

Lasers and Light Sources to Activate Fibroblasts

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There is a decrease in normal collagen in aged and sun-damaged skin. Neocollagenesis can promote a more youthful appearance. A key target in the mitigation of the pathophysiology of photoaging is fibroblasts. Various therapeutic modalities can be employed, including topical retinoids, dermabrasion, radiofrequency or ultrasound energy, and filler injections. This review focuses on the molecular-level effects of lasers and light sources to activate fibroblasts. Fractional ablative and nonablative resurfacing lasers are the gold standard for stimulating aged fibroblasts and inducing neocollagenesis; however, other laser and light modalities can be employed to activate quiescent fibroblasts.

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Clinical characteristics of aged and sun-damaged skin include rhytides, dyspigmentation, and atrophy. Histologically, the organized epidermal and dermal architecture is lost, and there is flattening of the rete ridges, which clinically corresponds with cutaneous thinning and fragility. Additionally, there is a decrease in types IV and VII collagen at the basement membrane.^{1,2} The dermis also is known to decrease in thickness by up to 20%.³ Interestingly, this reduction is not seen in photoprotected sites until 80 years of age, indicating a

prominent role for UV light in the aging process.⁴ Both in vitro and in vivo, there is a decreased production of collagen and glycosaminoglycans by fibroblasts.⁵ Collagen content in the dermis decreases by approximately 1% per year throughout adulthood.⁶ Furthermore, senile cultured fibroblasts are less responsive to stimulation by growth factors, indicating an intrinsic functional change in the fibroblasts that comes with aging.⁵

Compounding this decrease in collagen production is an increase in its degradation. Matrix metalloproteinases (MMPs), such as collagenase, are induced by UV exposure and other stressors and are capable of degrading virtually all extracellular matrix components. Histologically, this phenomenon is characterized by short, irregular, and disorganized collagen fibers. These collagen bundles are more highly cross-linked than those of youthful skin. The ratio of collagen types also changes, with an increased proportion of type III collagen. The most dramatic loss of collagen, measured by procollagen gene expression, is noted in the upper third of the dermis, presumably related to the depth of UV penetration into the skin.⁷

The cumulative result of these processes is a decrease in normal collagen; therefore, a key target in the mitigation of the pathophysiology of photoaging is the

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fibroblast. Neocollagenesis can promote a more youthful appearance. Specifically, dermal remodeling is thought to occur via increased deposition of types I and III collagen, with collagen reorganization into parallel arrays of compact fibrils.⁸

Dermatologists employ diverse therapeutic modalities, including topical retinoids, dermabrasion, radiofrequency or ultrasound energy, and filler injections, to stimulate collagen production; this review focuses on the molecular-level effects of lasers and light sources utilized to achieve this goal.

ABLATIVE LASERS

Ablative laser resurfacing entails vaporization of the superficial layers of the skin and coagulative necrosis. The 10,600-nm CO₂, 2940-nm erbium:YAG (Er:YAG), and 2790-nm erbium:YSGG lasers are the most commonly used ablative lasers. Traditional continuous-wave ablative lasers have given way to short-pulsed, high-energy fractionated systems. Ablative laser resurfacing elicits notable improvement in dyspigmentation, rhytides, and atrophic scars; however, there is a prolonged postoperative recovery period and potentially permanent adverse sequelae, such as scarring. Following ablative laser procedures, patients also can experience prolonged erythema, edema, milia formation, pigment alteration, reactivation of herpes simplex virus, and delayed wound healing.^{9,10}

10,600-nm CO₂ Laser

Despite the potential risks of ablative laser resurfacing, the CO₂ laser remains one of the most effective modalities available for facial rejuvenation.¹¹ Pulsed CO₂ lasers have been shown to vaporize epidermal and dermal cells and cause coagulative necrosis of the underlying cell layers. These lasers act further to denature extracellular proteins in adjacent zones.¹²

The seminal work by Orringer et al¹³ quantified the molecular-level effects of a CO₂ laser (Ultrapulse, Coherent, Inc) by analyzing messenger RNA (mRNA) transcripts of types I and III collagen. A total of 28 patients with photodamage of the forearms were treated with 2 passes of the CO₂ laser at 60 W in a single treatment session. Tissue biopsies of the treatment area were obtained at baseline and 5 additional times following treatment. Production of types I and III procollagen mRNA peaked 21 days posttreatment and remained elevated for at least 6 months. Increases in several cytokines (IL-1 β , tumor necrosis factor α , and transforming growth factor β 1) preceded and/or accompanied changes in collagen levels. Marked increases in mRNA levels of MMP-1, MMP-3, MMP-9, and MMP-13 also were noted. The

increased expression of MMPs preceded the increased production of types I and III procollagen.¹³

