Advances in fractional technology for skin rejuvenation, skin tightening, drug delivery, and treating scars and skin defects

Deirdre Connolly, MD; Laura Schilling, MD; and Nazanin Saedi, MD

■ **Abstract**

The development of fractional photothermolysis has revolutionized the treatment of skin scarring, rejuvenation, and tightening. By creating targeted microthermal zones and leaving surrounding tissue intact, this concept has provided the field with efficacious results, with less downtime and a better safety profile. This has started to change the paradigm of what is considered first-line treatment for scarring and rejuvenation. While originally applied to nonablative lasers, fractionation has now been employed in ablative, quality-switched, picosecond, and novel hybrid fractional lasers. Furthermore, other energy-based technologies, such as radiofrequency, have adopted the concept of fractionation in an attempt to optimize the balance of efficacy, downtime, and side effects. Herein, we describe how the ever-expanding repertoire of fractional devices is applied to the treatment of scarring, skin rejuvenation, and tightening. In addition, newer applications, such as transdermal drug delivery, are being developed by using fractional devices. Growing experience with these devices has broadened their relevance to more skin types and body sites than ever. Ultimately, the knowledge of appropriate treatment parameters is paramount and allows for the safe and effective treatment of a variety of patients with numerous devices.

Semin Cutan Med Surg 36:138-147

In recent decades, there has been a revolution in energy-based treatment options for skin scarring, rejuvenation, and tightening. One of the most promising developments has been the introduction of fractional photothermolysis, developed by Anderson and Manstein in 2004. Fractionated systems deliver laser energy in a grid-like pattern, creating microscopic columns of ablative and/or coagulative damage termed microthermal zones (MTZs), which stimulate collagen remodeling.[1] The incorporation of fractional photothermolysis into energy-based devices has allowed less destruction to surrounding tissue, leading to desired results with the minimization of unwanted side effects, leading to both ablative and nonablative laser devices becoming desirable treatment options for cutaneous scarring and rejuvenation. Given their impressive results, newer fractional laser treatment options, including picosecond lasers, quality-switched (QS) lasers, and combined ablative and nonablative lasers, are being investigated for the treatment of these common skin conditions.

The following review addresses the current and emerging topics on fractional laser treatment of skin scarring and rejuvenation based on the device type, including ablative, nonablative, QS, picosecond, and hybrid fractional lasers (HFLs). Additionally, newer energy-based fractional devices, such as radiofrequency (RF) with and without microneedling and the use of fractionated technology for drug delivery, are discussed in the context of these common skin conditions.

Fractionated lasers

Treatment options for cutaneous scars and skin rejuvenation have evolved significantly since the rise in popularity of ablative lasers in the 1990s. Newer treatment options, including ablative fractional lasers (AFL) and nonablative fractional lasers (NAFL), have garnered favor, given the milder side effect profile in comparison with traditional fully ablative lasers.

Ablative fractional lasers

Acne scarring

AFLs were developed in an attempt to achieve the efficacy of traditional ablative lasers with the milder side effect profile of fractional technology. Although a single treatment produces less dramatic, albeit noticeable, results than traditional fully ablative lasers can, multiple treatments result in greater clinical improvement.[2] Currently, there are 3 types of AFLs available for scar treatment: the 10600-nm carbon dioxide (CO_2), the 2940-nm erbium:yttrium aluminum garnet (Er:YAG), and the 2740-nm yttrium scandium gallium garnet (YSGG) lasers. AFL is associated with the increased risk of both protracted erythema and postinflammatory hyperpigmentation (PIH) in darker skin types, which has led many clinicians to prefer a longer series of NAFL treatments over AFL treatments to achieve similar results with a lower risk of side effects.

Multiple studies support the efficacy of the fractional CO_2 laser in acne scars. The overwhelming majority of these studies investigate the utility of these lasers in atrophic facial scars. While NAFLs typically require multiple sessions to achieve modest to marked efficacy, 1 AFL treatment alone can rival that of multiple NAFL treatments. Three studies (42 total patients) have shown that a single treatment with a fractional CO_2 laser can result in an overall improvement of greater than 50%.[3] A high-fluence, low-density setting has been shown to be more efficacious than a low-fluence, high-density setting.[4] Similar to the fractional CO_2 laser, the fractional Er:YAG and the YSGG have been shown to produce comparable rates of improvement in atrophic acne scars after multiple treatments.[5-7]

In 2012, Ong and Bashir[2] performed a comprehensive review of 26 heterogeneous studies investigating AFL (13 studies) versus

Thomas Jefferson University Hospital, Department of Dermatology and Cutaneous Biology, Philadelphia, Pennsylvania.
Disclosures: Dr Connolly and Dr Schilling have nothing to disclose. Dr Saedi is a consultant for Cynosure, Solta, and Alastin.
Correspondence: Nazanin Saedi, MD; nazanin.saedi@jefferson.edu

1085-5629/13$-see front matter © 2017 Frontline Medical Communications
https://doi.org/10.12788/j.sder.2017.039

NAFL (13 studies) in the treatment of facial acne scarring. For AFLs, improvement ranged from 26% to 83% for 1 to 3 treatments, whereas for NAFLs, improvement ranged from 26% to 50% for 1 to 5 treatments. Regardless of which AFL is used, the potential for scar improvement is greater with AFL than with NAFL. In addition, the time interval between treatments does not impact efficacy. In a study comparing 2 fractional CO_2 treatments at 1- versus 3-month intervals, no difference in scar improvement was noted between groups.[8]

AFLs also have lasting effects on scar appearance. Ortiz et al conducted a follow-up study on 10 patients who had previously received fractional CO_2 treatments. Patients were seen at 1 and 2 years after the treatment and were found to maintain an average of 74% improvement in scar appearance in addition to preserved patient satisfaction rates.[9]

Hypertrophic scars and keloids

While steroid injections, and more recently the injection of 5-Fluorouracil (5-FU), remain a mainstay in the treatment of keloids and hypertrophic scars (HTS),[10,11] AFL is gaining momentum in this arena due to its proven efficacy. In a consensus statement by Anderson et al in 2014 regarding the use of lasers in scarring, a panel of experts concluded that AFLs should be considered in the first-line management of HTS and/or traumatic scars.[12] The literature addressing scar types other than atrophic acne scars is not as robust; however, a split-scar, randomized controlled trial of 30 patients (18 with keloids, 12 with HTS) treated with 4 sessions of fractional CO_2 at 6-week intervals showed a significant reduction in the Vancouver Scar Scale (VSS) scores at 3 months, which remained stable at 6 months on the treated side as compared with nontreated. The VSS is based on the grade of pigmentation, vascularity, pliability, and height of scars. The pliability of the scars was markedly improved, but scar height was the least improved trait after treatment.[13]

The thickness of scars plays a role in how they respond to AFL. One study of 15 raised burn scars (11 HTS, 4 keloids, mean scar age 8.1 years) showed that fractional CO_2 improved the Patient and Observer Scar Assessment Scale (POSAS) and the VSS for HTS but not for thicker keloids after 3 treatment sessions every 4 to 6 weeks.[14,15] HTS on the limbs responded better than those on the face or trunk. Authors purported that the dermal penetration depth of the laser light (400 to 1,000 μm) was insufficient to reach the depth of the scar tissue in the treated keloids, leaving deeper fibrosis untreated. They further suggested that keloids may need to be treated using the stack parameter (on the DEKA: 30 W, 800 μm spacing, 800 μs dwelling time, stack 1 during the first session, followed by 30 W, 300 μm spacing, 800 μs dwelling time, stack 1 in the following 2 sessions), with higher stacks (3 to 4) to increase the depth of ablation.[14]

Surgical and traumatic scars

Surgical and traumatic scars show significant improvement in appearance when treated with AFL. A study of 18 patients with burn scars treated with 3 monthly sessions of AFL CO_2 showed a mean VSS decrease from 8.5 at baseline to 4.9 posttreatment, with a significant reduction of the POSAS score.[16] Multiple small case reports support the efficacy and low side effect profile of AFL in the treatment of burn scars.[17-19]

Previously, it was thought that waiting several months before laser treatment of traumatic scars was ideal, but now early intervention as soon as reepithelization is complete is best. Postlaceration scars treated with AFL at 4 weeks after repair showed improvement on all elements of the VSS in 1 study involving 15 facial lacerations.[20] While scars with contracture are a rare but known side effect of AFLs, most notably after treatment of the neck,[21] these laser devices may also be employed in the treatment of scar contractures related to burn and trauma. It is important to use settings with lower energies when treating areas of the face because they are at greater risk for scarring.

Skin rejuvenation and skin tightening

Traditional ablative resurfacing, specifically with CO_2, has long been considered the gold standard for skin rejuvenation and scar treatment. The introduction of the revolutionary NAFLs naturally led to the later development and use of AFLs in 2007[22] in order to more closely mimic the superior results of traditional ablative resurfacing while maintaining a milder side effect profile. Improvements can be seen in mild to moderate rhytides, skin laxity, pore size, skin texture, and skin tone of the face, neck, and chest.

