Photodamage, Part 2: Management of Photoaging

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The management of photodamage can be discussed under the management of photoaging as well as of precancerous and cancerous lesions. Because it is beyond the scope of this review to discuss these aspects in details, we will limit our discussion mainly to the management of photoaging and briefly enlist the management of precancerous and cancerous lesions.

MANAGEMENT OF PHOTOAGING

Topical Therapy

Retinoids are vitamin A derivatives that bind to intracellular receptors to cause cellular proliferation and differentiation. One reason to treat the signs of photodamage is to reduce wrinkling. The mechanism of action is the enhanced synthesis of new collagen in the dermis, particularly type I collagen.[1-3] There also is evidence that it may increase type VII collagen, the anchoring fibers at the dermal-epidermal junction.[3] Topical application of retinoids can lead to wrinkle reduction within a few months.[4] There is variability in response to treatment and those that do not see improvement within 6 months likely are nonresponders.[4] In addition to decreasing wrinkles, retinoids are able to ameliorate roughness and mottled hyperpigmentation.[4] Hyperpigmentation is reduced because retinoids are able to decrease epidermal melanin content.[1-3]

Aside from their therapeutic effects, retinoids also seem to have a preventive property. A theory of the mechanism of action of retinoids is the inhibition of AP1, thereby decreasing matrix metalloproteinase (MMP) expression. Studies have shown that pretreatment with tretinoin (all-*trans*-retinoic acid) can inhibit MMP induction by 70% to 80%.[5] It was found to block the expression and activity of collagenase, gelatinase, and stromelysin in the epidermis and dermis.[5] Interestingly, the down-regulation of AP1 did not decrease the production of the tissue inhibitors of MMPs.[5] Tretinoin actually was found to induce the production of tissue inhibitors of MMP through a different mechanism.[6,7]

There is a combination cream containing fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% that is used to treat melasma, which is uneven pigmentation.[8] Hydroquinone is used as a bleaching agent to correct dark spots and unevenness.[8]

α-Hydroxy acids are organic compounds with the ability to disrupt the stratum corneum of the skin, thereby stimulating cell proliferation.[8] The end result is the generation of new, younger-appearing skin. Common α-hydroxy acids used are lactic acid, malic acid, and glycolic acid. These acids initially damage the stratum corneum, which leads to decreased corneocyte cohesion. Reduced cohesion translates into desquamation or complete severance in sheetlike pieces. This continuous insult leads to epidermal thickening and an increase in dermal glycosaminoglycans content.[9] Transient side effects are erythema and burning after application.[8]

Because reactive oxygen species (ROS) are one of the main contributors to photodamage, it is logical that antioxidants are a viable approach to treating these changes. However, there is controversy about whether

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antioxidant treatment is effective in preventing and reversing photodamage.[10] Administration through an oral route is less than ideal because of difficulties related to absorption from the gastrointestinal tract and the delivery to skin, though this is under debate.[11] Currently, topical antioxidants are preferred. The advantages of topical application lie in greater concentration of the antioxidant in the skin and the extended protection of lasting a few days without concern of rubbing off.[10] The controversial issue that arises is the inherent instability of antioxidants, which make formulating a stable cosmetic compound more difficult. Three major topical antioxidants used today are vitamin C, vitamin E, and selenium (Table 1).

TABLE 1

Topical Antioxidants for Prevention and Management of Photodamage

Topical Antioxidant	Method of Action	Clinical Improvement
Vitamin C	Anti-inflammatory agent that decreases erythema and sunburn[11] Cofactor for 2 essential enzymes involved in collagen synthesis[11] Increases transcription rate and stabilizes messenger RNA of procollagen[12] Stimulates production of lipids in the skin[13]	Improved moisture and natural protective barrier capability of the skin[13] Decreased wrinkles, solar lentigines, solar elastosis, and mottled pigmentation with several months of application[10]
Vitamin E	Concentrated mainly in the stratum corneum, the first line of defense in trying to absorb the oxidative stress from UV radiation, effectively depleting vitamin E in doing so[10] Decreases immunosuppression[14-16] Repairs collagen and elastin; restores basement membrane attachment by correcting anchoring fibers[10]	Decreased inflammation, hyperpigmentation, and skin carcinogenesis[15-17]
Selenium	Required factor for antioxidant-generating enzymes Glutathione peroxidase and thioredoxin reductase rely on the presence of selenium[17] Inhibits carcinogen binding to DNA, DNA oxidation, neoplastic conversion, and cytotoxicity of DNA[10] Increases minimal erythema dose and amount of light energy needed to elicit a uniform, demarcated, erythematous reaction[18] Decreased plasma selenium levels are associated with increased incidence of nonmelanoma skin cancer[19]	Reduced skin carcinogenesis Increased threshold of producing a sunburn reaction

ORAL THERAPIES AND PREVENTIVE TREATMENTS

Green tea is a known antioxidant that has been used in the prevention of photodamage. Various constituents of green tea have potent effects on preventing DNA damage and decreasing alteration of collagen. Green tea phenols (GTP) have been found to prevent UVB-induced cyclobutane pyrimidine dimer formation.[20] Topical GTP on animal models, particularly its most chemopreventive agent (-)-epigallocatechin-3-gallate (EGCG), protects against both local and systemic immune suppression from UVB rays.[21] Katiyar et al[20] also found decreased erythema with GTP application, which they relate to decreased cyclobutane pyrimidine dimer formation as well. EGCG has additional anticancer properties such as inhibiting nitric oxide synthase[21] and tumor necrosis factor α.[22] Song et al[23] found an additional benefit of EGCG is that it decreases the expression of Jun protein, a transcription factor of MMP-1. There appears to be a protective effect of EGCG on fibroblasts, which decreases collagen degradation. An additional green tea epicatechin derivative, (-)-epicatechin-3-gallate (ECG), decreases oxidative stress by inhibiting UVA-induced hydrogen peroxide production, rendering a protective effect on keratinocytes.[24] Huang et al[24] also found reversal of hydrogen peroxide–induced cell damage with ECG treatment on a cell model.

β-Carotene is a potent dietary antioxidant known as a ROS quencher, particularly oxygen.[25] Another photoprotective effect includes strengthened immunity through heightened macrophage and B-cell and T-cell activities.[26] β-Carotene is more effective in preventing UVA-induced rather than UVB-induced damage.[27] It has been found to offer protection from UVA damage such as decreasing extracellular matrix degradation, reducing oxidative stress, reducing MMP-10 expression, and promoting protease inhibitor expression. A recent systematic review and meta-analysis of randomized control trials evaluating the effectiveness of β-carotene in decreasing cancer risk determined that it does not decrease the incidence of skin cancer.[28] Statistical significance was not achieved and additional randomized control trials are needed to arrive at a conclusion.

MECHANICAL EXFOLIATION

Mechanical exfoliation using microdermabrasion has been used as a minimally invasive treatment of photodamage as well as to improve absorption of topical agents. Phonophoresis, a method of electrically assisted percutaneous delivery of macromolecules, relies on ultrasonic waves that produce alterations within the stratum corneum resulting in increased absorption of topically applied drugs.

LASER AND LIGHT DEVICES

Different types of lasers are used for resurfacing and collagen remodeling in cutaneous laser surgery. These laser and light devices will be discussed in this review under ablative lasers, nonablative lasers, fractional lasers, radiofrequency (RF) devices, and photodynamic therapy.