Based on their findings, Orringer et al¹³ proposed the following model: Proinflammatory cytokines (IL-1 β , tumor necrosis factor α) induce the expression of MMPs. The MMPs, including collagenase (MMP-1 and MMP-3) and gelatinase-B (MMP-9), break down existing collagen. Levels of MMP-9 remain elevated in the postoperative period, evidence of continued collagen removal. The degradation of photodamaged collagen facilitates replacement by new, well-organized collagen bundles.¹³

Orringer et al¹³ also found that collagenase-3 (MMP-13), known to have a role in the collagen remodeling of fetal wounds¹⁴ but not normally healing adult wounds,¹⁵ was maximally expressed on postoperative day 14. Interestingly, the upregulation of MMP-13 may occur in a temperature-dependent fashion, as it also is seen in human skin that has been treated with fractional radiofrequency energy to a temperature of 72°C.¹⁶

In a similar report, Reilly et al¹⁷ examined the molecular effects of a fractional CO₂ laser (Pixel Perfect, Alma Lasers, Ltd) in 9 patients on infra-auricular skin that was sampled preoperative, immediately postoperative, and at 2 of 3 other time points (days 7, 14, or 21). They found that MMP-1, MMP-3, MMP-9, and MMP-13 also were upregulated; however, upregulation of 2 additional MMPs (MMP-10 and MMP-11) was demonstrated after treatment with the fractional CO₂ laser.¹⁷ Based on these findings, the mechanisms by which fractional and full-field CO₂ lasers induce neocollagenesis appear to be similar.

2940-nm Er:YAG Laser

The Er:YAG laser has a greater water absorption coefficient than the CO₂ laser and a subsequently more shallow absorption depth. In one study, 10 patients with clinically evident photodamage of the forearms were treated with a single pass (750 mJ; 5-mm spot size) of the full-field Er:YAG laser (SmoothPeel, Candela Corporation); then skin biopsies were taken at 1, 3, 7, and 14 days posttreatment.¹⁸ Molecular studies following treatment with the Er:YAG laser revealed induction of epidermal expression of keratin 16, a marker of epidermal injury; however, immunostaining with laminin γ 2 confirmed that, despite epidermal damage, the basement membrane remained intact following treatment. Interestingly, heat shock protein 70 (Hsp70), which is thought to participate in procollagen synthesis in normal wound healing, was not shown to be elevated.¹⁸

As with CO₂ lasers, resurfacing with the Er:YAG laser increases MMP-1, MMP-3, MMP-9, and types I and III

collagen,¹⁸ a process that has been clinically shown to improve mild to moderate atrophic acne scars.¹⁹ According to the authors, the evidence that epidermal injury with the Er:YAG laser significantly induces dermal neocollagenesis could shift the paradigm for activating quiescent fibroblasts to less-invasive interventions.¹⁸ Of note, the 2790-nm erbium:YSGG laser was introduced in 2007 (Pearl, Cutera, Inc). Its water absorption coefficient is one-third that of the Er:YAG laser and 5 times that of the CO₂ laser.²⁰ Although there are studies evaluating the clinical and histologic efficacy of this device,^{21,22} we were unable to find any published evidence of its molecular effects.

NONABLATIVE LASERS AND LIGHT SOURCES

Nonablative lasers can be classified into 3 main groups: near-infrared lasers, such as the 1550-nm and 1540-nm erbium glass fractional resurfacing lasers and 1320-nm and 1064-nm Nd:YAG lasers; visible light lasers such as the pulsed dye laser (PDL) and the pulsed potassium titanyl phosphate (KTP) laser; and broadband intense pulsed light (IPL) sources.²³

Traditional nonablative laser treatments are effective for improving rhytides and scars, but the results of a single nonablative session are less impressive than a single treatment with an ablative counterpart. Nonablative lasers function to stimulate dermal collagen formation without visible epidermal wounding. The concept of fractional photothermolysis (FP) that was first published in 2004 revolutionized resurfacing lasers.²⁴ During nonablative FP procedures, infrared laser irradiation is delivered in microthermal zone columns, sparing intervening areas of skin while the stratum corneum remains intact. The undamaged surrounding skin rapidly repopulates the injured tissue columns, resulting in less downtime and risk for scarring than traditional homogenous laser interventions.