The efficacy of AFLs in skin rejuvenation and the treatment of photoaging and skin laxity is now well established. In an early study by Rahman et al,[23] significant clinical improvement was appreciated in 30 patients after 1 to 2 full-face and neck treatments with a fractional CO_2 laser (Fraxel Re:pair) with a range of energies and densities. Moderate to significant improvement was seen in rhytides, skin laxity, texture, pigmentation, and vasculaturity.[23] Further studies have continued to substantiate such efficacy. Tierney and Hanke[24] prospectively studied the clinical benefits of 2 to 3 treatments of a different fractional CO_2 laser (Smartxide DOT; Calenzano, Italy) in 45 patients (Fitzpatrick Skin Types I-III). They showed a mean improvement of 50.3% in skin laxity, 48.5% in skin texture, 53.9% in dyschromia, and an average 52.4% improvement in overall cosmetic outcome.[24] Collagen remodeling has been shown to continue for at least 3 months after treatment.[22] Full-face resurfacing with AFLs has a shorter recovery period and milder side effect profile than fully ablative resurfacing.[25]

In general, the aesthetic results of AFLs do not match those of the fully ablative lasers in regards to rhytides and photoaging.[26,27] However, the AFLs may theoretically produce superior skin-tightening results in comparison with the traditional ablative laser due to the greater depth of ablation created by the fractional technology.[28] While few truly comparative studies exist between the 2 methods, several studies have shown the marked skin-tightening effects of AFL.23,[28-30] For example, Tierney and Hanke[29] showed a 57% mean improvement in skin tightening of the neck after 1 to 2 treatments with an AFL. To achieve optimal results, AFL treatments may be combined with surgical procedures, such as facelifts, or with other energy-based devices.

While the notable results achieved with AFLs are well known at this time, the notable developments in their use include their safe but cautious application to very delicate facial sites and nonfacial sites. AFLs can be safely used for treatment of the eyelids, neck, and chest. One prominent strength for the AFLs has been periorbital rejuvenation and eyelid tightening. Lower eyelid laxity is due to a combination of dermatochalasis with festooning caused by a redundant orbicularis oculi muscle and its overlying fat and skin.[27]

While surgical blepharoplasty has been the long-standing gold standard in periorbital rejuvenation, AFLs have become a noteworthy option for this indication. They can also provide the additional benefits of improving fine lines, pore size, dyspigmentation, skin texture, and tone.[31]

Nonfacial sites have a relative paucity of adnexal structures and vascular supply in comparison with the face, which leads to an increased risk of side effects, such as dyspigmentation, scarring, and infection.[32,33] Therefore, treatments must be cautiously pursued with conservative settings, such as decreased density. Nonfacial indications beyond neck and chest rejuvenation that have shown benefit with AFLs include hand rejuvenation and, most recently, vaginal rejuvenation.

The vulvovaginal region is not exempt from the effects of aging. Decreasing levels of estrogen cause thinning and atrophy, loss of elasticity, and loss of functionality of the vaginal mucosa, leading to dryness, itching, burning, dysuria, and dyspareunia.[34-36] AFLs can play a role in stimulating the tissue to restore structure and function. In a large study of 386 patients, 3 treatments with a fractional microablative CO_2 laser showed a resolution of the aforementioned symptoms in a majority of patients.[34] Much of the improvement was appreciated even after the first treatment. Histological studies have confirmed a successful remodeling of the vaginal mucosa, with a thickened epithelium with increased glycogen content, as well as increased collagen in the lamina propria.[35] Vaginal laser treatments are tolerated with minimal pain, while vulvar treatments can be more uncomfortable.

While a single treatment with AFLs is often sufficient to show a significant benefit, studies performed multiple treatments to obtain optimal results. The efficacy of a single AFL treatment can certainly be operator dependent and contingent on various treatment parameters, such as fluence, pulse duration, and density. Aggressive treatment parameters in order to achieve maximum efficacy must be balanced with the heightened risk of side effects.

Safety and adverse events

While AFLs offer a milder safety profile than fully ablative lasers, unwanted side effects can still occur.[37,38] The expected effects of AFL lasers include erythema, edema, and scaling that last for 3 to 14 days and typically resolve by 2 weeks.[2,3] Unwanted side effects include hypo- or hyperpigmentation, acneiform eruption, herpes reactivation, scarring, and persistent ulceration.[3,21] Higher fluences have been associated with higher procedural pain scores.[39,40] Small case series reporting scarring located on the neck or ectropion, preceded by infection or nonhealing ulcers, have been described.[21,41]

PIH is a substantial risk when treating darkly pigmented patients, as multiple studies performed in Asian patients conclude. PIH rates in darker skin types III, IV, and V have been as high as 50%, 55.5%, and 92%, respectively, after fractional CO_2 treatment.[39,42,43] PIH has been associated with higher-density settings.[44-46]

Nonablative fractional lasers

NAFLs utilize a wavelength of light in the midinfrared spectrum that penetrates into the midreticular dermis, inducing new collagen formation and tissue remodeling. These lasers create a grid of MTZs that leave intervening areas of skin unaffected. The skin adjacent to sites of laser injury remains intact, allowing for rapid postprocedural reepithelialization because of the migration of intact cells into the damaged microcolumns. The preservation of an intact epidermis with minimal disruption of the dermal–epidermal junction decreases recovery time to an average of 3 days and leads to a milder side effect profile.[2] Rapid recovery comes at the expense of efficacy because NAFLs have a more modest effect on collagen remodeling,[47] and multiple treatment sessions are required to reach a typically less dramatic clinical result.

Acne scarring

In a consensus statement by Anderson et al in 2014 regarding the use of lasers in acne scarring, a panel of experts concluded, based on clinical evidence and personal experience, that while AFLs and NAFLs result in comparable improvement in acne scarring, the latter is generally more tolerable for patients, with the understanding that more treatment sessions are required.[12]

Multiple studies have shown that, as the first available fractional laser, the 1550-nm erbium-doped laser (EDL) decreases bleeding and postprocedure erythema, edema, infection, and scarring, as compared with its contemporary ablative counterparts. In 2 studies investigating the efficacy of EDL in acne scarring with 2 to 6 monthly treatments (82 patients, skin types I-V), 62% to 87% of patients experienced a 51% to 75% scar improvement.[48,49] The average improvement increased proportionally after each treatment and did not significantly differ depending on skin type.[48] More recent studies have confirmed the laser's safety and efficacy in treating acne scarring, even in darker skin types.[50] For acne scars and surgical scars located off the face, lower fluences (20 to 50 mJ) are recommended.[51]

The 1540-nm Er:glass has also been shown to improve atrophic acne scars in multiple trials. A large study of 87 Italian patients (skin types I-V) revealed a greater than 50% improvement in atrophic scars in 89% of patients after 3 months and in 92% of patients after 6 months.[52] Similar studies in Asian patients corroborate these results.[53] The Er:glass has been shown to perform best on boxcar scars (52.9% improvement), followed by rolling (43.1% improvement) and ice-pick scars (25.9% improvement).[54]

Hypertrophic scars and keloids

While the pulsed dye laser is the nonablative energy-based device that has traditionally been used to treat HTS and keloids, fewer and smaller studies have been performed on the use of NAFL for these scars. Small studies have shown mild to no significant difference in treated versus untreated HTS with the Er:glass after 4 treatments.[55] While HTS and keloids have been reported as a complication of AFL, the subsequent use of NAFLs like the EDL has been shown to improve the resultant elevated scars.[21]

Surgical and traumatic scars

Surgical and traumatic scars may benefit from early treatment with NAFL. One study of 27 post-thyroidectomy patients (skin types I-IV) who underwent 4 monthly treatments with the EDL at a low fluence (10 mJ), starting 2 to 3 weeks after surgery, compared the surgical scars to untreated post-thyroidectomy patients. At the follow-up, the VSS was significantly different between treated and untreated patients (1.52 versus 3.00, respectively).[56]

Early treatment with NAFL is more effective than later treatment in improving the appearance of postsurgical scars. Laser treatments for scars had historically been postponed to a minimum of 2 to 3 months after surgery because of concerns regarding scar stabilization[57]; however, Park et al concluded that early treatment (within 3 weeks) was more effective than delayed treatment (within 3 to 6 months) in 65 patients with post-thyroidectomy scars treated with 3 monthly treatments of NAFL.[58]

NAFLs may improve scar appearance in mature scars, albeit to a lesser extent than in newly formed scars. In a randomized split-scar study in which 17 patients with mature burn scars underwent 3 monthly treatments with the Er:glass, some improvement in skin texture was noted as compared with control areas.[59]

Skin rejuvenation and tightening

NAFLs have recently become the mainstay of skin rejuvenation because they have a shorter downtime and lower side effect profile but still achieve desirable results. While NAFLs do not achieve the results of traditional ablative resurfacing, the efficacy of NAFLs in skin rejuvenation is well established. The assortment of devices available is continuing to grow. The wavelengths of NAFLs currently available for skin rejuvenation and tightening include 1410-nm, 1440-nm, 1540-nm, 1550-nm, and 1927-nm. Unlike the AFLs, in general, a series of 3 to 6 treatments is recommended for optimal results.

The 1550-nm erbium-doped fiber laser was the first of its kind and continues to be one of the most prominent and most studied players in NAFL rejuvenation. Initial studies revealed an 18% improvement of the wrinkle score and a 2.1% tissue shrinkage effect at 3 months after 4 treatments.[1] After 3 treatments spaced 3 to 4 weeks apart, the 1550-nm NAFL achieved a subjective improvement in overall facial photodamage of at least 51% to 75% in 73% of patients at 9 months.[60] In the same study, the results were slightly inferior on nonfacial skin, with 55% of patients displaying at least 51% to 75% improvement of overall photodamage at 9 months. The 1540-nm has been shown to achieve comparable results. Beyond pigmentation, rhytides, and texture, NAFLs have also demonstrated an improvement in facial pores. Saedi et al[61] reported a 17% improvement in facial pore score after 6 treatments with a 1440-nm NAFL spaced 2 weeks apart.