Ablative Laser Resurfacing for Photorejuvenation

Ablative lasers remain the gold standard for the treatment of photoaging. They work by creating a controlled thermal injury in the dermis that induces new collagen formation. It is important to confine the ablation to a thin surface layer (20–50 μm) and deliver enough energy to vaporize tissue (5 J/cm^2) in a time shorter than the thermal relaxation time of the skin (1 ms). Epidermal vaporization with minimal thermal damage to the papillary dermis was first achieved by 2 different types of CO_2 lasers: the superpulsed laser, whereby the laser tube is pumped electronically to produce high-power, repetitive, short pulses, and a laser controlled with an optomechanical flash scanner. However, because of the associated epidermal ablation with loss of barrier function, these ablative lasers were associated with a long recovery period and adverse effects such as prolonged erythema, substantial downtime, skin discomfort, pigmentary changes, infection, and scarring.[29]

The newer superpulsed lasers cause pure steam vaporization with minimal thermal injury diffusing into adjacent tissue, and deliver pulse energies 5 to 7 times higher than conventional lasers. This therapy follows the principle of selective photothermolysis and maximizes tissue vaporization and pulse duration of less than 1 ms.[30] The newer generation of ablative lasers include the high-energy pulsed or scanned CO_2 lasers, which emit a wavelength of 10,600 nm, and single- or variable-pulse or erbium:YAG (Er:YAG) lasers, which emit a wavelength of 2940 nm and have a dual ablation and coagulation mode. These lasers allow for precise skin vaporization with minimal postoperative complications due to accurately adjustable parameters.

In the histologic analysis of the effect of CO_2 lasers, it has been found that granulation tissue is formed at day 30 and new collagen is formed at day 100 posttreatment, and is dependent on the depth of the zone of thermal damage.[31,23]

Patient selection for these laser procedures is the most important aspect to be considered for the success of treatment and avoidance of complications. Facial rhytides and perioral and periorbital areas seem to respond best to therapy, while nasolabial folds do not seem to respond adequately. Complications from skin pigmentation arise more often in darker skin types, making it necessary to provide pretreatment and posttreatment care, though

the recent evidence and previous clinical experience are contradictory. The clinical experience emphasizes the use of a hydroquinone cream or tretinoin cream nightly or α-hydroxy acid and broad-spectrum sunscreen during the day in darker-skinned individuals. However, evidence demonstrates there is no usefulness of this pretreatment.[33] Additionally, antiviral therapy starting 2 days prior to the procedure and continued until reepithelization occurs approximately 10 to 14 days later is standard practice as prophylaxis against herpes infection.

The short-term complications associated with CO_2 laser resurfacing are transient erythema, pruritus, milia formation, acneiform pustules, and transient scarring. The long-term complications may be hypopigmentation, hyperpigmentation, and permanent scarring. Hypopigmentation is a late complication that may worsen with time and generally is seen in areas that previously were abraded with other modalities that lead to injury to deep follicular melanocytes and permanent pigment loss. Hyperpigmentation is a postinflammatory phenomenon that can be avoided with pretreatment.[29]

The pulsed Er:YAG laser is in the infrared spectrum (2940 nm) and, like the CO_2 laser, uses water as its chromophore, though its water absorption coefficient is 16 times greater than the CO_2 laser. The penetration depth is 5 µm per pulse with an energy of 2.8 J/cm^2. These properties endow this laser with precise ablation with high selectivity to tissue water and negligible thermal damage.[34-36] The advantages of the Er:YAG laser over the CO_2 laser are the reduced thermal damage, shorter downtime, less erythema, and fewer anesthesia requirements. Pinpoint bleeding appears after 4 to 5 passes of the Er:YAG laser, which is a problem with this laser when treating deep wrinkles. It is the clinical end point with the Er:YAG laser. Ross et al[37] compared a short-pulsed CO_2 laser and an Er:YAG laser over a range of parameters intended to produce equivalent microscopic and clinical injuries. They observed no substanial differences between the lasers for hyperpigmentation and wrinkle reduction. Less erythema was noted at the CO_2 laser–treated sites 2 weeks after treatment; the differences had resolved by 6 weeks after treatment. Histologic examination demonstrated equivalent dermal thermal injury on immediate postoperative biopsy results and equivalent fibroplasia on subsequent biopsy results. Both CO_2 and Er:YAG laser–treated sites showed overall modest wrinkle improvement.

The best candidates for Er:YAG laser resurfacing are patients with moderate to severe photodamaged skin, acne scars, and postsurgical and hypertrophic scars.[38-40] Photodamaged skin of nonfacial areas also can be treated with the Er:YAG laser, while the CO_2 laser is avoided. Darker skin types also can be treated safely with this laser.[36,38,39] Perioral and periorbital wrinkling, facial and neck dyschromia, lentigines, and actinic keratoses also respond substantially to Er:YAG laser resurfacing.

The complications encountered with the Er:YAG laser are similar to those with the CO_2 laser but generally are less common and less severe.

Certain novel systems delivering simultaneous irradiation from a combined 2940-nm Er:YAG and continuous-wave 10,600-nm CO_2 laser with low power densities and millisecond exposures have been developed. Also, variable-pulse Er:YAG and dual mode ablation and coagulation Er:YAG lasers have been designed with the purpose of achieving great clinical improvement and minimal morbidity.

Nonablative Laser Resurfacing for Photorejuvenation

Nonablative laser skin rejuvenation was developed to improve different aspects of skin aging. This alternative to ablative laser resurfacing, which was a comparatively invasive procedure associated with various complications, was established by Zelickson et al[41] who found that the purpurogenic doses of the pulsed dye laser (PDL)–induced fibroblast proliferation and neocollagenesis in the papillary dermis. A multicenter, prospective, randomized, controlled, split-face study on 58 individuals was conducted by Hsu et al[42] where 585-nm PDL was used in the treatment of periorbital rhytides. They concluded that the nonablative lasers induced selective dermal injury while keeping the overlying epidermis intact. The healing process begins after the dermal injury, followed by the production of new type I collagen that aligns in parallel arrays, bringing about the clinical improvement in rhytides, pore size, and scars.

Various devices are available to achieve nonablative rejuvenation. They can be subclassified as infrared lasers, visible light lasers, broadband light sources, low-intensity sources, and photodynamic therapy.

Infrared Lasers

These lasers target and heat tissue water without epidermal sparing. With the use of concomitant cooling, the epidermis is protected.

