Clinical Experience with Light-Emitting Diode (LED) Photomodulation

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BACKGROUND. Light-emitting diode (LED) photomodulation is a novel nonthermal technology used to modulate cellular activity with light.

OBJECTIVE. We describe our experience over the last 2 years using 590 nm LED photomodulation within a dermatologic surgery environment.

METHODS. Practical use of nonthermal light energy and emerging applications in 3,500 treatments delivered to 900 patients is detailed.

RESULTS. LED photomodulation has been used alone for skin rejuvenation in over 300 patients but has been effective in augmentation of results in 600 patients receiving concomitant nonablative thermal and vascular treatments such as intense pulsed light, pulsed dye laser, KTP and infrared lasers, radiofrequency energy, and ablative lasers.

CONCLUSION. LED photomodulation reverses signs of photoaging using a new nonthermal mechanism. The anti-inflammatory component of LED in combination with the cell regulatory component helps improve the outcome of other thermal-based rejuvenation treatments.

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PHOTOREJUVENATION IS the process whereby light energy sources are used to reverse or repair the process of sun-induced aging or environmental damage to the skin. Nonablative photorejuvenation refers to the controlled use of thermal energy to accomplish this without disturbance of the overlying epidermis. Nonablative modalities include intense pulsed light (IPL), pulsed dye laser (PDL), 532 nm green light (KTP laser), and various infrared wavelengths, including 1,064, 1,320, 1,450, and 1,540 nm.[1] New uses being explored include combinations with fractional resurfacing. All of these devices involve thermal injury either by heating the dermis to stimulate fibroblast proliferation or by heating blood vessels for photocoagulation.[2,3] Light-emitting diode (LED) photomodulation is a novel category of nonthermal light-based treatment designed to regulate activity of cells rather than to invoke thermal wound healing mechanisms.[4]

The primary goal of nonablative rejuvenation is induction of new collagen and dermal extracellular matrix substances that visibly improve the appearance of rhytids and skin texture without disturbance or damage to the overlying epidermis. An additional goal includes the improvement of pigmented and vascular signs of photoaging, which include a reduction in superficial dyspigmentation (both dermal and epidermal), a reduction in dermal telangiectasias, and the appearance of an overall smoother texture.

There has been considerable interest recently in nonthermal low-intensity laser therapy, low-level laser therapy, or cold laser (very low doses of laser). Using a variety of LED light sources, we demonstrated that varying fluence and pulse duration lead to up-regulation of collagen type I synthesis in fibroblast culture using reverse transcriptase–polymerase chain reaction (RT-PCR) to measure collagen type I.[5] The up-regulation of fibroblast collagen synthesis correlates with the clinical observation of increased dermal collagen on treated human skin biopsies.[6] Both in the fibroblast and clinical model, collagen synthesis was accompanied by reduction or down-regula-

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tion of matrix metalloproteinases (MMPs), with MMP-1 being significantly down-regulated (MMP-1 = collagenase). The concept of using low-energy, narrow-band light with specific pulse sequences and durations was termed *photomodulation*.[5] The concept that cell activity can be up- or down-regulated by lower-energy light has been confirmed by other groups.[7,8]

This article presents an overview of LED photomodulation used both alone and in combination with a variety of common nonablative rejuvenation procedures in an office setting. It also reports preliminary results with anti-inflammatory and wound healing applications, as well as potential use with levulinic acid in photodynamic therapy.

Methods

Treatment records and digital images from over 900 patients were used in the assessment of results. Treatments were delivered using the Gentlewaves yellow light 590 nm LED photomodulation unit (LightBioScience, Virginia Beach, VA, USA) with a full-face panel device (Figure 1). Patients were positioned 2 cm away from the light source. This device is capable of either varying pulse regimens or continuous output with fluences starting at 0.01 J/cm^2 and ranging up to several Joules/cm^2. For photorejuvenation, energy density was preset at 0.10 J/cm^2. The pulse settings were 250 milliseconds on time and 100 milliseconds off time, for a series of 100 pulses. Treatment time was less than 60 seconds per treatment. Treatment outcomes were recorded in patient charts. Over 3,500 treatments were delivered to 900 patients over a 2-year period. Three hundred patients received LED photomodulation alone, and 600 received a combination of LED photomodulation concomitant with a thermal-based photorejuvenation procedure.