The 1927-nm thulium fiber lasers differ from the lower wavelengths in that they have a higher absorption coefficient for water. This leads to an increased ability to target the epidermis and treat more superficial processes, such as dyspigmentation.[62] After 2 treatments with the 1927-nm thulium laser, 82% of patients achieved a moderate to significant improvement in photopigmentation at 1 month after treatment.[63] There was also appreciable improvement, albeit to a lesser degree, in both fine and coarse wrinkling.[62] In addition, there is a report of successful treatment of macular seborrheic keratoses with the 1927-nm NAFL.[64]

While the improvement in pigmentation, fine rhytides, and overall texture is well established with NAFLs, there has been some controversy over whether the NAFLs truly have a skin-tightening effect, despite several studies reporting this benefit.[1,65,66] A true skin-tightening effect comes from dermal fibroplasia and wound contraction, thought to be at least partially induced by heat shock protein 70. The histologic studies performed have had inconsistent results. However, many of those studies that do not show evidence of significant fibroplasia employed low-energy, low-density treatments and/or only single treatments.[65]

While caution is still needed due to increased risks of side effects, there have been multiple studies showing the safety and efficacy of NAFLs on the neck, chest, arms, and hands.[62,67-70] As with the AFLs, the growing interest in vaginal rejuvenation has also led to the use of NAFLs for this purpose. The newer nonablative 2940-nm Er:YAG laser, delivered through a collimated patterned handpiece, has been shown to improve vaginal laxity by inducing neocollagenesis.[36]

In addition, while the vast majority of patients seeking skin rejuvenation and tightening are female, interest is growing among male patients. Specifically, NAFL treatments are favored among men because of the shorter downtime.[71] While the primary goals of skin rejuvenation are the same among men and women, there are a few gender-specific indications. For example, the male scalp can exhibit substantial photodamage, resulting in lentigines, solar keratoses, and rhytides. In a recent study composed of 4 male patients, Boen et al[72] revealed the benefit of a single scalp treatment with a fractional 1927-nm thulium fiber laser. Patients achieved a 60% to 90% improvement in photodamage, consisting of dyschromia, lentigines, and actinic keratoses, after a single treatment.

Safety and adverse events

Side effects of treatment with the NAFLs include transient facial erythema lasting 1 to 3 days and PIH in up to 13% of patients.[2] In 1 large, single-center retrospective review of 961 consecutive treatments with the EDL for scarring and photorejuvenation in patients with skin types I-V, treatments were well tolerated with a side effect rate of 7.6%. The most frequent complications were acneiform eruptions (1.87%) and herpes simplex virus (HSV) outbreaks (1.77%). Side effects did not vary depending on underlying condition or skin type, except for PIH, which occurred with an increased frequency in patients with darker skin types.[73] Similar to AFLs, lower densities and fewer treatment passes have been associated with a lower risk for hyperpigmentation at the expense of more treatment sessions,[43] whereas higher densities result in more side effects without improved results.[40] Pre- and posttreatment with hydroquinone 4% may help decrease the incidence of PIH, even in darker patients.[74]

Quality-switched lasers

While the technology for QS lasers and the more recent picosecond lasers is primarily being used for endogenous and exogenous pigmentation correction, its use naturally expanded to the broader and sought-after goal of skin rejuvenation and tightening. Nonablative QS lasers have also adopted fractionation, and specifically, the fractional QS Nd:YAG 1064-nm laser has been shown to provide benefits in skin rejuvenation and tightening. QS Nd:YAG lasers have pulse durations in the nanosecond range and create a photoacoustic effect, contributing to an increased dermal collagen response.[75] As with the other lasers, the fractionated technology allows for higher energies in each microscopic treatment zone, as well as deeper penetration. The standard QS Nd:YAG (1064-nm) laser targets melanin near the skin surface, which can lead to epidermal damage and crusting. However, the fractional QS Nd:YAG has a deeper focal point of 100 um with an expected penetration depth of up to 3.5 to 4 mm.[76] This deeper penetration may lead to efficacy in dermal rejuvenation while avoiding epidermal crusting, allowing for faster healing.

Fractional QS Nd:YAG (1064-nm) lasers have demonstrated an

11.3% improvement rate in superficial rhytides at 1 month after a series of 3 treatments to the face, neck, and chest spaced at 2- to 4-week intervals.[76] Gold et al[77] showed that there was a greater than 60% improvement in hyperpigmentation, telangiectasias, laxity, roughness, and identifiable actinic keratoses after 4 treatments with the same laser done at 2- to 4-week intervals. These treatments are well tolerated with little to no pain and only temporary erythema lasting up to 24 hours. No other adverse events, such as dyspigmentation, edema, ecchymoses, vesiculation, crusting, or scarring, have been reported in the limited studies performed.[76-78] This modality is thought to be safe for all skin types, with slightly lower fluences suggested for darker skin types.[77]

Picosecond lasers

Compared with traditional nanosecond lasers, picosecond lasers deliver shorter pulse durations at lower fluences, creating both photomechanical and photothermal effects. They may lead to fewer adverse effects because they confine energy to their target, and lower fluences are required.[79-81] Fractionated picosecond handpieces have been developed for resurfacing and rejuvenation, including the 755-nm picosecond alexandrite laser PicoSure (Cynosure, Westford, MA), which contains a diffractive lens array (DLA) and the dual-wavelength 532/1064-nm holographic fractionated picosecond laser, PicoWay Resolve (Syneron Candela, Irvine, CA). The PicoSure with DLA received US Food and Drug Administration (FDA) approval in 2014 to treat acne scarring and rhytides,[81] while the PicoWay received FDA approval in 2014 to treat all tattoo colors. The DLA delivers high-energy pulses 500 μm apart, which allows for the treatment of a larger surface area and a higher density per pulse. Less than 10% of the skin surface is exposed to the higher energies, and the total fluence remains low, creating a favorable safety profile.[81] Microscopically, this modality leads to localized epidermal vacuoles with no collateral thermal damage, which then eventuates increased dermal collagen and elastin fibers.[82,83]

Thus far, only a small number of studies have been conducted on these lasers. The PicoSure has been shown to improve the appearance and texture of atrophic facial acne scars, with similar efficacy to other fractional lasers.[80] The dual-wavelength fractionated PicoWay is currently being investigated for the treatment of acne scars (clinicaltrials.gov, NCT02592993).

In terms of skin rejuvenation, these devices can provide improvement in dyspigmentation secondary to photodamage as expected but also improve the skin texture and rhytides associated with photoaging. The PicoSure has FDA clearance for the treatment of rhytides in skin types I-IV. After 4 full-face treatments with the picosecond alexandrite laser spaced 1 month apart, a significant improvement in the Fitzpatrick wrinkle score was noted; specifically, from an average of 5.48 before treatment to an average of 3.47 at the 6-month follow-up.[83] This study also showed a moderate improvement in dyschromia. Multiple studies have shown safety and efficacy in the picosecond alexandrite laser for facial rejuvenation by using shorter treatment intervals of 2 to 3 weeks.[84,85] Wu et al showed an improvement in pigmentation, keratoses, and skin texture of the décolletage after treatment with the picosecond alexandrite laser.[86]

Importantly, this technology has a favorable safety profile that is reproducible across most skin types. The mean pain score was mild, and downtime was minimal, with only transient side effects and no PIH reported during treatments.[80] Transient adverse effects include edema, erythema, crusting, scabbing, and hyperpigmentation, with most resolving within a few days.[81,83,84]

Combined fractional resurfacing

One of the latest advancements in fractional lasers is an HFL, combining both ablative and nonablative technologies. In a single treatment spot, the Halo (Sciton, Palo Alto, CA) can provide ablation of the epidermis up to 100 μm by using the 2940-nm Er:YAG as well as nonablative coagulative damage to the epidermis and dermis from 100 to 700 μm by using the 1470-nm diode. The depth and coverage of both ablative and nonablative effects can be individualized as necessary, and the 1470-nm wavelength is thought to optimally target the depth in the dermis where most photodamage occurs.[87] The goal of this hybrid approach is to achieve ablative-like results with very little downtime and in fewer treatments. Not only does the ablative damage promote a stronger wound healing response for better results, ablating the epidermis in treatment zones helps eliminate necrotic debris produced by the nonablative heating, promoting faster healing times than nonablative treatments alone.[87] Investigators have reported significant improvements in texture, pigmentation, and pore size and/or number in just 1 to 2 treatments, followed by a healing time of just a few days.[87] Future studies are required to accurately compare the effects of HFL technology to other devices for skin rejuvenation.

Another similar, novel device that achieves combined fractional resurfacing is the YOULASER MT (QuantaSystem SPA, Italy). This device has the ability to simultaneously emit a fractional ablative CO_2 10600-nm wavelength and a fractional nonablative gallium arsenide 1540 nm. Mezzana et al performed a single full-face resurfacing procedure with both wavelengths in 1 group of patients and with only the fractional CO_2 wavelength in another group of well-matched patients.[88] The group treated with the combined wavelengths displayed a 32.3% improvement in wrinkle depth after 3 months as compared with a 20.7% improvement in the fractional ablative CO_2 wavelength alone. Combined fractional laser resurfacing is certainly a promising new modality, with the potential for equal or better outcomes with less pain and downtime.