1320-nm Pulsed Nd:YAG Laser—The first of these devices, the CoolTouch laser, was a 1320-nm pulsed Nd:YAG laser delivering energy through a 10-mm spot size and protecting the epidermis with a cryogen dynamic cooling spray. This laser was found to be efficacious in nonablative improvement in wrinkles mainly after 5 or 6 treatments. The higher the fluence used without causing blistering, the greater the degree

TABLE 2

Intense Pulsed Light for Photorejuvenation

Investigators	Objective	Results/Conclusions
Bitter PH[69]	To evaluate and quantify the degree of visible improvement in photodamaged skin following a series of full-face IPL treatments	All aspects of photodamage (wrinkling, skin coarseness, irregular pigmentation, pore size, telangiectasias) showed visible improvement in >90% of participants with minimal downtime and no scarring 88% of participants were satisfied with their overall treatment results
Brazil and Owen[70]	To evaluate quantitatively the short-term and long-term clinical effectiveness of multiple full-face IPL treatments for nonablative facial photorejuvenation	Standardized evaluation of rhytides showed a statistically significant ($P<.05$) improvement in wrinkles at both evaluation end points Facial vascularity, dyschromia, and large pore size progressively improved from the 6-week to the 6-month measurement
Sadick et al[71]	To evaluate the clinical efficacy and safety of using IPL in treating clinical indications associated with photoaged skin	The average Fitzpatrick-Goldman classification of W/ES improved significantly ($P<.001$) by 1.39 and 1.32 U at the 4- and 6-month follow-up, respectively; an improved W/ES evaluation was recorded for 82% and 75% of the patients at each of these time points, respectively
Negishi et al[72]	To determine the effectiveness of photorejuvenation for Asian skin using IPL	Treatment results were evaluated and rated by both patients and physicians at the end of the third treatment based on improvement in pigmentation, telangiectasia, and skin texture A combined rating of "good" or "excellent" was given to >90% of the patients for pigmentation, >83% for telangiectasia, and >65% for skin texture There were minor complications in 4 patients: 1 had erythema that continued to the next day and 3 had minor blisters that left no marks
Negishi et al[73]	To perform a subjective evaluation of overall skin rejuvenation effects of relatively short-wavelength IPL and objective changes in basic skin tone as measured by a spectrophotometer	A series of 3 IPL treatments were performed on 25 Japanese women. Relatively short 2.5-ms double pulses with a delay time of 10 ms were employed to elicit a sufficient response in the melanin-saturated epidermis Subjective improvement of ≥50% were seen in 18 of 25 patients for pigmentation In the spectrophotometric analysis, the mean value of L^*-function increased from a baseline value of 60.86 to 63.22 at 3-month follow-up, with statistical significance ($P=.001$) It was concluded that IPL skin rejuvenation using relatively shorter wavelengths and pulse widths brought about significant ($P=.001$) macroscopic and quantitative improvements, especially in the treatment of epidermal pigmentation and in improvement of basic skin tone

TABLE 2 (CONTINUED)

Intense Pulsed Light for Photorejuvenation

Investigators	Objective	Results/Conclusions
Weiss et al[74]	To determine the response and side effects of poikiloderma of Civatte of the neck and chest when treated by IPL	Clearance of >75% of telangiectasias and hyperpigmentation comprising poikiloderma was observed The incidence of side effects was 5%, including pigment changes. In many cases, improved skin texture was noted both by patients and physicians
Prieto et al[75]	To evaluate through ultrastructural analysis the effect of IPL and 1064-nm Nd:YAG laser therapies on photodamaged skin of 9 participants	Routine histology and immunohistochemistry were taken on 2-mm punch biopsy specimens before treatment and then at 3 and 6 months Pretreatment biopsy specimens contained solar damage. After treatment with the 1064-nm Nd:YAG laser, the amount of collagen in the papillary dermis was slightly thicker than in those participants treated with the IPL device Scattered dendritic cells in the papillary and upper reticular dermis expressed heat shock protein 70 and procollagen I after treatment with either light device

Abbreviations: IPL, intense pulsed light; W/ES, wrinkling and degree of elastosis.

of observed improvement, but the more discomfort for the patient.[43-46]

1450-nm Diode Laser—Demonstrating efficacy in the treatment of a wide range of cutaneous disorders, including facial rhytides, acne vulgaris, and atrophic scars, the 1450-nm diode laser is a useful addition to the nonablative laser armamentarium. While investigating the clinical and microscopic changes produced by a midinfrared laser coupled with a contact cooling device, Ross et al[47] observed immediate epidermal necrosis and subsequent scarring for larger pulse energy–pulse number combinations. At sites with epidermal preservation, biopsy results showed immediate dermal thermal damage in a bandlike pattern. The deep boundaries of this band were dependent on pulse energy and pulse number. After 8 weeks, biopsy results showed dermal fibroplasia approximately correlating to the band of immediate dermal thermal damage. In this study, the range of fibroplasia and lack of clinically substantial cosmetic enhancement suggested that the dermal thermal damage achieved may be too deep and that the injury should be confined to more superficial levels to alter the most severely photodamaged dermis. Interestingly, histology noted sebaceous gland shrinkage, which raised the possibility of the use of this laser for treatment of acne. Subsequent to this, several studies showed the efficacy of this laser in acne treatment.[48-50]

Regarding photorejuvenation, the 1450-nm diode laser uses a cryogen spray similar to the 1350-nm pulsed Nd:YAG laser to cool the epidermis, and it delivers energy through a 4- or 6-mm spot size.

Goldberg et al[51] evaluated the efficacy and complication rate of a 1450-nm diode laser and compared the clinical effect when the laser was used in conjunction with cryogen cooling compared with the use of cryogen. Thirteen participants showed clinical improvement on the laser and cryogen–treated side of the face. No participants were noted to have any improvement on the side of the face treated with cryogen alone.

1540-nm Erbium:Glass Laser—The 1540-nm Erbium (Er):glass laser has a 4-mm spot size to deliver energy. The epidermis is protected during laser irradiation by a cooling system (+5°C) that uses a sapphire window directly applied to the skin and through which the laser pulse may be fired. Its role in nonablative tissue remodeling was studied by

Fournier et al[52] who evaluated the efficacy and safety of a 1540-nm Er:glass laser with contact cooling in nonablative skin remodeling in perioral and periorbital rhytides. They reported subjective improvement in the quality and visual aspect of the skin of all participants. Using ultrasound imaging, a 17% increase in dermis thickness was demonstrated and a biopsy specimen showed evidence of new collagen formation. Dahan et al[53] demonstrated similar findings on neck lines and forehead rhytides and concluded that irradiation with a 1540-nm Er:glass laser emitting in a pulsed mode and coupled with an efficient contact cooling system increases dermal thickness and firmness, leading to a clinical improvement of neck lines and forehead rhytides.

The efficacy and safety of 1540-nm Er:glass laser also has been studied. Results of these studies showed the laser to be an effective treatment of rhytides and scars.[54,55]

Also, unlike with 1320- and 1450-nm devices, treatments with the 1540-nm laser are relatively comfortable because of the smaller spot size and lower energies delivered.

Q-Switched Nanosecond and Domain 1064-nm Nd:YAG Laser—Although originally developed and used for the treatment of lentigines, dermal pigmentations, and tattoos, the Q-switched laser has been found to be modestly effective in the treatment of wrinkles and scarring.[56] In a pilot study by Goldberg and Whitworth,[57] the rhytide resurfacing capability of the Q-switched Nd:YAG laser at 1064 nm was compared with that of the char-free CO_2 laser at 10,600 nm. All of the 11 participants treated with the char-free CO_2 laser improved while only 9 of 11 participants treated with the 1064-nm Q-switched Nd:YAG laser improved. Healing (complete reepithelization) was noted to occur 3 to 6 days earlier in the sites treated with the Q-switched Nd:YAG laser than in the sites treated with the char-free CO_2 laser. Also, erythema was observed at 1 month posttreatment in all areas treated with the char-free CO_2 laser, but only 3 participants treated with the Q-switched Nd:YAG laser exhibited erythema.

