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Beneath the Surface: A Review of Laser Remodeling of Hypertrophic Scars and Burns

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Significance: Hypertrophic scars, keloids, and burn injuries of the skin have a significant impact on patients' lives and impact the health care system tremendously. Treating skin wounds and lesions can be challenging, with a variety of choices available for treatment. Scar and burn managements range from invasive, surgical options such as scar excision to less invasive, nonsurgical alternatives such as laser therapy or topical drug application.
Recent Advances: Laser treatment has become increasingly popular, with a growing body of research supporting its use for scars and burns. Numerous methods are available for the treatment of these skin diseases, including different nonsurgical laser therapies.
Critical Issues: To date, the optimal treatment method for scars, keloids, and burn injuries of the skin has not yet been established, although it is an area of increasing clinical concern.
Future Directions: This review provides an updated summary of the treatment of scars and burn wounds of the skin using different laser treatments, including the most recent technologies. It addresses their indications, mechanisms of action, differences, efficacies, and complications.

Keywords: critical review, laser technologies, hypertrophic scars, keloids, burn injuries of the skin

SCOPE AND SIGNIFICANCE

This review will focus on the different available laser therapies to give an up-to-date report for doctors, surgeons, and researchers. We give a short overview of the development of lasers, compare different laser treatments for scar types and burns, and show the most recent innovations in laser therapy. All addressed lasers in this review have multiple indications and show promising outcomes for the treatment of different scars and burns.

TRANSLATIONAL RELEVANCE

A multitude of treatments is available for the therapy of cutaneous scars and burn injuries, including laser technologies. By understanding the pathophysiology of cutaneous wounds and the use of different laser applications, nonsurgical laser ther-

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apies can be beneficial for the treatment of scars with the potential to improve clinical outcomes.

CLINICAL RELEVANCE

Excessive scar formation after cutaneous wound healing results in poor functional and esthetic outcomes. The economic impact is greater when the costs of disability and revision surgeries due to dysfunctional tissue and disfiguring scars are included.[1] The use of laser therapies can have the potential to treat cutaneous scars and burn injuries, resulting in improved outcomes and quality of life. The methods discussed in this review are aimed to give an updated summary of the treatment of scars and burn wounds of the skin using different laser treatments, including the most recent technologies.

BACKGROUND

Cutaneous scar formation and burns represent a significant medical burden with billions of dollars spent annually on scar treatments in the United States. Hypertrophic scars (HTS) and keloids represent pathologic, fibrotic responses to cutaneous insult. The hallmark of both lesions is excessive deposition of collagen and other extracellular matrix (ECM) proteins within the skin, as well as proliferation of fibroblasts. In cases of HTS, the lesion typically does not extend beyond the margins of the original wound and growth is self-limiting with regression commonly observed within 2 years.[2] Keloids are more aggressive, with advancing margins and minimal chance of spontaneous regression (Fig. 1).

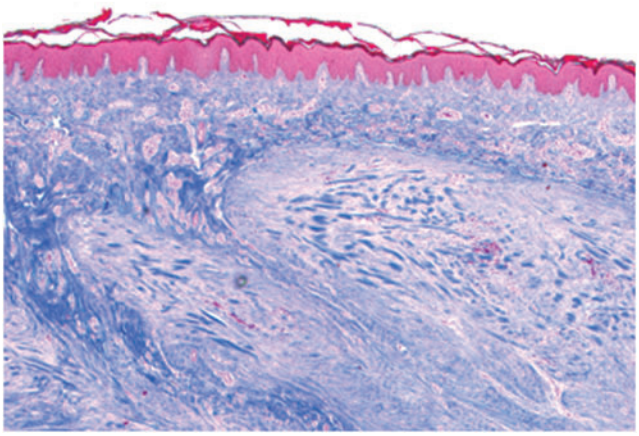

Figure 1. Histology of Keloid. Trichrome Stain. 10×magnification. Color images are available online.