Fractional radiofrequency

While originally intended for lasers, the concept of fractionation has since been applied to other technologies, including RF. RF uses electric current to produce thermal energy as it passes through tissue and meets resistance.[89] Fractional RF (FRF) devices transmit bipolar current through electrodes in contact with the skin or via arrays of paired microneedles that penetrate the skin. Both types of devices form closed circuits of bipolar current.[89] The devices with electrodes produce a pyramid-shaped distribution of thermal energy, with the smaller peak of the pyramid at the epidermis and the broader base deeper within the dermis.[90] This allows for large volumes of dermal heat diffusion with minimal epidermal damage. Less than 5% of the skin surface is disrupted with 1 pass of the device.[90] The high temperatures at the epidermis lead to focal ablation, while the effects within the dermis are mainly secondary to coagulative damage.[90,91] The relative degree of these effects, as well as the maximal depth of tissue effect, can be tailored by adjusting parameters such as energy level, coverage, and/or density.[91]

For acne scarring, a moderate improvement of 25% to 75% can be expected after 3 to 4 treatment sessions with FRF.[92] Numerous studies on the use of FRF for acne scarring in darker skin types have shown it to be effective, with a relatively low risk of PIH.[93-95] While moderate improvement in acne scarring is possible, it remains to be seen how FRF compares to more well-established treatments, such as AFL.

FRF has also shown efficacy in nonacne scarring. In an uncontrolled study of 95 patients with nonhypertrophic burn scars of at least 1 year in duration treated with 3 to 5 sessions at varying time intervals, there was a significant decrease in POSAS score from 53.41 to 46.35 (both observer and patient reported). There were individual improvements in the scar color, thickness, and pliability; however, no significant improvement was noted in vascularity, pain, or itch.[96]

FRF can be used for skin rejuvenation, which some term sublative rejuvenation.[90] It most notably leads to an improvement in skin laxity, texture, and rhytides. Specifically, Hruza et al[91] found that almost 90% of patients exhibited an improvement in skin tightness, smoothness, and wrinkling after 3 treatments, with approximately half of patients achieving an improvement of 40% or greater. Among facial treatments, periorbital sites responded the most, while perioral sites had the least improvement.[91] Studies have noted consistent results among all subjects.[97] Because there is little epidermal disruption, FRF is generally not used for superficial pigment alteration.[90] However, studies have shown an improvement in dyschromias and skin "brightness."[90,91]

Most recommend a series of 3 to 6 treatments to obtain optimal improvement and rejuvenation, depending on the patients' needs and goals.[90,91,98] One can undergo an additional treatment every 3 to 4 months thereafter to maintain improvement.[98] Anecdotally, many practitioners use higher energies and coverage in patients with lighter skin types and in older individuals with increased baseline damage, while using lower energies and coverage in darker skin types.[90,91] There is also a lower risk for sharp demarcation lines when only treating certain cosmetic units as opposed to the whole face, which can be seen with other energy-based fractional devices.[90]

Radiofrequency with microneedling

FRF for scarring and skin rejuvenation may be augmented by the use of RF with microneedling (RFM). RFM includes devices with insulated microneedles that produce small, spherical thermal injury zones with coagulative damage around the tip of the needle or noninsulated microneedles that produce larger cylindrical thermal injury zones with coagulative damage spanning the dermis.[99] The depth of the needles can be adjusted from a minimum of 0.5 mm to a maximum of 3.5 mm.[100] The trauma to the dermis initiates wound healing and growth factor release, leading to collagen production and deposition in the upper dermis.[101]

Numerous studies support the utility of microneedling without the augmentation of an energy-based device in the treatment of acne and other scar types.[102-105] In 3 studies involving 91 patients (skin types III-V) investigating RFM in atrophic acne, various acne scar scoring systems consistently reported a moderate improvement in scar appearance after treatment.[100,106,107] RFM offers superior results for ice-pick and boxcar acne scars than rolling scars[108] and appears to offer a more dramatic improvement in acne scarring than bipolar RF alone.

FRF delivered via microneedles has also been implemented in skin rejuvenation and tightening. Six months after a single microneedle fractionated bipolar RF treatment, patients were noted to have a 25.6% mean improvement in facial rhytides and a 24.1% improvement in facial and neck laxity.[109] Other studies have substantiated significant improvements in skin laxity and rhytides at 6 months following a single treatment with such a device.[99,110] The noninsulated microneedle devices have advantages over the earlier, fully insulated microneedles. They are able to span the depth of the dermis in a single treatment and produce more effective skin tightening.[99]

Common adverse reactions associated with FRF and RFM include transient pain, erythema, edema, and scabbing that resolve within 3 to 5 days.[92,95,107] Prolonged erythema, edema, and purpura are rarely seen. Rare instances of acne exacerbations[93] and HSV outbreaks[96] have been reported. In treatment with RFM, transient postprocedure track marks have been noted (6%).[100] Reported rates of PIH are generally low; PIH occurred in only 2 out of 72 patients (3%) (skin types III-V) treated with FRF for acne scarring and resolved within 4 to 12 weeks.[93,95,107] When used for skin rejuvenation and tightening, PIH was rare across all skin types.[90,91,98,99,111]

Drug delivery

Many of the energy-based fractional therapies for skin scarring, rejuvenation, and tightening have been accompanied in recent years by the delivery of various compounds because of the natural conduit created by ablative tissue columns and MTZs, which allow for penetration into the dermis. Drug delivery by lasers and microneedling bypass the issue of percutaneous penetration through the stratum corneum, through which only 1% to 5% of topically applied drugs absorb into the skin.[112]

Laser-assisted drug delivery (LADD) was first introduced in 2002 with the use of the Er:YAG for the delivery of topical anesthetics.[113] Since that time, LADD has been used to synergistically treat scars and rhytides with corticosteroids, ascorbic acid, 5-FU, platelet-rich plasma (PRP), and various cosmeceuticals.[114] In general with LADD, the drug is immediately applied topically or injected in the treated area.[114]

Drug delivery in cutaneous scars

Various topical and injectable medications have been used to augment the use of fractional energy-based devices in the treatment of atrophic acne scarring. Poly-L-lactic acid (PLLA) (Sculptra; Galderma, Fort Worth, TX) delivery via fractional CO_2 has been investigated for the treatment of atrophic scars on the face and body. Nineteen patients underwent fractional CO_2 treatment, followed by topical PLLA application, with an average of 1 treatment session per patient in 1 uncontrolled study, which revealed an overall improvement score of 2.18 on a 0 to 3 scale.[115]

LADD may also improve hypopigmented scars, purportedly due to the repopulation of melanocytes from surrounding hair follicles and basal-layer melanocytes.[114] Bimatoprost, a drug originally used to treat glaucoma with a known side effect of periocular hyperpigmentation, has been applied to hypopigmented scars after NAFL treatment, leading to greater than 50% improvement in hypopigmentation.[116] A novel epidermal harvesting method in early investigative stages involves the transfer of autologous epidermis with live melanocytes to atrophic, hypopigmented scars. The harvesting system induces microsuction blisters, known as microdomes, at the donor site by using a combination of vacuum and warmth, followed by implantation into the recipient site that has been treated by AFL.[114]

Autologous PRP can enhance wound healing by accelerating tissue repair and reducing postoperative pain.[117,118] Intradermal injections of PRP were first noted to improve acne scarring when used for skin rejuvenation.[119] PRP as both an intradermal injection and topical application after fractional ablative CO_2 therapy enhanced the recovery of laser-treated skin and improved the clinical appearance of acne scars as compared with a control.[120,121] Whether injected or topically applied, PRP can lead to a greater improvement in scars versus AFL alone.[121]

Microneedling also provides a clear channel for the efficient absorption of topical agents, whether applied topically after treatment, coated onto microneedles, or in conjunction with hollow needles impregnated with an agent.[122] In a split-face study that investigated the use of microneedling followed by PRP application on one side of the face versus microneedling plus distilled water on the contralateral side, the PRP-treated face showed a greater improvement in acne scarring after 3 monthly sessions (62% versus 46% improvement, respectively).[123]

As discussed above, HTS and keloids have been successfully treated with AFL. Combining AFL or microneedling with agents such as steroids and 5-FU may lead to synergistic therapeutic effects. In an uncontrolled study, Waibel et al studied the efficacy of fractional CO_2 treatment followed by the immediate application of triamcinolone acetonide to HTS on the face and body in 15 patients. The study demonstrated an overall scar improvement of 2.73 on a scale of 0 to 3 by blinded investigators. Texture was the most improved scar element, while dyschromia was the least.[124]

Drug delivery in skin rejuvenation

Several studies have demonstrated the successful permeation and enhanced accumulation of multiple compounds that may aid in skin rejuvenation.[125,126] Drugs found to have a successful permeation with AFLs include tranexamic acid, tretinoin, multiple vitamin C derivatives, autologous cells, and PRP.[127-132]

When used for drug delivery, laser fluences are typically lower than those used for skin rejuvenation. Most preclinical studies have demonstrated an increased flux and accumulation of the drug with increasing numbers of passes.[127-130] Four passes of a fractional CO_2 laser showed an equivalent flux to that achieved with a fully ablative laser with the ex vivo application of both tranexamic acid and ascorbic acid 2-glucoside on porcine skin.[127,129] Vitamin C derivatives have been shown to have a 13- to 42-fold higher transdermal flux across porcine skin after fractional CO_2 pretreatment, depending on the fluence and the particular derivative.[130] A single fractional CO_2 treatment increased the flux of tretinoin by 9-fold in mouse skin.[128] In general, AFLs produce increased transdermal flux of active agents in comparison with NAFLs.[133]

As expected, there is a growing interest in this field and in the future application of collagen-mimicking peptides, antioxidants, and alpha and beta hydroxy acids, amongst others.[134] However, the risks of LADD must not be overlooked: foreign body reactions to administered agents can occur, and LADD may allow access to the dermal vascular system, thus increasing the risk of systemic absorption of drugs and immunologic sensitization.[125]

Conclusion

The development of fractional photothermolysis has revolutionized the treatment of scarring as well as skin rejuvenation and tightening. The constant broadening of the utilization of fractionation to different lasers and other energy-based technologies provides a continually growing repertoire of devices for practitioners. Ultimately, knowledge of these devices and their appropriate treatment parameters can allow for the safe and effective treatment of a myriad of conditions in almost all skin types.