In another study, Dayan et al[58] evaluated the use of the 1064-nm Nd:YAG laser for rejuvenating the aging face. Thirty-four of 51 participants completed at least 7 treatments and had posttreatment photographs taken. Follow-up ranged from 1 to 6 months. No adverse effects were noted. Although improvements in photodamaged skin were subtle and gradual, the 1064-nm Nd:YAG laser was well-tolerated by participants of all skin types.[58]

Recently, Koh et al[59] evaluated the submillisecond 1064-nm long-pulse Nd:YAG laser in the rejuvenation of photodamaged skin in 12 Korean women and demonstrated substantial improvement in skin roughness, texture, pigmentation, and pore size as confirmed by Mexameter and Visiometer.

The 1540-nm Er:glass laser has been used for a "laser toning" full-face procedure to improve photoaging associated with dyspigmentation, improved skin tone, and texture.[60]

Visible Light Lasers

Long-Pulsed 532-nm Potassium Titanyl Phosphate Laser—The 532-nm potassium titanyl phosphate (KTP) laser beam is obtained by using a double crystal to halve the 1064-nm wavelength. The KTP laser contains a green light wavelength suitable for treating facial telangiectasias and pigment because it is absorbed by both hemoglobin and melanin. If larger areas such as the entire face are treated with this laser, other benefits of skin texture improvement can be obtained, though not to the same extent as the spot treatment for pigmentary lesions. It is best used for patients with facial telangiectasias and/or UV-induced nonmelasma pigmentation with or without wrinkles.[61,62] Lee[61] studied a combination technique using a long-pulsed KTP laser and a long-pulsed 1064-nm Nd:YAG laser, both alone and combined, for noninvasive photorejuvenation, skin toning, collagen enhancement, and to establish efficacy and degree of success. After 3 to 6 treatments, 50 patients treated with the 532-nm KTP laser alone showed improvements of 70% to 80% in redness and pigmentation, 30% to 50% in skin tone/tightening, 30% to 40% in skin texture, and 20% to 30% in rhytides. Another 50 patients treated with the 1064-nm Nd:YAG laser alone showed improvements of 10% to 20% in redness, 0% to 10% in pigmentation, 10% to 30% in skin tone/tightening, 20% to 30% in skin texture, and 10% to 30% in rhytides. The third group of 50 patients were treated with a combination of both KTP and Nd:YAG lasers and showed improvements of 70% to 80% in redness and pigmentation, 40% to 60% in skin tone/tightening, 40% to 60% in skin texture, and 30% to 40% in rhytides. Skin biopsy specimens taken at 1-, 2-, 3-, and 6-month intervals demonstrated new collagen formation. The KTP laser used alone produced results superior to those of the Nd:YAG laser. Results from combination treatment with both KTP and Nd:YAG lasers were slightly superior to those achieved with either laser alone.

Pulsed Dye Laser—Originally developed to treat vascular lesions, the 585- and 595-nm PDLs were found to directly affect the adjacent dermis to alter the collagen.[63,64] In a randomized, controlled, split-face trial to evaluate efficacy and adverse effects from rejuvenation with long-pulsed dye laser versus intense pulsed light (IPL), it was found that long-pulsed dye laser rejuvenation is advantageous to IPL rejuvenation because of superior vessel clearance and less pain, though improvement in telangiectasia, irregular pigmentation, and skin texture were seen with both lasers.[65]

TABLE 3

Photodynamic Therapy for Photorejuvenation

Investigators	Objective	Results/Conclusions
Dover et al[82]	To study the effects of IPL on signs of photoaging in a prospective, randomized, controlled, split-face study of 20 participants	Participants received treatment with both 5-ALA and IPL on one side of the face and with IPL alone on the other side The side pretreated with 5-ALA resulted in a greater percentage of improvement in global score for photoaging and in mottled pigmentation than IPL treatment alone Both the final investigator cosmetic evaluations and participant satisfaction scores were significantly ($P=.0002$) better for the 5-ALA pretreated side
Gold et al[83]	To evaluate short-contact (30–60 min) ALA-PDT with IPL activation by comparing ALA-PDT-IPL with IPL alone	Thirteen participants completed the trial in terms of edema ($P<.001$) Three months after the final treatment, improvement was greater in the ALA-PDT-IPL side than in IPL-alone side for all facets of photodamage—crow's-feet appearance, tactile skin roughness, mottled hyperpigmentation, and telangiectasias The clearance rate of AK lesions also was higher
Park et al[84]	To investigate whether 5-ALA–PDT induced histologic changes suggesting photorejuvenation	After ALA-PDT, the mean epidermal thickness and dermal inflammatory infiltrate were reduced The total collagen volume in the dermis significantly ($P<.001$) increased with expression of types I and III procollagen The level of TGF-β and TGF-β type II receptors in the epidermis also increased The elastotic material with co-localizing fibrillin 1 and tropoelastin expression in the dermis decreased after treatment The expression of MMP-1, -3, and -12 also decreased

Abbreviations: IPL, intense pulsed light; ALA, aminolevulinic acid; PDT, photodynamic therapy; AK, actinic keratosis; TGF, transforming growth factor; MMP, matrix metalloproteinase.

Different wavelengths target different cells in different ways.[66] Therefore, a single nonablative modality, for example a PDL at 585 or 590 nm, will not affect all of the target cells equally. On the other hand, a polychromatic source, such as an IPL system, has wavelengths ranging from near infrared to approximately 550 nm delivered simultaneously. This concept led to combining modalities. The combination of a 595-nm PDL with a 1450-nm diode laser applied sequentially, with the diode laser being applied immediately after the PDL, produced better results.[67] This can be attributed to the individual properties of the 2 lasers. The 595-nm subpurpuric PDL targets hemoglobin, melanin, and cytochrome *c* oxidase enzyme in the redox chain in the mitochondria of fibroblasts; the 1450-nm infrared wavelength targets the molecules constituting the cellular membrane of dermal cells as well as water. The combination of the 2 wavelengths, coupled with the epidermal cooling systems used in both lasers, gives a controlled and enhanced buildup of upper dermal heat under an intact, cooled epidermis, which results in a high level of controlled accumulative heat damage. This leads to enhanced collagenesis, elastogenesis, and angiogenesis in the superficial and upper reticular dermis during the

TABLE 4

Radiofrequency in Photorejuvenation

Investigators	Objective	Results/Conclusions
Fitzpatrick et al[86]	To evaluate the efficacy and safety of treatment with a nonablative RF device in the treatment of wrinkles	In this 6-month follow-up, 86 participants received a single treatment with the ThermaCool TC System Fifty percent of participants reported being satisfied or very satisfied with periorbital wrinkle reductions Objective photographic analysis showed that 61.5% of eyebrows were lifted by at least 0.5 mm Three participants had small areas of residual scarring at 6 months
Bassichis et al[87]	To evaluate the use of the ThermaCool TC nonablative RF device for rejuvenation of the upper one-third of the face, as determined by brow elevation	Twenty-four participants in a facial plastic surgery office were treated with the nonablative RF device Brow elevation measurements were used to gauge efficacy of the procedure Results were compared with an untreated control group of 12 participants Compared with the control group, the posttreatment measurements were improved ($P<.05$). The posttreatment measurements also were improved from pretreatment baseline ($P<.05$) Subjective results obtained from participant satisfaction questionnaires did not correlate to the objective data The data also showed that improvement in brow elevation was not uniform in each participant
Alster and Tanzi[88]	To evaluate the efficacy and safety of a novel nonablative RF device in the treatment of cheek and neck skin laxity	Significant ($P<.05$) improvement in cheek and neck skin laxity was observed in most participants Participant satisfaction scores paralleled the clinical improvements observed Side effects were mild and limited to transient erythema, edema, and rare dysesthesia. No scarring or pigmentary alteration was seen

Abbreviation: RF, radiofrequency.

proliferative phase of wound healing, followed by good linear alignment of the collagen fibers running under the dermal-epidermal junction and firmly attached to its basement membrane.