1550-nm Erbium Glass Laser

The near-infrared 1550-nm erbium glass laser's primary chromophore is intracellular water, and it penetrates to a depth of up to 2 mm. Compared to shorter-wavelength, 1320-nm and 1450-nm infrared laser systems, the 1550-nm wavelength induces the least amount of melanin and hemoglobin absorption. In 2010, Orringer et al²⁵ published their findings of a 1550-nm erbium-doped fiber laser (Fraxel SR1500/Fraxel re:store, Solta Medical, Inc) used to treat the actinically damaged forearms of 20 patients and performed analyses similar to those used in their prior study of CO₂ lasers.¹³ Histologic examination 24 hours after treatment revealed thermally altered columns in the epidermis and dermis of treated skin. Despite epidermal damage, the

basement membrane remained intact as indicated by laminin γ 2 staining.²⁵

Following treatment, the investigators found an acute inflammatory response in the form of neutrophil infiltration and elevation of proinflammatory cytokines IL-1 β and tumor necrosis factor α . They also found that FP induced rapid and transient expression of Hsp70,²⁵ which potentiates procollagen synthesis by protecting against misfolding of proteins during heat stress.²⁶ Production of types I and III collagen also was increased, and elevated mRNA levels of MMP-1, MMP-3, and MMP-9 were observed. With respect to molecular mediators, minimal differences were observed between lower and higher microbeam energy settings (15 vs 70 mJ) and collagen production was not statistically different between the two. Based on these findings, the authors suggested that lower microbeam energy and higher microbeam density treatment parameters might be optimal for achieving the best combination of patient tolerability and clinical outcome.²⁵ The molecular changes observed after nonablative FP were remarkably similar to those observed after traditional ablative resurfacing.¹³

1540-nm Erbium Glass Laser

The 1540-nm fractional erbium glass laser is similar in nature to the 1550-nm device. Lupton et al²⁷ evaluated 24 female patients with mild to moderate periorbital and perioral rhytides following a series of 3 monthly treatments with a near-infrared 1540-nm erbium-doped phosphate glass laser (Aramis, Quantel Medical). Skin biopsies were obtained at baseline, immediately following laser irradiation, and at 1 and 6 months posttreatment. Six months after the final treatment, a mild but noticeable increase in dermal fibroplasia was evident. Molecular analysis was not performed on the specimens.²⁷

Fournier et al²⁸ used ultrasonography to quantify the posttreatment changes. Sixty patients with perioral and periorbital rhytides were treated 4 times over 6-week intervals with a 1540-nm erbium-doped phosphate glass laser (Aramis). Participants were evaluated using photographs, histology, ultrasound imaging, and profilometry using silicone imprints. Ultrasound imaging demonstrated a 17% increase in dermal thickness and biopsy specimens qualitatively showed new collagen formation.²⁸

In a recent study by de Angelis et al,²⁹ a 1540-nm erbium glass laser (Lux1540, Palomar Medical Technologies, Inc) was used to treat striae distensae in 51 patients and demonstrated clinical improvement as well as histologic evidence of dermal thickening, neocollagenesis, and increased elastin deposition 1 month after a series of 2 to 4 treatments. Although there was no molecular analysis of the posttreatment

wound-healing process, one would expect that it would be similar to that observed following treatment with the 1550-nm laser.

1320-nm Nd:YAG Laser

The 1320-nm Nd:YAG laser for nonablative dermal remodeling has a high scattering coefficient. Consequently, the laser energy largely is confined to the dermis. This wavelength is coupled with cryogen cooling so that dermal damage can be induced with less risk of epidermal injury. This device has been used for the treatment of photoaging as well as acne scarring.^{30,31}

Goldberg³⁰ qualitatively assessed the efficacy of this laser in a study of 10 female participants with photoaging. Unique to this analysis was the use of a thermal sensor to measure epidermal temperature. Peak surface therapeutic temperatures, as measured by a thermal sensor contained within the laser handpiece, ranged from 40°C to 48°C, which corresponded to a dermal temperature of 60°C to 65°C.³⁰

The clinical improvements noted by Goldberg³⁰ were more remarkable than a prior study by Menaker et al³² in which improvement was noted in only 4 of 10 patients and pitted scarring was found in 3 participants during this 3-month study; however, in the Menaker et al³² study, all participants were treated with a constant set of parameters, as opposed to Goldberg's³⁰ study in which treatment fluences varied.