Figure 1. A 590 nm light-emitting diode full-face device. Courtesy of LightBioScience, Virginia Beach, VA, USA.

When LED photomodulation was given alone, patients with mild to moderately severe photoaging received eight treatments over a 4-week period (n = 300). Alternatively, patients received LED photomodulation immediately following a nonablative treatment, such as IPL, PDL, and KTP or infrared lasers, including 1,064, 1,320, or 1,450 nm (n = 600). Skin types ranged from Fitzpatrick types I to V. All patients were coached on the daily use of sunscreen with a sun protection factor of 30 or higher.

Patients performed a subjective self-assessment of improvement on a simple 2-point scale, and physician assessment of improvement was also recorded in the chart. If patients had received thermal nonablative treatments in the past without subsequent LED photomodulation, they were asked if they observed any difference with LED photomodulation immediately post-treatment.

In addition, 10 patients received a series of LED photomodulation treatments for atopic eczema and another 15 patients received treatments for bruising and/or second-degree burns. An additional 10 patients received photodynamic therapy using Levulan (DUSA, Wilmington, MA, USA). This therapy was delivered by application of levulinic acid for 45 minutes and exposure to continuous (nonpulsed) 590 nm LED for 15 minutes at over 5 J/cm2.

Results

Patients who received LED photorejuvenation alone without concomitant treatment reported that they observed a softening of skin texture and a reduction in roughness and fine lines that ranged from a significant reduction to sometimes subtle changes. Improvement was noted by 90% of patients, with only 10% reporting themselves as nonresponders. Similar to previous reports, 60% of patients were noted in the treatment record by the physician to demonstrate global improvement in a combination of facial texture, fine lines, background erythema, and pigmentation.

Patients with a thermal photorejuvenation laser or light source treatment with no LED photomodulation versus those with an LED treatment (n = 152) reported a noticeable reduction in post-treatment erythema and an overall impression of increased efficacy with an accompanying LED treatment. Treating physicians noted that patients returning for follow-up visits consistently requested LED treatment following their nonablative photorejuvenation treatment when they had received LED treatment with a previous treatment. Recorded comments often confirmed that LED photomodulation following nonablative rejuvenation increased patient's perception of efficacy and a reduction in erythema. (Clinical trials are now ongoing to validate this initial clinical observation.)

Another group of patients (n = 9) who had a variety of second-degree burns (n = 9) from nonablative devices were offered LED modulation treatments once a day for 1 week.

It was both the patients' and the physicians' impression that healing occurred 50% more quickly. In a pilot study, one forearm was injured by a CO_2 laser using a computer pattern generator to deliver the identical treatment to both test sites; accelerated reepithelialization was observed at the LED photomodulation treated site versus the untreated control. Both sites received daily dressing changes using a nonstick dressing and Polysporin ointment, but only one site also received one daily LED treatment (Figure 2).

Ten patients received LED treatment for acute sunburn using a once- or twice-daily treatment regimen for 3 days and treating only half of the affected anatomic area. Decreased symptoms of burning, redness, swelling, and peeling were observed. One 42-year-old male patient was treated twice daily for 3 days to half of his back, with the other half left untreated. Skin biopsies with immunofluorescence staining showed decreased MMP-1 on the LED-treated side compared with the untreated side (Figure 3). Other significant changes were noted that affected inflammation and dermal matrix composition at 4 days post–ultraviolet (UV) exposure with and without LED treatments (Figure 4). RT-PCR gene expression analysis showed a significant decrease in MMP-1 gene activity on the LED-treated side at both 4 and 24 hours post–UV injury compared with the untreated side (Figure 5).