Broadband Light Sources

Intense Pulsed Light—Modern IPL devices are sophisticated computer-controlled systems that have minimized the "spectral jitter" encountered with older IPL

TABLE 5

Fractional Laser Resurfacing

Investigators	Objective	Results/Conclusions
Wanner et al[90]	To evaluate the effectiveness and safety of a novel nonablative 1550-nm erbium-doped fiber laser in the treatment of facial and nonfacial photodamaged skin	Mean clinical improvement at 3, 6, and 9 months for the face was 2.23, 2.10, and 1.96, respectively, and for nonfacial skin was 1.85, 1.81, and 1.70, respectively. At least 51% to 75% improvement in photodamage at the 9-month follow-up was achieved in 73% and 55% of facial and nonfacial treated skin, respectively. Adverse effects were limited to transient erythema and edema in most participants
Lee et al[91]	To evaluate the efficacy and safety of FP in the treatment of facial wrinkles in Asians	The physicians' assessed degrees of improvement were excellent in 3 participants (12%), notable in 10 (40%), and moderate in 7 (28%)
Geraghty and Biesman[92]	Clinical evaluation of a single wavelength fractional laser (1440-nm Nd:YAG) and a novel multiwavelength fractional laser (1320/1440-nm multiplex Nd:YAG) in the treatment of photodamaged hands	Participants demonstrated the greatest average 6-month improvements in surface texture and global skin appearance. Participants treated with the multiplex laser reported more skin tightening than the group treated only with the 1440-nm laser. Histologic evaluation revealed wound healing within 10 days and substantial neocollagenesis at 3 months
Cohen et al[93]	To investigate postprocedure patient satisfaction after FP with the Fraxel SR laser	Fifty-nine participants underwent Fraxel SR laser resurfacing and completed the survey. A total of 202 treatments were performed. Of all participants, 75% were very satisfied (4 or 5 rating) with treatment. Of the participants, 75% with dyschromia, 74% with texture abnormalities, and 100% with scarring had a satisfaction score of 4 or 5. Multivariate analysis found scarring, 4 or more treatments, and age 56 years and older to be associated with a score of 4 or 5. The odds of giving a satisfaction score of 4 or 5 increased ~2-fold for each additional treatment a patient received

Abbreviation: FP, fractional photothermolysis.

devices.[68] Spectral jitter refers to variation in the beam of the IPL as the pulse progresses. This caused the light emitted at the beginning and end of the pulse to be more in the red to infrared range, and during the center of the pulse to be in the shorter blue part of the spectrum. Intense pulsed light devices emit a broad spectrum of light with wavelengths between 515 and 1200 nm. Intense pulsed light can improve telangiectasia, redness, lentigines, dyspigmentation, and fine wrinkling. It has the advantages of larger spot size and ease of use. If used by experienced hands, there is minimal downtime for the patient. The concept of photorejuvenation using IPL was proposed by Bitter et al[69] (Table 2).

Prieto et al[76] also reported that with IPL treatment of sun-damaged facial skin in 5 female participants collagen and elastic fibers appeared unaffected by treatment. At week 1, *Demodex* organisms appeared coagulated. Thus, the clinical improvement that was noted was attributed to clearing of *Demodex* organisms and reduction of associated lymphocytic infiltrate.

Low-Intensity Sources

Light-Emitting Diode—Light-emitting diodes (LEDs) are complex semiconductors that convert electrical current into incoherent narrow spectrum lights ranging from UV to the visible and infrared wavelengths.[77-79] Light-emitting diodes operate using the principle of photomodulation, wherein they modulate the biologic activity of keratinocytes and fibroblasts by affecting the mitochondria, without inducing a thermal effect. Light-emitting diode photomodulation reverses signs of photoaging using a new nonthermal mechanism. Studies have shown the usefulness of LED in photorejuvenation. Weiss et al[80] investigated the use of a nonthermal low-dose LED array for improving the appearance of a wide range of photoaged skin in a random cohort of 90 participants. The participants were treated by LED photomodulation using a full-panel, 590-nm, nonthermal, full-face LED array delivering 0.1 J/cm^2 with a specific sequence of pulsing. Digital imaging data showed a reduction in the signs of photoaging in 90% of participants, with smoother skin texture and a reduction in periorbital rhytides, erythema, and pigmentation. Histologic data showed markedly increased collagen in the papillary dermis of 100% of posttreatment specimens. Staining with anticollagen type I antibodies demonstrated a 28% average increase in density while staining with anti–MMP-1 showed an average reduction of 4%. No side effects or pain were noted.

In a study by Lee at al,[81] the clinical efficacy of LED phototherapy for skin rejuvenation through the comparison of 3 different treatment parameters and a control, and the LED-induced histologic, ultrastructural, and biochemical changes, were investigated. Seventy-six participants with facial wrinkles were divided into 4 groups treated with either 830 nm, 633 nm, a combination of 830 and 633 nm, or a placebo, in a split-face manner twice a week for 4 weeks. Histologically, a marked increase in the amount of collagen and elastic fibers in all treatment groups was observed. Ultrastructural examination demonstrated highly activated fibroblasts surrounded by abundant elastic and collagen fibers. Immunohistochemistry showed an increase of tissue inhibitor of MMP-1 and MMP-2. Reverse transcription polymerase chain reaction results showed the messenger RNA levels of IL-1ss, tumor necrosis factor α, intercellular adhesion molecule 1, and connexin 43 increased after LED phototherapy whereas that of IL-6 decreased.

PHOTODYNAMIC THERAPY

Photodynamic therapy consists of the application of a photosensitizing agent on the skin followed by an incubation period and then exposure to a light source. The photosensitizers are metabolized to protoporphyrin IX (PpIX) in the mitochondria. The maximum absorption of PpIX is at 410, 630, and 690 nm. When this PpIX is exposed to light, a photochemical reaction is set off, generating cytotoxic ROS that brings about cell damage. The photosensitizers localize themselves mostly in proliferating cells such as neoplastic cells rather than in healthy tissue, thus making photodynamic therapy a useful modality for treating precancerous lesions and certain cancers. Photodynamic therapy with aminolevulinic acid and blue light as the light source, and methylaminolevulinic acid with red light, has been approved by the US Food and Drug Administration for treatment of actinic keratoses. Photodynamic therapy also has been used for photorejuvenation because it has been shown to improve signs of photoaging (Table 3).

RADIOFREQUENCY

Radiofrequency devices work on the principle of Ohm law and are different from that of the photothermal effect produced by optical lasers.[85] Radiofrequency leads to generation of heat due to natural resistance or impedance of the tissue to the movement of electrons within an RF field. The impedance varies with depth as well as with the type of tissue, such as skin, fat, and muscle.[85] The effect of RF is 2-fold: initial immediate collagen contraction and a secondary wound-healing response, which involves collagen deposition and remodeling with tightening over time.