Both types of lesions are commonly thought to arise from fibroblast overactivity during the proliferative phase of wound healing in a process driven by IL-6, IL-10 and TGF-β.[3] It has more recently been proposed that HTS and keloids are manifestations of endothelial dysfunction during the early, inflammatory stage of wound healing.[4] These pathologic scars are only seen following injuries that penetrate at least to the depth of the reticular dermis, suggesting that any insult causing chronic inflammation within this tissue layer could lead to the development of HTS or keloid. Recruitment of deep dermal fibroblasts, a resident fibroblast subpopulation with diminished collagenase activity, then leads to increased production of ECM and inflammatory cytokines.[5] Indeed, it has long been understood that neutralization of proinflammatory factors such as transforming growth factor beta (TGF-β) can help attenuate scar formation.[6] On histology, HTS are characterized by an accumulation of wavy collagen (type III predominates) bundles running parallel to the epithelial surface, while keloids contain sheets of loosely organized collagen I and III.[7]

Many HTS result from burns, and some 32–72% of patients with burn injury will go on to develop HTS.[8] Approximately half a million cases of burn injury are reported annually in the United States.[9] Advances in the acute care of burn patients have pushed survival rates for even the most severe burns involving 80% of the total body surface area above 50%.[10] As a result, many more patients go on to experience the sequelae of serious, life-threatening burn injuries such as HTS (Fig. 2).

Risk factors for HTS include dark skin, female gender, young age, burn site on neck and upper limb, multiple surgical procedures, time to healing, and burn severity.[8] Contracture, in which scar tissue involving a joint can grow to limit its range of motion, is another common complication of burns, along with pruritus, chronic pain, and cosmetic disfigurement.

Among subjective measures of scar severity, the Vancouver Scar Scale (VSS), developed in 1990, is perhaps most widely used. Four criteria: pigmentation, vascularity, pliability and scar height are assessed independently, with increasing score representing more advanced disease (Table 1).[11] Normal skin receives a score of zero. More recently the Patient and Observer Scar Assessment Scale (POSAS) in which the lesion is also scored by the patient with added criteria for pain and pruritus has also entered into regular use (Table 2).[12]

Attempts to establish an objective scale of scar measurement that can accurately predict which

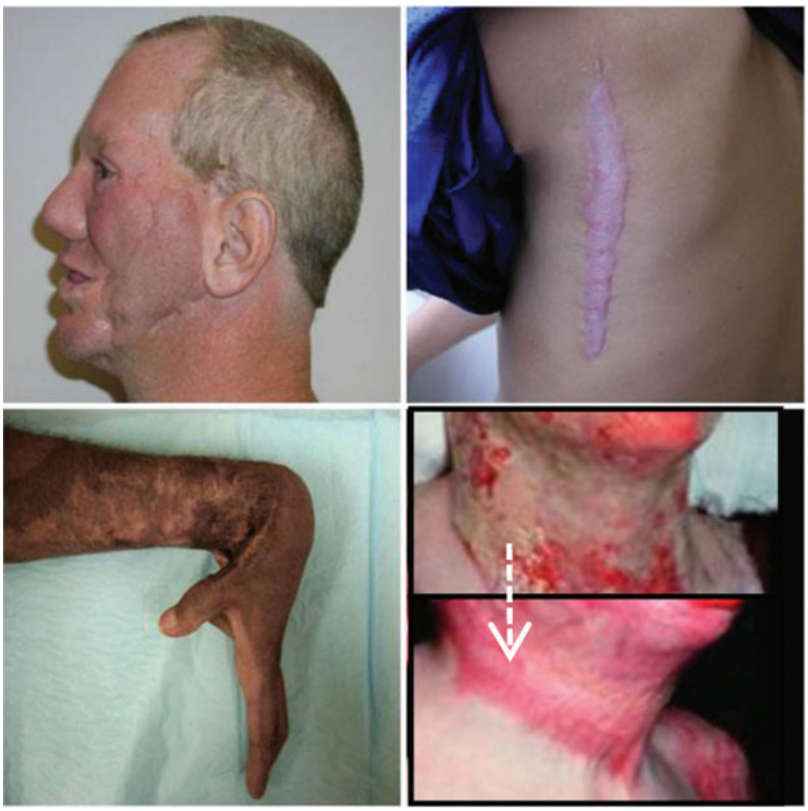

Figure 2. Excessive scar formation. Color images are available online.

lesions will progress to become HTS have been proposed, but at present, there is no "gold standard" scale for the evaluation of scars.[13] Of the criteria commonly evaluated, pliability and erythema, but not pigmentation, correlated significantly with clinical evaluation of hypertrophy.[2]

Current recommendations for treatment of HTS include multimodal combination therapy with steroid injections, 5-fluorouracil and laser treatment.[14] Many such regimens are justified empirically and there is a lack of evidence-based algorithms.[15] Research in molecular biology and regenerative medicine addressed to specific inflammatory mediators or cell-cell interactions is ongoing, but clinical applications in the treatment of HTS remain limited.[1] To date, there are no adequately powered randomized control trials to evaluate whether lasers work to improve hypertrophic burn scars. There remains a need to better characterize the myriad emerging laser and light-based therapies, which are increasingly available and relatively noninvasive.

