71(1):1–14
109. Trottier V, Marceau-Fortier G, Germain L, Vincent C, Fradette J (2008) IFATS collection: using human adipose-derived stem/stromal cells for the production of new skin substitutes. Stem Cells 26(10):2713–2723
110. Condé-Green A, Marano AA, Lee ES, Reisler T, Price LA, Milner SM et al (2016) Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: a systematic review of the literature. Plast Reconstr Surg 137(1): 302–312
111. Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA (2014) Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. Ann Surg 260(3):519–529; discussion 529–532
112. Goldberg DJ (2012) Laser dermatology. Springer, New York, 150 p
113. Issler-Fisher AC, Waibel JS, Donelan MB (2017) Laser modulation of hypertrophic scars. Clin Plast Surg 44(4):757–766
114. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR (2004) Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med 34(5):426–438
115. Tannous Z (2007) Fractional resurfacing. Clin Dermatol 25(5):480–486
116. Laubach H-J, Tannous Z, Anderson RR, Manstein D (2006) Skin responses to fractional photothermolysis. Lasers Surg Med 38(2):142–149
117. Makboul M, Makboul R, Abdelhafez AH, Hassan SS, Youssif SM (2014) Evaluation of the effect of fractional CO_2 laser on histopathological picture and TGF- β 1 expression in hypertrophic scar. J Cosmet Dermatol 13(3):169–179
118. Choi JE, Oh GN, Kim JY, Seo SH, Ahn HH, Kye YC (2014) Ablative fractional laser treatment for hypertrophic scars: comparison between Er:YAG and CO_2 fractional lasers. J Dermatol Treat 25(4):299–303
119. Poetschke J, Dornseifer U, Clementoni MT, Reinholz M, Schwaiger H, Steckmeier S et al (2017) Ultrapulsed fractional ablative carbon dioxide laser treatment of hypertrophic burn scars: evaluation of an in-patient controlled, standardized treatment approach. Lasers Med Sci 32(5):1031–1040
120. Majid I, Imran S (2018) Fractional carbon dioxide laser resurfacing in combination with potent topical corticosteroids for hypertrophic burn scars in the pediatric age group: an open label study. Dermatol Surg 44(8):1102–1108
121. Lee S-J, Suh D-H, Lee JM, Song K-Y, Ryu HJ (2016) Dermal remodeling of burn scar by fractional CO_2 laser. Aesthet Plast Surg 40(5):761–768
122. Issler-Fisher AC, Fisher OM, Smialkowski AO, Li F, van Schalkwyk CP, Haertsch P et al (2017) Ablative fractional CO_2 laser for burn scar reconstruction: an extensive subjective and objective short-term outcome analysis of a prospective treatment cohort. Burns 43(3):573–582
123. El-Zawahry BM, Sobhi RM, Bassiouny DA, Tabak SA (2015) Ablative CO2 fractional resurfacing in treatment of thermal burn scars: an open-label controlled clinical and histopathological study. J Cosmet Dermatol 14(4):324–331
124. Schmitt L, Huth S, Amann PM, Marquardt Y, Heise R, Fietkau K et al (2018) Direct biological effects of fractional ultrapulsed CO_2 laser irradiation on keratinocytes and fibroblasts in human organotypic full-thickness 3D skin models. Lasers Med Sci 33(4):765–772
125. Taudorf EH, Danielsen PL, Paulsen IF, Togsverd-Bo K, Dierickx C, Paasch U et al (2015) Non-ablative fractional laser provides long-term improvement of mature burn scars—a randomized controlled trial with histological assessment. Lasers Surg Med 47(2):141–147
126. Clayton JL, Edkins R, Cairns BA, Hultman CS (2013) Incidence and management of adverse events after the use of laser therapies for the treatment of hypertrophic burn scars. Ann Plast Surg 70(5):500–505
127. Żądkowski T, Nachulewicz P, Mazgaj M, Woźniak M, Cielecki C, Wieczorek AP et al (2016) A new CO_2 laser technique for the treatment of pediatric hypertrophic burn scars: an observational study. Medicine (Baltimore) 95(42):e5168
128. Anderson RR, Donelan MB, Hivnor C, Greeson E, Ross EV, Shumaker PR et al (2014) Laser treatment of traumatic scars with an emphasis on ablative fractional laser resurfacing: consensus report. JAMA Dermatol 150(2):187–193
129. Brewin MP, Lister TS (2014) Prevention or treatment of hypertrophic burn scarring: a review of when and how to treat with the pulsed dye laser. Burns 40(5):797–804