Histologic analysis of nonablative remodeling using a microsecond-pulse, 1320-nm Nd:YAG laser (Cool Touch I, CoolTouch Corporation) demonstrated epidermal spongiosis and basal cell layer edema visible 1 hour after treatment with 3 passes of the laser.³³ Three days following treatment, there was evidence of dermal microthrombi, sclerosis of blood vessels, and neutrophilic infiltration. These findings correlated with clinical improvement, suggesting that epidermal and vascular injury may play a role in inducing neocollagenesis.³³

1064-nm Nd:YAG Laser and 532-nm KTP Laser

The 1064-nm Nd:YAG laser in the near-infrared spectrum offers greater cutaneous depth of penetration than the KTP laser or PDL, with capabilities reaching 5 to 10 mm when used with epidermal cooling. A variety of Nd:YAG lasers are available with pulse widths ranging from the Q-switched nanosecond lasers to long-pulsed millisecond devices. Oxyhemoglobin absorbs 1064-nm light 10 times more effectively than water, which makes this device an ideal choice for darker skin types because 1064-nm light is poorly absorbed by melanin. The nonspecific thermal damage induced by the Nd:YAG laser stimulates dermal remodeling.³⁴

In a split-face study of 11 participants receiving treatment of rhytides in the periorbital or perioral regions, Goldberg and Whitworth³⁴ compared the resurfacing capability of the Q-switched Nd:YAG versus 2 CO₂ lasers (Silk Touch, Sharplan, Inc; UltraPulse, Coherent, Inc). Although all 11 (100%) participants treated with both CO₂ lasers showed clinical improvement, only 9 (82%) participants treated with the Q-switched Nd:YAG laser showed improvement, which was notably less impressive.³⁴ In a follow-up study, Goldberg and Silapunt³⁵ conducted a histologic analysis of sun-damaged, infra-auricular skin specimens 3 months following a single treatment with the 1064-nm Q-switched Nd:YAG laser, which revealed inconsistent papillary dermal collagen formation. Four of 6 (67%) participants demonstrated increased fibrosis in the papillary dermis, which is evidence of collagen remodeling, 3 months following treatment; however, the authors noted that histologic changes are not always directly correlated with clinical improvement.³⁵

Using a submillisecond (300-microsecond pulse duration) 1064-nm Nd:YAG laser (CoolGlide, Cutera, Inc), Schmults et al³⁶ examined the effects on dermal remodeling using histology and electron micrography. Nine female patients were treated at 2-week intervals for a total of 3 treatment sessions. Electron micrograph analysis showed a decrease in overall collagen fiber diameter in the papillary dermis at 1 and 3 months after treatment, indicating the formation of new collagen; however, no quantitative analysis of collagen production was performed.³⁶

When 1064-nm light passes through a KTP crystal, it is frequency doubled (wavelength halved) to 532-nm green light. The strong melanin absorption level of this wavelength limits its depth of penetration to 1 to 2 mm. The long-pulsed KTP is an excellent vascular laser and its Q-switched variant is effective at removing the pigment of lentigines and tattoos. Reported clinical improvement in scars and rhytides after treatment with KTP and Nd:YAG lasers suggest their effectiveness at delivering heat to induce neocollagenesis.^{37,38}

A study by Dang et al³⁹ elucidated the *in vitro* effects of the 532-nm KTP and 1064-nm Q-switched Nd:YAG lasers on human skin fibroblasts. The investigators found increased expression of types I and III procollagen after irradiation with Q-switched KTP or Nd:YAG lasers. Both lasers markedly downregulated the expression of MMP-1 and MMP-2 and upregulated the expression of tissue inhibitors of metalloproteinases. Interestingly, the authors contended that the increased tissue inhibitors of metalloproteinases and reduced expression of collagen-digesting MMPs facilitates neocollagenesis,³⁹ whereas the aforementioned Orringer et al¹³ study with ablative

lasers found elevated MMPs and theorized that they were necessary to clear actinically damaged collagen prior to fibroblast deposition of new collagen. Dang et al³⁹ found that the KTP laser induced IL-6, a potent mediator of fibroblast proliferation that decreases with aging, and Hsp70. In contrast, they found that the Nd:YAG laser induced transforming growth factor β , a major inducer of procollagen synthesis in wound healing, suggesting a different mechanism of action for neocollagenesis for each laser.³⁹ A more recent study by this same group found that in vitro irradiation of human skin fibroblasts by both the KTP and Nd:YAG lasers led to upregulation of the major antioxidant enzymes superoxide dismutase and glutathione peroxidase, demonstrating that reduced oxidative stress potentiates fibroblast neocollagenesis.⁴⁰ The contributions of these investigators have remarkably advanced the understanding of the molecular mechanisms driving the activation of fibroblasts by KTP and Nd:YAG lasers.