Table 1. *Vancouver scar scale*

Vancouver Scar Scale							
Pigmentation		*Vascularity*		*Pliability*		*Height*	
Normal	0	Normal	0	Normal	0	Flat, Normal	0
Hypopigmentation	1	Pink	1	Supple	1	<2 mm	1
Mixed	2	Red	2	Yielding	2	2–5 mm	2
Hyperpigmentation	3	Purple	3	Firm	3	>5 mm	3
				Banding	4		
				Contracture	5		

OVERVIEW

Historical background on laser

The word *laser* is an acronym for "light amplification by stimulated emission of radiation." An external energy source, or pump, is used to stimulate an active medium housed within a resonant chamber. Active media may be liquid, solid, or gas and are selected based on their ability to emit radiation of desired wavelengths. Lasers are distinguished as radiation sources by their emission being monochromatic (single, fixed wavelength), unidirectional and perfectly in-phase, or coherent.

Crucially, these special properties allow for the precise application of a predictable amount of energy. Lasers vary broadly in their design and purpose, but certain parameters bear special medical significance. Beam energy can be applied either

Table 2. *Patient and observer scar assessment scale*

Patient Scale										
	1 = No; Yes = 10									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Is the scar painful?										
Is the scar itching?										
Is the color of the scar different?										
Is the scar more stiff?										
Is the thickness of the scar different?										
Is the scar irregular?										
1 = As Normal Skin; Very Different To Normal Skin = 10										
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Overall opinion of the scar										

Observer Scale					
	1 = Normal Skin; Worst Scar Imaginable = 10				
Parameter	1 2 3 4 5 6 7 8 9 10	*Category*			
Vascularity		Pale	Pink	Red	Purple Mix
Pigmentation		Hypo	Hyper	Mix	
Thickness		Thicker	Thinner		
Relief		More	Less	Mix	
Pliability		Supple	Stiff	Mix	
Surface area		Expansion	Contraction	Mix	
Overall opinion					

continuously or in a pulsatile manner depending upon the desired effect. Medical lasers are characterized as either ablative or nonablative, with the former disrupting the epidermis and the latter leaving the outermost layer of skin intact en route to targets or *chromophores*, in the dermis. The operative principle of laser-based therapy is photothermolysis. Energy absorption by chromophores within the skin generates heat, leading to targeted destruction and a local inflammatory response. Interruption of the microvasculature starves the tissue of oxygen, limiting cellular proliferation and protein deposition, and therefore attenuates scar formation. Synthesis of new collagen and reorganization of fiber bundles lead to better approximation of healthy, prewound tissue.[16]

While the theoretical underpinnings of laser technology were first described in the work of Albert Einstein,[17] the practical history of lasers began in the early 1950 s when the first "stimulated" emissions of microwave radiation (Microwave Amplification by Stimulated Emission of Radiation, or MASER) were generated by J.P. Gordon and C.H. Townes at Bell Telephone Laboratories. Publishing in Nature in 1960, Dr. T. H. Maiman at Hughes Aircraft Company presented the first working laser using a synthetic ruby crystal stimulated by high-intensity flash lamps, which generated millisecond pulses of coherent 694 nm (near infrared) ruby laser light.[18] It was not until 1962 that the first medical application for laser was reported by Goldman, when he used a ruby laser in dermatology.[19]

1964 saw the development of both the carbon dioxide (CO_2) and neodymium:yttrium aluminum Garnet (Nd:YAG) lasers. The CO_2 proved useful in surgery on highly vascularized organs, owing to its focused beam and high degree of absorption by water. Because soft tissue consists mostly of water, the CO_2 laser beam cuts tissue like a scalpel following immediate hemostasis. Further discoveries in fiberoptics allowed for the transmission of far-infrared laser beams, which broadened the utility of CO_2 lasers to include endoscopic surgery.