References

1. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med*. 2004;34(5):426-438. https://doi.org/10.1002/lsm.20048.
2. Ong MW, Bashir SJ. Fractional laser resurfacing for acne scars: a review. *Br J Dermatol*. 2012;166(6):1160-1169. https://doi.org/10.1111/j.1365-2133.2012.10870.x.
3. Magnani LR, Schweiger ES. Fractional CO2 lasers for the treatment of atrophic acne scars: a review of the literature. *J Cosmet Laser Ther*. 2014;16(2):48-56. https://doi.org/10.3109/14764172.2013.854639.
4. Jung JY, Lee JH, Ryu DJ, Lee SJ, Bang D, Cho SB. Lower-fluence, higher-density versus higher-fluence, lower-density treatment with a 10,600-nm carbon dioxide fractional laser system: a split-face, evaluator-blinded study. *Dermatol Surg*. 2010;36(12):2022-2029. https://doi.org/10.1111/j.1524-4725.2010.01803.x.
5. Kim S. Treatment of acne scars in Asian patients using a 2,790-nm fractional yttrium scandium gallium garnet laser. *Dermatol Surg*. 2011;37(10):1464-1469. https://doi.org/10.1111/j.1524-4725.2011.02050.x.
6. Zhu JT, Xuan M, Zhang YN, et al. The efficacy of autologous platelet-rich plasma combined with erbium fractional laser therapy for facial acne scars or acne. *Mol Med Rep*. 2013;8(1):233-237. https://doi.org/10.3892/mmr.2013.1455.
7. Nirmal B, Pai SB, Sripathi H, et al. Efficacy and safety of erbium-doped yttrium aluminium garnet fractional resurfacing laser for treatment of facial acne scars. *Indian J Dermatol Venereol Leprol*. 2013;79(2):193-198. https://doi.org/10.4103/0378-6323.107635.
8. Bjørn M, Stausbøl-Grøn B, Braae Olesen A, Hedelund L. Treatment of acne scars with fractional CO2 laser at 1-month versus 3-month intervals: an intra-individual randomized controlled trial. *Lasers Surg Med*. 2014;46(2):89-93. https://doi.org/10.1002/lsm.22165.
9. Ortiz AE, Tremaine AM, Zachary CB. Long term efficacy of fractional resurfacing. *Lasers Surg Med.* 2010;42(2):168–170. https://doi.org/10.1002/lsm.20885.
10. Kiil J. Keloids treated with topical injections of triamcinolone acetonide (kenalog). Immediate and long-term results. *Scand J Plast Reconstr Surg*. 1977;11(2):169-172.
11. Ren Y, Zhou X, Wei Z, Lin W, Fan B, Feng S. Efficacy and safety of triamcinolone acetonide alone and in combination with 5-fluorouracil for treating hypertrophic scars and keloids: a systematic review and meta-analysis. *Int Wound J*. 2016;14(3):480-487. https://doi.org/Doi:10.1111/iwj.12629.
12. Anderson RR, Donelan MB, Hivnor C, et al. Laser treatment of traumatic scars with an emphasis on ablative fractional laser resurfacing: consensus report. *JAMA Dermatol*. 2014;150(2):187-193. https://doi.org/10.1001/jamadermatol.2013.7761.
13. Azzam OA, Bassiouny DA, El-Hawary MS, El Maadawi ZM, Sobhi RM, El-Mesidy MS. Treatment of hypertrophic scars and keloids by fractional carbon dioxide laser: a clinical, histological, and immunohistochemical study. *Lasers Med Sci*. 2016;31(1):9-18. https://doi.org/10.1007/s10103-015-1824-4.
14. El-Zawahry BM, Sobhi RM, Bassiouny DA, Tabak SA. Ablative CO2 fractional resurfacing in treatment of thermal burn scars: an open-label controlled clinical and histopathological study. *J Cosmet Dermatol.* 2015;14(4):324-331. https://doi.org/10.1111/jocd.12163.
15. Taudorf EH, Danielsen PL, Paulsen IF, et al. Non-ablative fractional laser provides long-term improvement of mature burn scars--a randomized controlled trial with histological assessment. *Lasers Surg Med*. 2015;47(2):141-147. https://doi.org/10.1002/lsm.22289.
16. Ozog DM, Liu A, Chaffins ML, et al. Evaluation of clinical results, histological architecture, and collagen expression following treatment of mature burn scars with a fractional carbon dioxide laser. *JAMA Dermatol*. 2013;149(1):50-57. https://doi.org/10.1001/2013.jamadermatol.668.
17. Waibel J, Beer K. Ablative fractional laser resurfacing for the treatment of a third-degree burn. *J Drugs Dermatol*. 2009;8(3):294-297.
18. Haedersdal M. Fractional ablative CO(2) laser resurfacing improves a thermal burn scar. *J Eur Acad Dermatol Venereol.* 2009;23(11):1340-1341. https://doi.org/10.1111/j.1468-3083.2009.03215.x.
19. Bowen RE. A novel approach to ablative fractional treatment of mature thermal burn

scars. *J Drugs Dermatol*. 2010;9(4):389-392.