Radiofrequency technology may be monopolar or bipolar. Monopolar RF application produces nonablative tissue tightening of the skin by volumetric heating of the deep dermis. Bipolar devices pass electrical currents between 2 positioned electrodes applied to the skin. It is believed that bipolar RF cannot produce uniform volumetric heating comparable with monopolar RF.[85] Table 4 highlights an investigation of RF for the treatment of photodamage.

Because RF is a new entry in the armamentarium of photoaging management, more research and experience are needed. Although not equivalent to results achieved by cosmetic surgeries, RF does offer a nonablative, noninvasive method of photorejuvenation with the advantages of very low downtime and potential complications.

TABLE 6
Management of Precancerous Lesions and Nonmelanoma Skin Cancers Enlisted

Medical	Retinoids, imiquimod, 5-FU, interferon-α-2b Newer therapies: erlotinib, T4 endonuclease V, ingenol mebutate
Surgical	Excision, desiccation and curettage, cryotherapy, Mohs micrographic surgery
Laser and light devices	PDL for BCC, PDT for actinic keratoses and BCCs, cryotherapy

Abbreviations: 5-FU, 5-fluorouracil; PDL, pulsed dye laser; PDT, photodynamic therapy; BCC, basal cell carcinoma.

FRACTIONAL LASER RESURFACING FOR PHOTOREJUVENATION

To overcome the complete epidermal ablation achieved by ablative lasers, a recent interest has grown in fractional photothermolysis. This technique was introduced by Huzaira et al[89] in 2003 and uses a midinfrared laser with a sophisticated optical tracking device to create microscopic columns of thermal injury to produce localized epidermal necrosis and collagen denaturation. The healing is reaped from the residual viable epidermal and dermal cells. The stratum corneum remains intact during this process and maintains epidermal barrier function. Fractional laser resurfacing has bridged the gap between ablative and nonablative laser modalities for photorejuvenation, and many studies have demonstrated its use (Table 5).

PRECANCEROUS AND CANCEROUS SKIN LESIONS

Photodamage can manifest as precancerous lesions and skin cancers (melanoma and nonmelanoma). The discussion of these cancers and their management is beyond the scope of this review; therefore, Table 6 lists the therapeutic options for precancerous lesions and nonmelanoma skin cancers.

Management of Melanoma—Modalities Enlisted

Adjuvant interferon-α-2b is the only adjuvant therapy approved by the US Food and Drug Administration for high-risk melanoma (defined as stages IIB, IIC, and III), which is associated with a 40% to 80% relapse rate.

Surgical margins of 5 mm currently are recommended for melanoma in situ and margins of 1 cm are recommended for melanomas up to 1 mm in depth.[94] In some settings, tissue sparing may be critical and Mohs margin-controlled excision may be appropriate. Margins of 2 cm are recommended for cutaneous melanomas greater than 4 mm in thickness (high-risk primaries) to prevent potential local recurrence in or around the scar site.

CONCLUSION

Various ablative lasers such as CO_2 and Er:YAG; nonablative lasers such as infrared, visible light, broadband light, LEDs, light devices, and fractional lasers have been studied and applied for photorejuvenation with the aim of clinical improvement with the least downtime and adverse events. Newer RF devices have nonablative tissue tightening effects. The prevention of photodamage is substantial and should be emphasized through the education of people of all ages. The future of photodamage management lies in improving our understanding of the intrinsic and extrinsic factors that affect the skin and lead to aging. This understanding will help us to enhance the preventive and treatment options for dealing with photodamaged skin.

REFERENCES

1. Gilchrest BA. Treatment of photodamage with topical tretinoin: an overview. *J Am Acad Dermatol.* 1997;36(suppl 3):S27-S36.
2. Goldman MP, Marchell N, Fitzpatrick RE. Laser skin resurfacing of the face with a combined CO_2/Er:YAG laser. *Dermatol Surg.* 2000;26:102-104.
3. Griffiths C, Russman AN, Majmudar G, et al. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med.* 1993;329:530-535.
4. Tsoureli NE, Watson RE, Griffiths CE. Photoageing: the darker side of the sun. *Photochem Photbiol Sci.* 2006;5:160-164.
5. Fisher GJ, Wang ZQ, Datta SC, et al. Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med.* 1997;337:1419-1428.
6. Bauer EA, Seltzer JL, Eisen AZ. Inhibition of collagen degradative enzymes by retinoic acid in vitro. *J Am Acad Dermatol.* 1982;6:603-607.
7. Clark SD, Kobayashi DK, Welgus HG. Regulation of the expression of tissue inhibitor of metalloproteinases and collagenase by