In 1986, the U.S. Food and Drug Administration approved the pulsed dye laser (PDL) for treatment of cutaneous vascular disorders. The PDL was based on the concept of selective photothermolysis introduced by Anderson and Parrish.

More recently, so-called fractional lasers, which ablate the skin in a grid-like pattern of miniscule columns called microscopic treatment zones (MTZs) and leave intervening tissue unharmed, have entered use. Fractional laser platforms can either be ablative or nonablative. *In vitro* studies suggest that skin treated with fractional Er:YAG laser expresses heightened levels of inflammatory cytokines such as IL-6, IL-8, and IL-24, as well as various chemokines (like CXCLs) and protein-digesting MMPs.[20]

DISCUSSION

Different laser therapies and their applications

Pulsed dye laser. The PDL functions by the excitation of a liquid dye medium, emitting photons of a wavelength absorbed avidly by the hemoglobin molecule (585 nm). This modality is therefore well suited to targeted remodeling of cutaneous vascular lesions. It was eventually applied to burn patients with hyperemic and pruritic scars and showed promising results.[16,21] PDL is thought to attenuate the formation of HTS by targeting their developing microvasculature.[22] Furthermore, PDL treatment is associated with decreased TGF-β expression, fibroblast proliferation, and collagen type III deposition.[23] Special care must be taken in treating darker skin where epidermal melanin competes with hemoglobin for laser absorption.[24]

PDL has shown promise[25] in the treatment of scars and some have suggested it to be the first-line treatment and prophylaxis cases of keloids and HTS at some centers.[26] The development of long-

PDL provided another treatment modality with comparable efficacy in HTS reduction, but significantly less risk of posttreatment purpura.[27] A systematic review of PDL treatment of HTS supports the use of 585 and 595 nm devices with consistent low to moderate improvement seen across included study populations.[25] Another systematic review of eight randomized controlled trials using 585 nm PDL for the treatment of HTS and keloid found that PDL was superior to conventional treatment in improving scar appearance.[28]

PDL treatment has long been used with favorable results in the setting of burn injury. The use of PDL on scars at the seams of newly healed skin grafts in pediatric burn patients helps to reduce erythema, scar height and tissue elasticity.[29] Facial burns that lead to HTS can be particularly difficult to treat, with excision sometimes resulting in unavoidable disfigurement. In a study of 57 patients with hypertrophic facial burn scars, PDL treatment was used in place of surgical excision. Of these patients, 34 (60%) received additional treatment with Z-plasty to relieve scar tension. Favorable outcomes were achieved, ranging from reversal of HTS to treatment of stable erythema, depending upon time from initial burn injury to laser treatment.[16] Scars can be "rehabilitated" through laser treatments and smaller procedures, while the use of larger surgical treatments may create deformities that are worse than the original scar.[16]

As the HTS develops and thickens, some hypothesize that the underlying microvasculature is better protected and less accessible to the PDL, and therefore recommend that PDL treatment begins as soon as possible following discovery of the lesion.[30] The energy required for effective treatment increases with scar thickness. By titrating up laser energy until pinpoint bleeding is observed, clinicians can ensure that the beam penetrates to the level of the dermal blood vessels.[31]

Ablative fractional laser therapies have shown to improve the uptake of topical medical drugs into the stratum corneum, epidermis, and dermis.[32,33] Studies in animal models suggest that pretreatment with CO_2 and erbium:yttrium-aluminum-garnet (Er:YAG) lasers can increase the permeability and depth of penetration of topically applied drugs.[34] In a prospective case series of 15 patients with HTS, fractional ablative CO_2 laser treatment combined with topical application of 20 mg/mL triamcinolone acetonide was successful in reducing scar burden, principally by the improvement of scar texture.[35] One major limitation of the existing studies on laser-assisted drug delivery (LAD) is their performance on animal models, but additional long-term studies in humans, including a large number of patients, are still missing.