20. Kim HS, Lee JH, Park YM, Lee JY. Comparison of the effectiveness of nonablative fractional laser versus ablative fractional laser in thyroidectomy scar prevention: a pilot study. *J Cosmet Laser Ther.* 2012;14(2):89-93. https://doi.org/10.3109/14764172.2012.672746.
21. Avram MM, Tope WD, Yu T, Szachowicz E, Nelson JS. Hypertrophic scarring of the neck following ablative fractional carbon dioxide laser resurfacing. *Lasers Surg Med*. 2009;41(3):185-188. https://doi.org/10.1002/lsm.20755.
22. Hantash BM, Bedi VP, Kapadia B, et al. In vivo histological evaluation of a novel ablative fractional resurfacing device. *Lasers Surg Med*. 2007;39(2):96-107. https://doi.org/10.1002/lsm.20468.
23. Rahman Z, MacFalls H, Jiang K, et al. Fractional deep dermal ablation induces tissue tightening. *Lasers Surg Med*. 2009;41(2):78-86. https://doi.org/10.1002/lsm.20715.
24. Tierney EP, Hanke CW. Fractionated carbon dioxide laser treatment of photoaging: Prospective study in 45 patients and review of literature. *Dermatol Surg*. 2011;37(9):1279-1290. https://doi.org/10.1111/j.1524-4725.2011.02082.x.
25. Tierney EP, Eisen RF, Hanke CW. Fractionated CO2 laser skin rejuvenation. *Dermatol Ther*. 2011;24(1):41-53. https://doi.org/10.1111/j.1529-8019.2010.01377.x.
26. Orringer JS, Sachs DL, Shao Y, et al. Direct quantitative comparison of molecular responses in photodamaged human skin to fractionated and fully ablative carbon dioxide laser resurfacing. *Dermatol Surg*. 2012;38(10):1668-1677. https://doi.org/10.1111/j.1524-4725.2012.02518.x.
27. Hunzeker CM, Weiss ET, Geronemus RG. Fractionated CO2 laser resurfacing: Our experience with more than 2000 treatments. *Aesthet Surg J.* 2009;29(4):317-322. https://doi.org/10.1016/j.asj.2009.05.004.
28. Ortiz AE, Goldman MP, Fitzpatrick RE. Ablative CO2 lasers for skin tightening: Traditional versus fractional. *Dermatol Surg*. 2014;40 Suppl 12:S147-S151. https://doi.org/10.1097/DSS.0000000000000230.
29. Tierney EP, Hanke CW. Ablative fractionated CO2 laser resurfacing for the neck: Prospective study and review of the literature. *J Drugs Dermatol*. 2009;8(8):723-731.
30. Tierney EP, Hanke CW, Watkins L. Treatment of lower eyelid rhytids and laxity with ablative fractionated carbon-dioxide laser resurfacing: Case series and review of the literature. *J Am Acad Dermatol*. 2011;64(4):730-740. https://doi.org/10.1016/j.jaad.2010.04.023.
31. Bae-Harboe YS, Geronemus RG. Eyelid tightening by CO2 fractional laser, alternative to blepharoplasty. *Dermatol Surg.* 2014;40 Suppl 12:S137-S141. https://doi.org/10.1097/DSS.0000000000000165.
32. Fabi SG, Goldman MP. Hand Rejuvenation: A review and our experience. *Dermatol Surg*. 2012;38(7 Pt 2):1112-1127. https://doi.org/10.1111/j.1524-4725.2011.02291.x.
33. Zachary CB. Facial Rejuvenation: 40th anniversary review. *Semin Cutan Med Surg*. 2016;35(6S):S122-S124. https://doi.org/10.12788/j.sder.2016.039.
34. Filippini M, Del Duca E, Negosanti F, et al. Fractional CO2 laser: From skin rejuvenation to vulvo-vaginal reshaping. *Photomed Laser Surg*. 2017;35(3):171-175. https://doi.org/10.1089/pho.2016.4173.
35. Zerbinati N, Serati M, Origoni M, et al. Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. *Lasers Med Sci*. 2015;30(1):429-436. https://doi.org/10.1007/s10103-014-1677-2.
36. Vanaman M, Bolton J, Placik O, Guillen Fabi S. Emerging trends in nonsurgical female genital rejuvenation. *Dermatol Surg*. 2016;42(9):1019-1029. https://doi.org/10.1097/DSS.0000000000000697.
37. Cho SB, Lee SJ, Kang JM, Kim YK, Chung WS, Oh SH. The efficacy and safety of 10,600-nm carbon dioxide fractional laser for acne scars in Asian patients. *Dermatol Surg.* 2009;35(12):1955-1961. https://doi.org/10.1111/j.1524-4725.2009.01316.x.
38. Asilian A, Salimi E, Faghihi G, Dehghani F, Tajmirriahi N, Hosseini SM. Comparison of Q-Switched 1064- nm Nd: YAG laser and fractional CO2 laser efficacies on improvement of atrophic facial acne scar. *J Res Med Sci*. 2011;16(9):1189-1195.
39. Manuskiatti W, Triwongwaranat D, Varothai S, Eimpunth S, Wanitphakdeedecha R. Efficacy and safety of a carbon-dioxide ablative fractional resurfacing device for treatment of atrophic acne scars in Asians. *J Am Acad Dermatol*. 2010;63(2):274-283. https://doi.org/10.1016/j.jaad.2009.08.051.
40. Kono T, Chan HH, Groff WF, et al. Prospective direct comparison study of fractional resurfacing using different fluences and densities for skin rejuvenation in Asians. *Lasers Surg Med.* 2007;39(4):311-314. https://doi.org/10.1002/lsm.20484.
41. Fife D. Practical evaluation and management of atrophic acne scars: tips for the general dermatologist. *J Clin Aesthet Dermatol*. 2011;4(8):50-57.
42. Huang L. A new modality for fractional CO2 laser resurfacing for acne scars in Asians. *Lasers Med Sci*. 2013;28(2):627-632. https://doi.org/10.1007/s10103-012-1120-5.
43. Chan NP, Ho SG, Yeung CK, Shek SY, Chan HH. Fractional ablative carbon dioxide laser resurfacing for skin rejuvenation and acne scars in Asians. *Lasers Surg Med*. 2010;42(9):615-623. https://doi.org/10.1002/lsm.20974.
44. Yuan XH, Zhong SX, Li SS. Comparison study of fractional carbon dioxide laser resurfacing using different fluences and densities for acne scars in Asians: A randomized split-face trial. *Dermatol Surg*. 2014; 40(5):545-552. https://doi.org/10.1111/dsu.12467.
45. Jung JY, Jeong JJ, Roh HJ, et al. Early postoperative treatment of thyroidectomy scars using a fractional carbon dioxide laser. *Dermatol Surg*. 2011;37(2):217-223. https://doi.org/10.1111/j.1524-4725.2010.01853.x.
46. Kim DH, Ryu HJ, Choi JE, Ahn HH, Kye YC, Seo SH. A comparison of the scar prevention effect between carbon dioxide fractional laser and pulsed dye laser in surgical scars. *Dermatol Surg*. 2014;40(9):973-978. https://doi.org/10.1097/01.DSS.0000452623.24760.9c.
47. Hedelund L, Moreau KE, Beyer DM, Nymann P, Haedersdal M. Fractional nonablative 1,540-nm laser resurfacing of atrophic acne scars. A randomized controlled trial with blinded response evaluation. *Lasers Med Sci*. 2010;25(5):749-754. https://doi.org/10.1007/s10103-010-0801-1.
48. Alster TS, Tanzi EL, Lazarus M. The use of fractional laser photothermolysis for the treatment of atrophic scars. *Dermatol Surg*. 2007;33(3):295-299. https://doi.org/10.1111/j.1524-4725.2007.33059.x.
49. Chrastil B, Glaich AS, Goldberg LH, Friedman PM. Second-generation 1,550-nm fractional photothermolysis for the treatment of acne scars. *Dermatol Surg*. 2008;34(10):1327-1332. https://doi.org/10.1111/j.1524-4725.2008.34284.x.
50. Yang Q, Huang W, Qian H, Chen S, Ma L, Lu Z. Efficacy and safety of 1550-nm fractional laser in the treatment of acne scars in Chinese patients: A split-face comparative study. *J Cosmet Laser Ther*. 2016;18(6):312-316. https://doi.org/10.1080/14764172.2016.1188211.
51. Sherling M, Friedman PM, Adrian R, et al. Consensus recommendations on the use of an erbium-doped 1,550-nm fractionated laser and its applications in dermatologic laser surgery. *Dermatol Surg*. 2010;36(4):461-469. https://doi.org/10.1111/j.1524-4725.2010.01483.x.
52. Bencini PL, Tourlaki A, Galimberti M, et al. Nonablative fractional photothermolysis for acne scars: clinical and in vivo microscopic documentation of treatment efficacy. *Dermatol Ther.* 2012;25(5):463-467. https://doi.org/10.1111/j.1529-8019.2012.01478.x.
53. Yoo KH, Ahn JY, Kim JY, Li K, Seo SJ, Hong CK. The use of 1540 nm fractional photothermolysis for the treatment of acne scars in Asian skin: a pilot study. *Photodermatol Photoimmunol Photomed*. 2009;25(3):138-142. https://doi.org/10.1111/j.1600-0781.2009.00430.x.
54. Sardana K, Manjhi M, Garg VK, Sagar V. Which type of atrophic acne scar (ice-pick, boxcar, or rolling) responds to nonablative fractional laser therapy? *Dermatol Surg*. 2014;40(3):288-300. https://doi.org/10.1111/dsu.12428.
55. Verhaeghe E, Ongenae K, Bostoen J, Lambert J. Nonablative fractional laser resurfacing for the treatment of hypertrophic scars: a randomized controlled trial. *Dermatol Surg.* 2013;39(3 Pt 1):426-434. https://doi.org/10.1111/dsu.12059.
56. Choe JH, Park YL, Kim BJ, et al. Prevention of thyroidectomy scar using a new 1,550-nm fractional erbium-glass laser. *Dermatol Surg*. 2009;35(8):1199-1205. https://doi.org/10.1111/j.1524-4725.2008.34428.x.
57. Kunishige JH, Katz TM, Goldberg LH, Friedman PM. Fractional photothermolysis for the treatment of surgical scars. *Dermatol Surg* 2010;36(4):538-541. https://doi.org/10.1111/j.1524-4725.2010.01491.x.
58. Park KY, Oh IY, Seo SJ, Kang KH, Park SJ. Appropriate timing for thyroidectomy scar treatment using a 1,550-nm fractional erbium-glass laser. *Dermatol Surg*. 2013;39(12):1827-1834. https://doi.org/10.1111/dsu.12355.
59. Haedersdal M, Moreau KE, Beyer DM, Nymann P, Alsbjørn B. 1540 nm laser resurfacing for thermal burn scars: a randomized controlled trial. *Lasers Surg Med*. 2009;41(3):189-195. https://doi.org/10.1002/lsm.20756.
60. Wanner M, Tanzi EL, Alster TS. Fractional photothermolysis: treatment of facial and nonfacial cutaneous photodamage with a 1,550-nm erbium-doped fiber laser. *Dermatol Surg.* 2007;33(1):23-28. https://doi.org/10.1111/j.1524-4725.2007.33003.x.
61. Saedi N, Petrell K, Arndt K, Dover J. Evaluating facial pores and skin texture after low-energy nonablative fractional 1440 nm laser treatments. *J Am Acad Dermatol*. 2013;68(1):113-118. https://doi.org/10.1016/j.jaad.2012.08.041.
62. Polder KD, Harrison A, Eubanks LE, Bruce S. 1927-nm fractional thulium fiber laser for the treatment of nonfacial photodamage: A pilot study. *Dermatol Surg*. 2011;37(3):342-348. https://doi.org/10.1111/j.1524-4725.2011.01884.x.
63. Brauer JA, McDaniel DH, Bloom BS, Reddy KK, Bernstein LJ, Geronemus RG. Nonablative 1927 nm fractional resurfacing for the treatment of photopigmentation. *J Drugs Dermatol.* 2014;13(11):1317-1322.
64. Polder KD, Mithani A, Harrison A, Bruce S. Treatment of macular seborrheic keratoses using a novel 1927-nm fractional thulium fiber laser. *Dermatol Surg*. 2012;38(7 Pt 1):1025-1031. https://doi.org/10.1111/j.1524-4725.2012.02427.x
65. Kauvar AN. Fractional nonablative laser resurfacing: Is there a skin tightening effect? *Dermatol Surg*. 2014;40 Suppl 12:S157-S163. https://doi.org/10.1097/DSS.0000000000000200.