Anecdotal treatment of atopic eczema in patients withdrawn from all topical medications led to rapid resolution within three to four treatments (Figure 6). Use of the LED array in the continuous and higher-energy mode (greater than 3 J/cm^2) in 10 patients for photodynamic therapy with levulinic acid incubation for 45 minutes demonstrated that erythema and peeling could be induced (Figure 7), which led to clinical improvement in photoaging changes of skin texture.

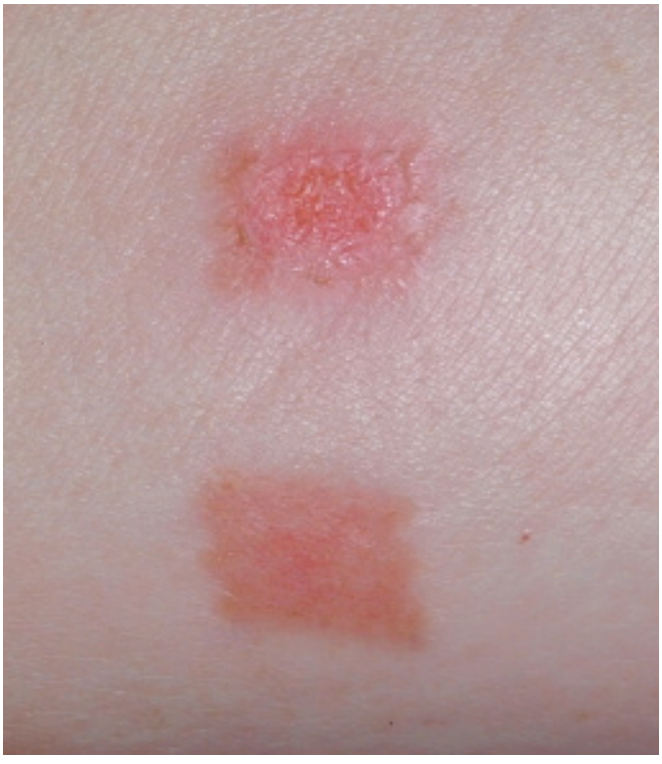


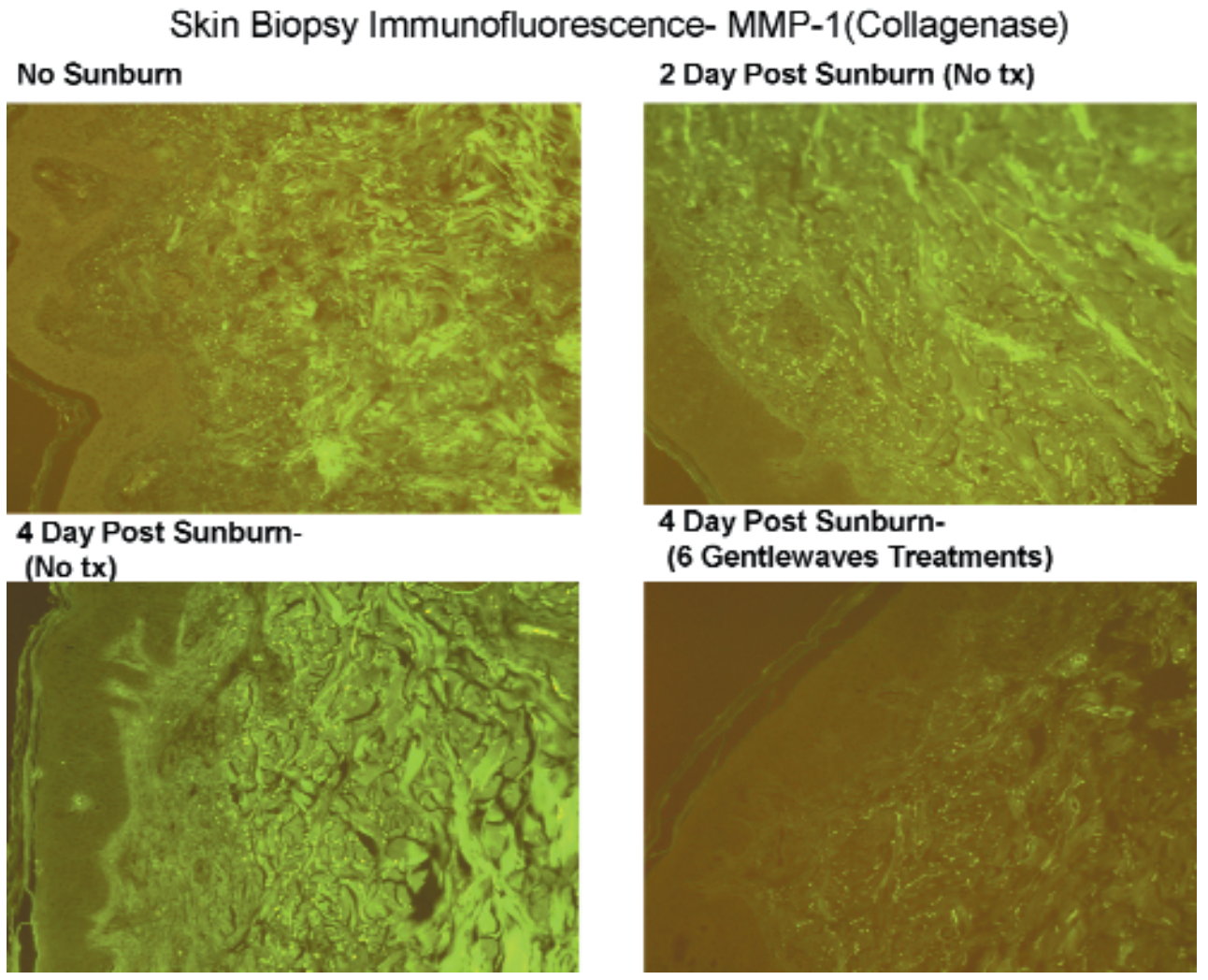
Figure 2. Wound healing is accelerated on the light-emitting diode photomodulation treated site at 3 days (*lower square*).