Recent research suggests that the coagulation zone around laser treatment sites in fractional ablative lasers may serve as a reservoir for topical drugs.[32] Tissue in this zone is thicker and tighter adjacent to the skin that was actually treated with a fractional ablative laser. Because of this tightness, the coagulation zone is thought to have a lower diffusity than the treated area surrounding it, which appears to make it serve as a storage depot for secondary drug delivery. This might postitively influence the treated skin exclusively without having a systemic effect.[32,35]

Interestingly, researchers have applied a similar pretreatment principle to sequential laser therapy. One group describes a laser "drilling" technique performed with pulsatile CO_2 laser followed by a second "deep" pass with a continuous fractional CO_2 device.[36] This regimen is thought to increase the penetration depth of the CO_2 laser in the treatment of HTS. VSS and UNC Scar Scale Score were significantly decreased in the treated cohort of 158 patients with HTS.

Fractional Ablative CO_2 laser. Evidence suggests that CO_2 lasers may be effective in the treatment of older, mature scars resistant to treatment by PDL. The fractional 10,600 nm CO_2 laser, which ablates skin and scar tissue in a columnar pattern to a depth of several millimeters, destroys disorganized ECM proteins leading to reepithelialization and the deposition of new collagen in physiologic orientation.[37] Even thick HTS resulting from severe burns can be targeted in this manner. $FXCO_2$ has also proven to be safe and effective in the pediatric population. In a study of 47 patients 6–16 years of age, treatment with CO_2 laser conferred improvement in VSS total score as assessed by both physician and parent, as well as decreased scar thickness measured by ultrasound.[38]

In the treatment of widespread hypertrophic burn scars, $FXCO_2$ laser offers the advantage of fewer treatment sessions compared with nonablative modalities.[13] In a study of 100 patients with either burn or traumatic scars, Keen *et al.* observed excellent response to CO_2 laser treatment with a mean of six sessions.[39] Treatment of keloids proves more challenging. Among 15 patients with hypertrophic and keloidal scars, only the HTS showed significant improvement after three CO_2 fractional laser sessions.[40] However, one published case series, including eight patients with 12 total keloids using superpulsed CO_2 laser treatment, reported good results with no recurrence.[41] In a recent split-

scar, evaluator-blinded study of patients with recent surgical scars of the head and neck who underwent ablative $FXCO_2$ therapy, patients, but not physician observers, saw improvement after three sessions.[42] Of note, significant improvement was seen in itch score and global patient evaluation; however, observer POSAS score was no better in the treated half of the scar than the untreated half.[42]

Other groups have reported good results with $FXCO_2$ in the treatment of HTS. Among 10 patients with hypertrophic burn scars who underwent treatment with fractional CO_2 laser therapy, VSS, POSAS score, and quality of life measures all showed significant improvement within 6 months of treatment.[43] Strikingly, scar firmness was observed to decrease by 30% after a single session. When 40 patients with HTS were treated over 4 monthly sessions with fractional CO_2 laser, there was a statistically significant improvement as measured by VSS.[44] Skin biopsy taken before treatment and then again 3 months afterward showed increased epidermal thickness along with thinning of the stratum corneum and replacement of irregular collagen bands with organized new collagen fibrils.[44] TGF-β1 expression after laser therapy was significantly decreased.[44]

Another study of 10 patients with mature, full-thickness, hypertrophic burn scars treated with a fractional CO_2 laser gives further insight into the mechanism of treatment.[45] Not only was significant improvement seen as evaluated with VSS and POSAS but also reverse transcription polymerase chain reaction analysis of fresh tissue samples (obtained before the initial treatment and again 48 h after the first treatment) showed that types I and III procollagen mRNA levels were greatly diminished after treatment.[45] Furthermore, $FXCO_2$-treated skin shows an increase in the ratio of type III to type I collagen after 2 months, suggesting that collagenogenic processes are first suppressed and then "reset," with subsequent collagen deposition more closely mirroring the subtype proportions seen in healthy skin.[45]

MMP-1 was also significantly upregulated after treatment, as was expression of miR-18α and miR-19α.[45] Metalloproteinase activity likely explains at least, in part, the ability of CO_2 laser to increase lesion pliability for both HTS and keloid.[46] Changes to collagen organization as well as increased expression of matrix metalloproteinase 9 (MMP-9) have been seen on histology.[46] Conversely, profibrotic growth factors, namely TGF-β2, -β3, and βFGF, are seen to be downregulated.[45]