66. de Sica RC, Rodrigues CJ, Maria DA, Cucé LC. Study of 1550nm erbium glass laser fractional non-ablative treatment of photoaging: Comparative clinical effects, histopathology, electron microscopy, and immunohistochemistry. *J Cosmet Laser Ther*. 2016;25:1-36. https://doi.org/10.1080/14764172.2016.1191647.
67. Bencini PL, Tourlaki A, Galimberti M, Pellacani G. Non-ablative fractionated laser skin resurfacing for the treatment of aged neck skin. *J Dermatolog Treat.* 2015;26(3):252-256. https://doi.org/10.3109/09546634.2014.933765.
68. Peterson JD, Goldman MP. Rejuvenation of the aging chest: A review and our experience. *Dermatol Surg*. 2011;37(5):555-571. https://doi.org/10.1111/j.1524-4725.2011.01972.x.
69. Wu DC, Green JB. Rejuvenation of the aging arm: Multimodal combination therapy for optimal results. *Dermatol Surg*. 2016;42(Suppl 2):S119-S123. https://doi.org/10.1097/DSS.0000000000000732.
70. Jih MH, Goldberg LH, Kimyai-Asadi A. Fractional photothermolysis for photoaging of hands. *Dermatol Surg*. 2008;34(1):73-78. https://doi.org/10.1111/j.1524-4725.2007.34011.x.
71. Narurkar VA. Nonablative fractional resurfacing in the male patient. *Dermatol Ther.* 2007;20(6):430-435. https://doi.org/10.1111/j.1529-8019.2007.00173.x.
72. Boen M, Wilson MJV, Goldman MP, Wu DC. Rejuvenation of the male scalp using 1927 nm non-ablative fractional thulium fiber laser. *Lasers Surg Med*. 2017;49(5):475-479. https://doi.org/10.1002/lsm.22624.
73. Graber EM, Tanzi EL, Alster TS. Side effects and complications of fractional laser photothermolysis: experience with 961 treatments. *Dermatol Surg.* 2008;34(3):301-305; discussion 305-307. https://doi.org/10.1111/j.1524-4725.2007.34062.x.
74. Clark CM, Silverberg JI, Alexis AF. A retrospective chart review to assess the safety on nonablative fractional laser resurfacing in Fitzpatrick skin types IV to VI. *J Drugs Dermatol.* 2013;12(4):428-431.
75. Yaghmai D, Garden JM, Bakus AD, et al. Photodamage therapy using an electro-optic Q-switched Nd:YAG laser. Lasers Surg Med. 2010;42(8):699-705. https://doi.org/10.1002/lsm.20957.
76. Leubberding S, Alexiades-Armenakas MR. Fractional, nonablative Q-switched 1,064-nm neodymium YAG laser to rejuvenate photoaged skin: A pilot case series. *J Drugs Dermatol.* 2012;11(11):1300-1304.
77. Gold MH, Sensing W, Biron J. Fractional Q-switched 1,064-nm laser for the treatment of photoaged-photodamaged skin. J Cosmet Laser Ther. 2014;16(2):69-76. https://doi.org/10.3109/14764172.2013.864197.
78. Won KH, Lee SH, Lee MH, Rhee DY, Yeo UC, Chang SE. A prospective, split-face, double-blinded, randomized study of the efficacy and safety of a fractional 1064-nm Q-switched Nd:YAG laser for photoaging-associated mottled pigmentation in Asian skin. *J Cosmet Laser Ther.* 2016;18(7):381-386.
79. Saedi N, Metelitsa A, Petrell K, Arndt KA, Dover JS. Treatment of tattoos with a picosecond alexandrite laser: a prospective trial. *Arch Dermatol.* 2012;148(12):1360-1363. https://doi.org/10.1001/archdermatol.2012.2894.
80. Brauer JA, Kazlouskaya V, Alabdulrazzaq H, et al. Use of a picosecond pulse duration laser with specialized optic for treatment of facial acne scarring. *JAMA Dermatol*. 2015;151(3):278-284. https://doi.org/10.1001/jamadermatol.2014.3045.
81. Haimovic A, Brauer JA, Cindy Bae YS, Geronemus RG. Safety of a picosecond laser with diffractive lens array (DLA) in the treatment of Fitzpatrick skin types IV to VI: A retrospective review. *J Am Acad Dermatol*. 2016;74(5):931-936. https://doi.org/10.1016/j.jaad.2015.12.010.
82. Tanghetti EA. The histology of skin treated with a picosecond alexandrite laser and a fractional lens array. *Lasers Surg Med.* 2016;48(7):646-652. https://doi.org/10.1002/lsm.22540.
83. Weiss RA, McDaniel DH, Weiss MA, Mahoney AM, Beasley KL, Halvorson CR. Safety and efficacy of a novel diffractive lens array using a picosecond 755 nm alexandrite laser for treatment of wrinkles. *Lasers Surg Med*. 2017;49(1):40-44. https://doi.org/10.1002/lsm.22577.
84. Khetarpal S, Desai S, Kruter L, et al. Picosecond laser with specialized optic for facial rejuvenation using a compressed treatment interval. *Lasers Surg Med*. 2016;48(8):723-726.
85. 85. Ge Y, Guo L, Wu Q, Zhang M, Zeng R, Lin T. A prospective split-face study of the picosecond alexandrite laser with specialized lens array for facial photoaging in Chinese. *J Drugs Dermatol.* 2016;15(11):1390-1396.
86. Wu DC, Fletcher L, Guiha I, Goldman MP. Evaluation of the safety and efficacy of the picosecond alexandrite laser with specialized lens array for treatment of the photoaging décolletage. *Lasers Surg Med*. 2016;48(2):188-192. https://doi.org/10.1002/lsm.22427.
87. Pozner J, Robb CW. *Hybrid fractional laser: The future of laser resurfacing*. Palo Alto, CA: Sciton; 2014.
88. Mezzana P, Valeriani M, Valeriani R. Combined fractional resurfacing (10600 nm/1540 nm): Tridimensional imaging evaluation of a new device for skin rejuvenation. *J Cosmet Laser Ther.* 2016;18(7):397-402. https://doi.org/10.1080/14764172.2016.1202417.
89. Lolis MS, Goldberg DJ. Radiofrequency in cosmetic dermatology: A review. *Dermatol Surg*. 2012;38(11):1765-1776. https://doi.org/10.1111/j.1524-4725.2012.02547.x.
90. Brightman L, Goldman MP, Taub AF. Sublative rejuvenation: experience with a new fractional radiofrequency system for skin rejuvenation and repair. *J Drugs Dermatol*. 2009;8(11 Suppl):s9-s13.
91. Hruza G, Taub AF, Collier SL, Mulholland SR. Skin rejuvenation and wrinkle reduction using a fractional radiofrequency system. *J Drugs Dermatol.* 2009;8(3):259-265.
92. Simmons BJ, Griffith RD, Falto-Aizpurua LA, Nouri K. Use of radiofrequency in cosmetic dermatology: focus on nonablative treatment of acne scars. *Clin Cosmet Investig Dermatol.* 2014;7:335-339. https://doi.org/10.2147/CCID.S74411.
93. Qin X, Li H, Jian X, Yu B. Evaluation of the efficacy and safety of fractional bipolar radiofrequency with high-energy strategy for treatment of acne scars in Chinese. *J Cosmet Laser Ther.* 2015;17(5):237-245. https://doi.org/10.3109/14764172.2015.1007070.
94. Phothong W, Wanitphakdeedecha R, Sathaworawong A, Manuskiatti W. High versus moderate energy use of bipolar fractional radiofrequency in the treatmhent of acne scars: a split-face double-blinded randomized control trial pilot study. *Lasers Med Sci.* 2016;31(2):229-234. https://doi.org/10.1007/s10103-015-1850-2.
95. Kaminaka C, Uede M, Matsunaka H, Furukawa F, Yamamoto Y. Clinical studies of the treatment of facial atrophic acne scars and acne with a bipolar fractional radiofrequency system. *J Dermatol*. 2015;42(6):580-587. https://doi.org/10.1111/1346-8138.12864.
96. Wang S, Mi J, Li Q, Jin R, Dong J. Fractional microplasma radiofrequency technology for non-hypertrophic post-burn scars in Asians: A prospective study of 95 patients. Lasers Surg Med. 2017;49(6):563-569. https://doi.org/10.1002/lsm.22640.
97. Bloom BS, Emer J, Goldberg DJ. Assessment of safety and efficacy of a bipolar fractionated radiofrequency device in the treatment of photodamaged skin. *J Cosmet Laser Ther.* 2012;14(5):208-211. https://doi.org/10.3109/14764172.2012.724534.
98. 98. Jiang Y, Zhang X, Lu Z, Gold MH. Assessment of efficacy and safety of a fractionated bipolar radiofrequency device for the treatment of lower face wrinkles and laxity. *J Cosmet Laser Ther*. 2016;21:1-20. https://doi.org/10.1080/14764172.2016.1262959.
99. Tanaka Y. Long-term three-dimensional volumetric assessment of skin tightening using a sharply tapered non-insulated microneedle radiofrequency applicator with novel fractionated pulse mode in Asians. *Lasers Surg Med*. 2015;47(8):626-633. https://doi.org/10.1002/lsm.22401.
100. Chandrashekar BS, Sriram R, Mysore R, Bhaskar S, Shetty A. Evaluation of microneedling fractional radiofrequency device for treatment of acne scars. *J Cutan Aesthet Surg*. 2014;7(2):93-97. https://doi.org/10.4103/0974-2077.138328.
101. Doddaballapur S. Microneedling with dermaroller. *J Cutan Aesthet Surg*. 2009;2(2):110-111. https://doi.org/10.4103/0974-2077.58529.
102. Dogra S, Yadav S, Sarangal R. Microneedling for acne scars in Asian skin type: an effective low cost treatment modality. *J Cosmet Dermatol*. 2014;13(3):180-187. https://doi.org/10.1111/jocd.12095.
103. Cachafeiro T, Escobar G, Maldonado G, Cestari T, Corleta O. Comparison of Nonablative Fractional Erbium Laser 1,340 nm and Microneedling for the Treatment of Atrophic Acne Scars: A Randomized Clinical Trial. *Dermatol Surg*. 2016;42(2):232-241. https://doi.org/10.1097/DSS.0000000000000597.
104. Alam M, Han S, Pongprutthipan M, et al. Efficacy of a needling device for the treatment of acne scars: a randomized clinical trial. *JAMA Dermatol.* 2014;150(8):844-849. https://doi.org/10.1001/jamadermatol.2013.8687.
105. Schwarz M, Laaff H. A prospective controlled assessment of microneedling with the Dermaroller device. *Plast Reconstr Surg*. 2011;127(6):146e-148e. https://doi.org/10.1097/PRS.0b013e3182131e0f.
106. Cho SI, Chung BY, Choi MG, et al. Evaluation of the clinical efficacy of fractional radiofrequency microneedle treatment in acne scars and large facial pores. *Dermatol Surg.* 2012;38(7 Pt 1):1017-1024. https://doi.org/10.1111/j.1524-4725.2012.02402.x.
107. Vejjabhinanta V, Wanitphakdeedecha R, Limtanyakul P, Manuskiatti W. The efficacy in treatment of facial atrophic acne scars in Asians with a fractional radiofrequency microneedle system. *J Eur Acad Dermatol Venereol*. 2014;28(9):1219-1225. https://doi.org/10.1111/jdv.12267.
108. Min S, Park SY, Yoon JY, Suh DH. Comparison of fractional microneedling radiofrequency and bipolar radiofrequency on acne and acne scar and investigation of mechanism: comparative randomized controlled clinical trial. *Arch Dermatol Res*. 2015;307(10):897-904. https://doi.org/10.1007/s00403-015-1601-z.
109. Alexiades-Armenakas M, Newman J, Wiley A, Kilmer S, Goldberg D, Garden J. Prospective multicenter clinical trial of a minimally invasive temperature-controlled bipolar fractional radiofrequency system for rhytid and laxity treatment. *Dermatol Surg*. 2013;39(2):263-273. https://doi.org/10.1111/dsu.12065.
110. Alexiades-Armenakas M, Rosenberg D, Renton B, Dover J, Arndt K. Blinded, randomized, quantitative grading comparison of minimally invasive, fractional radiofrequency and surgical face-lift to treat skin laxity. *Arch Dermatol*. 2010;146(4):396-405. https://doi.org/10.1001/archdermatol.2010.24.
111. Man J, Goldberg DJ. Safety and efficacy of fractional bipolar radiofrequency treat-