retinoids and glucocorticoids in human fibroblasts. *J Clin Invest*. 1987;80:1280-1288.
8. Hegedus F, Diecidue R, Taub D, et al. Non-surgical treatment modalities of facial photodamage: practical knowledge for the oral and maxillofacial professional. *Int J Oral Maxillofac Surg.* 2006;35:389-398.
9. Van Scott EJ, Ditre CM, Yu RJ. Alpha-hydroxyacids in the treatment of signs of photoaging. *Clin Dermatol.* 1996;14:217-226.
10. Burke KE. Photodamage of the skin: protection and reversal with topical antioxidants. *J Cosmet Dermatol.* 2004;3:149-155.
11. Pinnell SR. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. *J Am Acad Dermatol.* 2003;48:1-19.
12. Savini I, Catni V, Duranti G, et al. Characterization of keratinocyte differentiation induced by ascorbic acid: protein kinase C involvement and vitamin C homeostasis. *J Invest Dermatol.* 2002;118:372-379.
13. Uchida Y, Behne M, Quiec D. Vitamin C stimulates sphingolipid production and markers of barrier formation in submerged human keratinocyte cultures. *J Invest Dermatol.* 2001;117:1307-1313.
14. Berton TR, Conti CJ, Mitchell DL, et al. The effect of vitamin E acetate on ultraviolet-induced mouse skin carcinogenesis. *Mol Carcin.* 1998;23:175-184.
15. Record IR, Dreosti IE, Konstantinopoulos M, et al. The influence of topical and systemic vitamin E on ultraviolet light-induced skin damage in hairless mice. *Nutr Cancer.* 1991;16:219-225.
16. Gerrish K, Gensler H. Prevention of photocarcinogenesis by dietary vitamin E. *Nutr Cancer.* 1993;19:125-133.
17. Stadtman TC. Mammalian selenoenzymes. *Ann NY Acad Sci.* 2000; 894:399-402.
18. Young AR, Potten CS, Nikaido O, et al. Human melanocytes and keratinocytes exposed to UVB or UVA in vivo show comparable levels of thymine dimmers. *J Invest Dermatol.* 1998;111:936-940.
19. Clark LC, Graham GF, Crainse RG, et al. Plasma selenium and skin neoplasms: a case–control study. *Nutr Cancer.* 1984;6:13-21.
20. Katiyar SK, Bergamo BM, Vyalil PK, et al. Green tea polyphenols: DNA photodamage and photoimmunology. *J Photochem Photobiol B.* 2001;65:109-114.
21. Lin YL, Lin JK. (-)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of transcription factor nuclear factor-kappaB. *Mol Pharmacol.* 1997;52:465-472.
22. Okabe S, Ochiai Y, Aida M, et al. Mechanistic aspects of green tea as a cancer preventive: effect of components on human stomach cancer cell lines. *Jpn J Cancer Res.* 1999;90:733-739.
23. Song XZ, Xia JP, Bi ZG. Effects of (-)-epigallocatechin-3-gallate on expression of matrix metalloproteinase-1 and tissue inhibitor of metalloproteinase-1 in fibroblasts irradiated with ultraviolet A. *Chin Med J (Engl).* 2004;117:1838-1841.
24. Huang CC, Fang JY, Wu WB, et al. Protective effects of (-)-epicatechin-3-gallate on UVA-induced damage in HaCaT keratinocytes. *Arch Dermatol Res.* 2005;296:473-481.
25. Cantrell A, McGarvey DJ, Truscott TG, et al. Singlet oxygen quenching by dietary carotenoids in a model membrane environment. *Arch Biochem Biophys.* 2003;412:47-54.
26. Maxwell SR. Prospects for the use of antioxidant therapies. *Drugs.* 1995;49:345-361.
27. Böhm F, Edge R, Lange L, et al. Enhanced protection of human cells against ultraviolet light by antioxidant combinations involving dietary carotenoids. *J Photochem Photobiol B.* 1998;44:211-215.
28. Druesne-Pecollo N, Latino-Martel P, Norat T, et al. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. *Int J Cancer.* 2010;127:172-184.
29. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. an evaluation of 500 patients. *Dermatol Surg.* 1998;24:315-320.
30. Goldman MP, Fitzpatrick RE. CO_2 laser surgery. In: Baxter SH, ed. *Cutaneous Laser Surgery: The Art and Science of Selective Photothermolysis.* 2nd ed. St Louis, MO: Mosby, Inc; 1994:198-258.
31. Khatri KA, Ross V, Grevelink JM, et al. Comparison of erbium:YAG and carbon dioxide lasers in resurfacing of facial rhytides. *Arch Dermatol.* 1999;135:391-397.
32. Ross EV, McKinlay JR, Anderson RR. Why does carbon dioxide laser resurfacing work? a review. *Arch Dermatol.* 1999;135:444-454.
33. West TB, Alster TS. Effect of pretreatment on the incidence of hyperpigmentation following cutaneous CO_2 laser resurfacing. *Dermatol Surg.* 1999;25:15-17.
34. Kaufmann R, Hibst R. Pulsed erbium:YAG laser ablation in cutaneous surgery. *Lasers Surg Med.* 1996;19:324-330.
35. Walsh JT Jr, Deutsch TF. Er:YAG ablation of tissue: measurement of ablation rates. *Lasers Surg Med.* 1989;9:327-337.
36. Hohenleutner U, Hohenleutner S, Baumier W, et al. Fast and effective skin ablation with an Er:YAG laser: determination of ablation rates and thermal damage zones. *Lasers Surg Med.* 1997;20:242-247.
37. Ross EV, Miller C, Meehan K, et al. One-pass CO_2 versus multiple-pass Er:YAG laser resurfacing in the treatment of rhytides: a comparison side-by-side study of pulsed CO_2 and Er:YAG lasers. *Dermatol Surg.* 2001;27:709-715.
38. Kye YC. Resurfacing of pitted facial scars with a pulsed Er:YAG laser. *Dermatol Surg.* 1997;23:880-883.
39. Perez MI, Bank DE, Silvers D. Skin resurfacing of the face with the erbium:YAG laser. *Dermatol Surg.* 1998;24:653-659.
40. Teikemeier G, Goldberg DJ. Skin resurfacing with the erbium:YAG laser. *Dermatol Surg.* 1997;23:685-687.
41. Zelickson BD, Kilmer SL, Bernstein E, et al. Pulsed dye laser therapy for sun damaged skin. *Lasers Surg Med.* 1999;25:229-236.
42. Hsu TS, Zelickson B, Dover JS, et al. Multicenter study of the safety and efficacy of a 585 nm pulsed-dye laser for the nonablative treatment of facial rhytides. *Dermatol Surg.* 2005;31:1-9.
43. Goldberg DJ. Full face nonablative dermal remodeling with a 1320 nm Nd:YAG laser. *Dermatol Surg.* 2000;26:915-918.
44. Fatemi A, Weiss MA, Weiss RA. Short-term histologic effects of nonablative resurfacing: results with a dynamically cooled millisecond-domain 1320 nm Nd:YAG laser. *Dermatol Surg.* 2002;28:172-176.
45. Kelly M, Nelson JS, Lask GP, et al. Cryogen spray cooling in combination with nonablative laser treatment of facial rhytides. *Arch Dermatol.* 1999;135:691-694.
46. Menaker GM, Wrone DA, Williams RM, et al. Treatment of facial rhytides with a nonablative laser: a clinical and histologic study. *Dermatol Surg.* 1999;25:440-444.
47. Ross EV, Sajben FP, Hsia J, et al. Nonablative skin remodeling: selective dermal heating with a mid-infrared laser and contact cooling combination. *Lasers Surg Med.* 2000;26:186-195.
48. Jih MH, Friedman PM, Goldberg LH, et al. The 1450-nm diode laser for facial inflammatory acne vulgaris: dose-response and 12-month follow-up study. *J Am Acad Dermatol.* 2006;55:80-87.
49. Bernstein EF. A pilot investigation comparing low-energy, double pass 1,450 nm laser treatment of acne to conventional single-pass, high-energy treatment. *Lasers Surg Med.* 2007;39:193-198.
50. Maruguchi Y, Maruguchi T. Treatment of inflammatory facial acne vulgaris: comparison of the 1450-nm diode laser and conventional physical treatment. *J Cosmet Laser Ther.* 2006;8:167-169.
51. Goldberg DJ, Rogachefsky AS, Silapunt S. Non-ablative laser treatment of facial rhytides: a comparison of 1450-nm diode laser treatment with dynamic cooling as opposed to treatment with dynamic cooling alone. *Lasers Surg Med.* 2002;30:79-81.
52. Fournier N, Dahan S, Barneon G, et al. Nonablative remodeling: clinical, histologic, ultrasound imaging, and profilometric evaluation of a 1540 nm Er:glass laser. *Dermatol Surg.* 2001;27:799-806.