585-nm to 595-nm PDL

Pulsed dye lasers emit yellow light (585–595 nm) that is well absorbed by blood vessels in the dermis. Prior investigations of PDL that demonstrated its ability to improve scars and striae distensae clinically and histologically by inducing neocollagenesis form the basis for its use in activating aged fibroblasts.^{41–43} An earlier investigation by Zelickson et al⁴⁴ evaluated the effects of PDL therapy in 10 patients with mild to moderate perioral or periorbital wrinkling and 10 patients with moderate to severe perioral or periorbital wrinkling after a single PDL (Photogenica V, Cynosure, Inc) treatment session (585-nm wavelength; 3.0–6.5 J/cm²; 450-microsecond pulse duration; 7–10-mm spot size). Fourteen months after the purpura-inducing, short-pulsed PDL treatment, 90% (9/10) of patients with mild to moderate rhytides and 40% (4/10) with moderate to severe rhytides demonstrated clinical improvement. Histologic analysis of treated areas demonstrated increased staining of elastin and collagen fibrils in the papillary dermis as well as increased mucin.⁴⁴

In a study by Rostan et al,⁴⁵ 15 women who received 4 monthly, long-pulsed, 595-nm PDL treatments demonstrated a modest 18% clinically graded improvement of photodamage. Clinical improvement correlated with histologic analysis that revealed increased numbers of active fibroblasts with positive procollagen staining; however, no quantitative analysis of collagen production was performed.⁴⁵ The PDL is predominately employed by the dermatologic laser surgeon to target vascular lesions, but it also is evident that the thermal effect of PDL on perivascular tissues can induce neocollagenesis.

500-nm to 1200-nm IPL

Intense pulsed light sources utilize flashlamps to emit polychromatic light ranging from 500 to 1300 nm. Cut-off filters can be used to adapt the wavelength range depending on the clinical application. Because IPL devices emit a spectrum of wavelengths, they can target the 3 major chromophores—hemoglobin, melanin, and water—in a single treatment. Clinical improvements in dyspigmentation and erythema are accompanied by histologic changes indicative of a dermal remodeling effect, such as an increase in extracellular matrix proteins and neocollagenesis.

In a study by Goldberg,⁴⁶ 5 patients underwent 4 IPL treatment sessions followed by a biopsy 6 months after the final treatment. Histologic analysis demonstrated new collagen formation in the papillary dermis that was associated with clinical improvement.⁴⁶ It has been theorized that the effect of IPL on dermal collagen is caused by heat diffusion from the vasculature with release of inflammatory mediators that are stimulated by vessel heating.⁴⁷ Another study by Feng et al⁴⁸ evaluated 4 patients after 2 to 4 IPL treatments (Lumenis One, Lumenis Aesthetic) and found an increase in types I and III collagen with immunohistochemistry. Transmission electron microscopy revealed “younger” fibroblasts and increased activity of cellular organelles.⁴⁸

Compared to ablative and nonablative resurfacing, IPL offers more modest clinical improvement in rhytides and texture and is the most beneficial for pigmented and vascular targets.⁴⁹ Nonetheless, there is histologic and molecular evidence that the dermal heat generated by IPL treatments induces neocollagenesis.

CONCLUSION

The dermatologic laser surgeon possesses an ever-expanding armamentarium of lasers and light-based devices to improve the appearance of photoaged skin. Fractional ablative and nonablative resurfacing lasers are the current gold standard for stimulating aged fibroblasts and inducing neocollagenesis; however, as this review has illustrated, other laser and light modalities are capable of delivering energy to the dermis to activate quiescent fibroblasts and improve the appearance of aged skin.

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Case Report: report and discussion of case(s) illustrating an important or interesting observation (photographs must be included)

Cosmetic Technique: detailed outline of the author's cosmetic technique; intended to be of practical use for the clinician (photographs must be included)

All submissions are peer-reviewed by experts in the field. The average length of

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Please refer to our Information for Authors online at www.cosderm.com for more detailed submission guidelines.

To help streamline the review process, *Cosmetic Dermatology* accepts submissions via e-mail. E-mail the manuscript and any accompanying figures and tables to Camille Malanka (camille.malanka@qhc.com).

For questions about submissions, please contact Melissa Steiger (melissa.steiger@qhc.com).

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- > Therapies
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- > Wound healing
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