ment in Fitzpatrick skin types V–VI. *J Cosmet Laser Ther*. 2012;87(6):179-183. https://doi.org/10.3109/14764172.2012.699682.
112. Sklar LR, Burnett CT, Waibel JS, Moy RL, Ozog DM. Laser assisted drug delivery: a review of an evolving technology. *Lasers Surg Med.* 2014;46(4):249-262. https://doi.org/10.1002/lsm.22227.
113. Yun PL, Tachihara R, Anderson RR. Efficacy of erbium:yttrium-aluminum-garnet laser-assisted delivery of topical anesthetic. *J Am Acad Dermatol*. 2002;47(4):542-547.
114. Waibel JS, Rudnick A. Laser-Assisted Delivery to Treat Facial Scars. *Facial Plast Surg Clin North Am*. 2017;25(1):105-117. https://doi.org/10.1016/j.fsc.2016.08.010.
115. Rkein A, Ozog D, Waibel JS. Treatment of atrophic scars with fractionated CO2 laser facilitating delivery of topically applied poly-L-lactic acid. *Dermatol Surg*. 2014;40(6):624-631. https://doi.org/10.1111/dsu.0000000000000010.
116. Massaki AB, Fabi SG, Fitzpatrick R. Repigmentation of hypopigmented scars using an erbium-doped 1,550-nm fractionated laser and topical bimatoprost. *Dermatol Surg*. 2012;38(7 Pt 1):995-1001. https://doi.org/10.1111/j.1524-4725.2012.02389.x.
117. Gardner MJ, Demetrakopoulos D, Klepchick PR, Mooar PA. The efficacy of autologous platelet gel in pain control and blood loss in total knee arthroplasty. An analysis of the haemoglobin, narcotic requirement and range of motion. *Int Orthop*. 2007;31(3):309-313. https://doi.org/10.1097/01.prs.0000239606.92676.cf.10.1007/s00264-006-0174-z.
118. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. *Plast Reconstr Surg*. 2006;118(6):147e-159e. https://doi.org/10.1097/01.prs.0000239606.92676.cf.
119. Redaelli A, Romano D, Marcianó A. Face and neck revitalization with platelet-rich plasma (PRP): clinical outcome in a series of 23 consecutively treated patients. *J Drugs Dermatol.* 2010;9(5):466-472.
120. Lee JW, Kim BJ, Kim MN, Mun SK. The efficacy of autologous platelet rich plasma combined with ablative carbon dioxide fractional resurfacing for acne scars: a simultaneous split-face trial. *Dermatol Surg.* 2011;37(7):931-938. https://doi.org/10.1111/j.1524-4725.2011.01999.x.
121. Gawdat HI, Hegazy RA, Fawzy MM, Fathy M. Autologous platelet rich plasma: topical versus intradermal after fractional ablative carbon dioxide laser treatment of atrophic acne scars. *Dermatol Surg* 2014;40(2):152-161. https://doi.org/10.1111/dsu.12392.
122. Vandervoort J, Ludwig A. Microneedles for transdermal drug delivery: a minireview. *Front Biosci.* 2008;13:1711-1715.
123. Asif M, Kanodia S, Singh K. Combined autologous platelet-rich plasma with microneedling verses microneedling with distilled water in the treatment of atrophic acne scars: a concurrent split-face study. *J Cosmet Dermatol*. 2016;15(4):434-443. https://doi.org/10.1111/jocd.12207.
124. Waibel JS, Wulkan AJ, Shumaker PR. Treatment of hypertrophic scars using laser and laser assisted corticosteroid delivery. *Lasers Surg Med*. 2013;45(3):135-140. https://doi.org/10.1002/lsm.22120.
125. Haedersdal M, Erlendsson AM, Paasch U, Anderson RR. Translational medicine in the field of ablative fractional laser (AFXL)-assisted drug delivery: A critical review from basics to current clinical status. *J Am Acad Dermatol*. 2016;74(5):981-1004. https://doi.org/10.1016/j.jaad.2015.12.008.
126. Zaleski-Larsen LA, Fabi SG. Laser-assisted drug delivery. *Dermatol Surg*. 2016;42(8):919-931. https://doi.org/10.1097/DSS.0000000000000556.
127. Hsiao CY, Sung HC, Hu S, and Huang CH. Fractional CO2 laser treatment to enhance skin permeation of tranexamic acid with minimal skin disruption. *Dermatology*. 2015;230(3):269-275. https://doi.org/10.1159/000371386.
128. Chen WY, Fang CL, Al-Suwayeh SA, Yang HH, Li YC, Fang JY. Risk assessment of excess drug and sunscreen absorption via skin with ablative fractional laser resurfacing. *Lasers Med Sci*. 2013;28(5):1363-1374. https://doi.org/10.1007/s10103-012-1257-2.
129. Hsiao CY, Huang CH, Hu S, et al. Fractional carbon dioxide laser treatment to enhance skin permeation of ascorbic acid 2-glucoside with minimal skin disruption. *Dermatol Surg.* 2012;38(8):1284-1293. https://doi.org/10.1111/j.1524-4725.2012.02454.x.
130. Hsiao CY, Sung HC, Hu S, Huang YL, Huang CH. Fractional CO2 laser pretreatment facilitates transdermal delivery of two vitamin C derivatives. *Molecules*. 2016;21(11):1547. https://doi.org/10.3390/molecules21111547
131. Beltraminelli H, Dietrich N, Hunziker T. Fractional transepidermal delivery: A histological analysis. *Dermatology*. 2011;223(4):321-324. https://doi.org/10.1159/000334165.
132. Na JI, Choi JW, Choi HR, et al. Rapid healing and reduced erythema after ablative fractional carbon dioxide laser resurfacing combined with the application of autologous platelet-rich plasma. *Dermatol Surg*. 2011;37(4):463-468. https://doi.org/10.1111/j.1524-4725.2011.01916.x.
133. Lee WR, Shen SC, Aljuffali IA, Lin YK, Huang CW, Fang JY. Non-ablative fractional laser assists cutaneous delivery of small- and macro-molecules with minimal bacterial infection risk. *Eur J Pharm Sci*. 2016;92:1-10. https://doi.org/10.1016/j.ejps.2016.06.016.
134. Bloom BS, Brauer JA, Geronemus RG. Ablative fractional resurfacing in topical drug delivery: An update and outlook. *Dermatol Surg*. 2013;39(6):839-848. https://doi.org/10.1111/dsu.12111.