53. Dahan S, Lagarde JM, Turlier V, et al. Treatment of neck lines and forehead rhytids with a nonablative 1540-nm Er:glass laser: a controlled clinical study combined with the measurement of the thickness and the mechanical properties of the skin. *Dermatol Surg.* 2004;30:872-880.
54. Nickell S, Hermann M, Essenpreis M, et al. Anisotropy of light propagation in human skin. *Phys Med Biol.* 2000;45:2873-2886.
55. Kopera D, Smolle J, Kaddu S, et al. Nonablative laser treatment of wrinkles: meeting the objective? assessment by 25 dermatologists. *Br J Dermatol.* 2004;150:936-939.
56. Friedman PM, Skover GR, Payonk G, et al. 3D in-vivo optical skin imaging for topographical quantitative assessment of non-ablative laser technology. *Dermatol Surg.* 2002;28:199-204.
57. Goldberg DJ, Whitworh J. Laser skin resurfacing with the Q-switched Nd:YAG laser. *Dermatol Surg.* 1997;23:903-907.
58. Dayan SH, Vartanian AJ, Menaker G, et al. Nonablative laser resurfacing using the long-pulse (1064-nm) Nd:YAG laser. *Arch Facial Plast Surg.* 2003;5:310-315.
59. Koh BK, Lee CK, Chae K. Photorejuvenation with submillisecond neodymium-doped yttrium aluminum garnet (1,064 nm) laser: a 24-week follow-up. *Dermatol Surg.* 2010;36:355-362.
60. Alam M, Dover JS. Nonablative laser and light therapy: an approach to patient and device selection. *Skin Therapy Lett.* 2003;8:4-7.
61. Lee MW. Combination 532-nm and 1064-nm lasers for noninvasive skin rejuvenation and toning [published correction appears in *Arch Dermatol.* 2004;140:625]. *Arch Dermatol.* 2003;139:1265-1276.
62. Tan MH, Dover JS, Hsu TS, et al. Clinical evaluation of enhanced nonablative skin rejuvenation using a combination of a 532 and a 1,064 nm laser. *Lasers Surg Med.* 2004;34:439-445.
63. Goldberg D, Tan M, Sarradet M, et al. Nonablative dermal remodeling with a 585-nm, 350-microsec, flashlamp pulsed dye laser: clinical and ultrastructural analysis. *Dermatol Surg.* 2003;29:161-164.
64. Tanghetti EA, Sherr EA, Alvarado SL. Multipass treatment of photodamage using pulse dye laser. *Dermatol Surg.* 2003;29:686-691.
65. Jørgensen GF, Hedelund L, Haedersdal M. Long-pulsed dye laser versus intense pulsed light for photodamaged skin: a randomized split-face trial with blinded response evaluation. *Lasers Surg Med.* 2008;40:293-299.
66. Karu T. Basics of the action of monochromatic visible and near infrared radiation on cells. In: Karu T, ed. *Science of Low-Power Laser Therapy.* London, England: Informa Healthcare; 1998:1-34.
67. Trelles MA, Allones I, Levy JL, et al. Combined nonablative skin rejuvenation with the 595- and 1450-nm lasers. *Dermatol Surg.* 2004;30:1292-1298.
68. Ross EV. Laser versus intense pulsed light: competing technologies in dermatology. *Lasers Surg Med.* 2006;38:261-272.
69. Bitter PH, Non-invasive rejuvenation of photodamaged skin using serial, full face intense pulsed light treatments. *Dermatol Surg.* 2000;26:835-843.
70. Brazil J, Owens P. Long-term clinical results of IPL photorejuvenation. *J Cosmet Laser Ther.* 2003;5:168-174.
71. Sadick NS, Weiss R, Kilmer S, et al. Photorejuvenation with intense pulsed light: results of a multi-center study. *J Drugs Dermatol.* 2004;3:41-49.
72. Negishi K, Tezuka Y, Kushikata N, et al. Photorejuvenation for Asian skin by intense pulsed light. *Dermatol Surg.* 2001;27:627-632.
73. Negishi K, Kushikata N, Takeuchi K, et al. Photorejuvenation by intense pulsed light with objective measurement of skin color in Japanese patients. *Dermatol Surg.* 2006;32:1380-1387.
74. Weiss RA, Goldman MP, Weiss MA, Treatment of poikiloderma of Civatte with an intense pulsed light source. *Dermatol Surg.* 2000;26:823-827.
75. Prieto VG, Diwan AH, Shea CR, et al. Effects of intense pulsed light and the 1,064 nm Nd:YAG laser on sun-damaged human skin: histologic and immunohistochemical analysis. *Dermatol Surg.* 2005:31:522-525.
76. Prieto VG, Sadick NS, Lloreta J, et al. Effects of intense pulsed light on sun-damaged human skin, routine, and ultrastructural analysis. *Lasers Surg Med.* 2002;30:82-85.
77. Weiss RA, McDaniel DH, Geronemus RG. Review of nonablative photorejuvenation: reversal of the aging effects of the sun and environmental damage using laser and light sources. *Semin Cutan Med Surg.* 2003;22:93-106.
78. Geronemus R, Weiss RA, Weiss MA, et al. Non-ablative LED photomodulation–light activated fibroblast stimulation clinical trial. *Lasers Surg Med.* 2003;25:22.
79. McDaniel DH, Newman J, Geronemus R, et al. Non-ablative non-thermal LED photomodulation—a multicenter clinical photoaging trial. *Lasers Surg Med.* 2003;15:22.
80. Weiss RA, McDaniel DH, Geronemus RG, et al. Clinical trial of a novel non-thermal LED array for reversal of photoaging: clinical, histologic, and surface profilometric results. *Lasers Surg Med.* 2005;36:85-91.
81. Lee SY, Park KH, Choi JW, et al. A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings. *J Photochem Photobiol B.* 2007;88:51-67.
82. Dover JS, Bhatia AC, Stewart B, et al. Topical 5-aminolevulinic acid combined with intense pulsed light in the treatment of photoaging. *Arch Dermatol.* 2005;141:1247-1252.
83. Gold MH, Bradshaw VL, Boring MM, et al. Split-face comparison of photodynamic therapy with 5-aminolevulinic acid and intense pulsed light versus intense pulsed light alone for photodamage. *Dermatol Surg.* 2006;32:795-803.
84. Park MY, Sohn S, Lee ES, et al. Photorejuvenation induced by 5-aminolevulinic acid photodynamic therapy in patients with actinic keratosis: a histologic analysis. *J Am Acad Dermatol.* 2010;62:85-95.
85. Burns JA. Thermage: monopolar radiofrequency. *Aesthet Surg J.* 2005;25:638-642.
86. Fitzpatrick R, Geronemus R, Goldberg D, et al. Multicenter study of noninvasive radiofrequency for periorbital tissue tightening. *Lasers Surg Med.* 2003;33:232-242.
87. Bassichis BA, Dayan S, Thomas JR. Use of a nonablative radiofrequency device to rejuvenate the upper one-third of the face. *Otolaryngol Head Neck Surg.* 2004;130:397-406.
88. Alster TS, Tanzi E. Improvement of neck and cheek laxity with a nonablative radiofrequency device: a lifting experience. *Dermatol Surg.* 2004;30:503-507.
89. Huzaira M, Anderson RR, Sink K, et al. Intradermal focusing of near-infrared optical pulses: a new approach for non-ablative laser therapy. *Lasers Surg Med.* 2003;32(suppl 15):17-38.
90. 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;33:23-28.
91. Lee H, Yoon JS, Lee SY. Fractional laser photothermolysis for treatment of facial wrinkles in Asians. *Korean J Ophthalmol.* 2009;23:235-239.
92. Geraghty LN, Biesman B. Clinical evaluation of a single-wavelength fractional laser and a novel multi-wavelength fractional laser in the treatment of photodamaged skin. *Lasers Surg Med.* 2009;41:408-416.
93. Cohen SR, Henssler C, Horton K, et al. Clinical experience with the Fraxel SR laser: 202 treatments in 59 consecutive patients. *Plast Reconstr Surg.* 2008;121:297e-304e.
94. NIH Consensus conference. Diagnosis and treatment of early melanoma. *JAMA.* 1992;268:1314-1319. ■