As $FXCO_2$ treatment enters into greater use and various treatment protocols develop, the need for scientific work, which better characterizes tissue-level effects of laser, has become clear. $FXCO_2$ treatment parameters such as MTZ density, energy level, and the number of sequential pulses, sometimes called "pulse stacking," can be adjusted with unclear implications for the treatment outcome. In a study of Red Duroc pigs with full-thickness burn wounds, eschar excision and split-thickness skin autograft were performed.[47] Three months later, scars were treated with a fractional CO_2 laser with 70mJ of energy delivered as either a single pulse or stacked for three consecutive pulses. Esthetic and functional criteria of the skin such as erythema and transepidermal water loss were recorded before treatment and then at regular intervals in the days following $FXCO_2$ therapy. Triple stacking of $FXCO_2$ pulses was found to cause only minor increases in MTZ depth and width. Somewhat surprisingly, reepithelialization of the skin was observed by 48 h in both treatment protocols, with local inflammation markers returning to baseline by 1 week postprocedure.

As mentioned previously, contracture remains a feared and debilitating sequela of pathologic scarring, which involves a joint. In a published case series of two pediatric patients, one group reports success in treating restrictive pediatric scar contractures with an ablative microfractionated 600 nm CO_2 laser.[48] Both patients demonstrated subjective and objective improvements in range of motion and function, and no operative complications were reported. In a study of red duroc pigs, who received skin autograft following third-degree burn, treatment with PDL, fractional CO_2, or PDL & fractional CO_2 resulted in significantly less contraction versus skin graft-only controls.[49] There were no statistically significant differences in contraction among laser therapy groups, although fractional CO_2 showed a slight advantage in reduction of erythema.[49]

$FXCO_2$ therapy has also been proposed as an adjunct in treatment of burn HTS hypopigmenta-

Table 3. *Overview of different scar types and commonly used laser treatments*

Scar Type	*Characteristics*	*Commonly Used Lasers*
Traumatic	Pink	PDL
Hypertrophic	Raised, erythematous Restricted to wound boundaries Can be symptomatic	PDL, CO_2
Keloid	Raised, firm, dark purple-reddish Overgrow outside of original wound margin Often symptomatic	PDL, CO_2
Hypertrophic burns	Contract, stiff, firm Hyperpigmentation, altered texture Often symptomatic	Fractional lasers

PDL, pulsed dye laser.

tion. In this study, LAD allows synthetic alpha-melanocyte-stimulating hormone analogs to cross the epidermis, leading to melanogenesis restoration of skin pigmentation.[50]

TAKE-HOME MESSAGES

- Scars and burn injuries of the skin are prevalent and highly impact the patients' lives as well as the health care system.
- Laser treatments have the potential to treat scars, keloids, and burn injuries of the skin, with a growing body of research supporting its use for scars and burns.
- Despite recent advances in laser technologies, there still is a lack of evidence-based strategies for their treatment of scar and burn injuries of the skin.
- The adequate use of laser treatments for scars can have the potential to reduce health care costs and improve the quality of scars.

SUMMARY

The efficacy, ease of use and minimal side effect profile of laser and light-based therapies virtually ensure that they will take on an increasingly central role in the treatment of HTS, keloids, and burns. The great range of laser platforms available make this a highly versatile modality (Table 3) that can be tailored to each lesion and even account for differences in patient skin type.

The level of evidence for laser therapies in managing HTS, keloids, and burns remains low. Additional research in the efficacy of multiple quantifiable parameters, like scar texture, recurrence rates, and adverse effects, is necessary to establish guidelines. Updated data on scar, keloid, and burn management using laser technologies will benefit both surgeons and patients in making optimal decisions regarding evidence-based strategies for the treatment of HTS, keloids, and burn injuries of the skin.

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Abbreviations and Acronyms

CO_2 = carbon dioxide
ECM = extracellular matrix
Er:YAG = erbium:yttrium-aluminum-garnet
FGF = fibroblast growth factor
$FXCO_2$ = Fractional Ablative CO_2 laser
HTS = hypertrophic scars
IL = interleukin
LAD = laser-assisted drug delivery
MASER = microwave amplification by stimulated emission of radiation
MMP = matrix metalloproteinase
MTZ = microscopic treatment zone
Nd:YAG = neodymium:yttrium aluminum garnet
PDL = pulsed dye laser
POSAS = patient and observer scar assessment scale
TGF-β = transforming growth factor beta
VSS = Vancouver Scar Scale