Discussion

LED photomodulation has an effect on human skin that is nonthermal and most likely mediated by mitochondrial cytochrome light absorption. This leads to increased cellular metabolic activity by targeted cells, such as increased collagen synthesis by fibroblasts. Studies have borne out that textural changes with a reduction in fine lines can be observed on photoaged skin. Our clinical experience over the last 2 years in a busy cosmetic dermatologic surgery practice indicates that these effects, although subtle, are observed on a much larger number of patients than reported in the original clinical studies.

Clinical and laboratory evidence supports beneficial effects for the rejuvenation and repair of chronic UV injury seen in photoaging but also for acute UV injury and thermal injuries. The potential to accelerate wound healing has broad implications in medicine. The ability to diminish undesired dermal matrix injury from popular nonablative cosmetic therapies while simultaneously enhancing some of the desired effects is another possible aspect of these wound healing effects.

The underlying mechanisms for LED photomodulation are believed to include the activation of energy switching mechanisms in mitochrondria, the energy source for cellular activity. Cytochrome molecules, in particular cytochrome oxidase within the mitochondrial membrane, are believed to be responsible for the light absorption in mitochrondria. Cytochromes are synthesized from protoporphyrin IX and absorb wavelengths of light from 562 to 600 nm. It is believed that light absorption causes conformational changes in antenna molecules within the mitochondrial membrane. Proton translocation initiates a pump that ultimately leads to energy for conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). This essentially recharges the "cell battery" and provides more energy for cellular activity. Previous work has demonstrated rapid ATP production within the mitochondria of cultured fibroblasts exposed to 590 nm yellow LED light only with the proper pulsing sequence.[4,9] New ATP production occurs rapidly after LED photomodulation, triggering subsequent metabolic activity of fibroblasts.[10] There also appear to be receptor-like mechanisms that result in modulation of the expression of gene activity, producing up- or down-regulation of gene activity and wide-ranging cell signaling pathway actions. The choice of photomodulation parameters plays a vital role in determining the overall pattern of gene up- or down-regulation.



Q14 **Figure 3.** Decreased matrix metalloproteinase 1 (MMP-1) staining with light-emitting diode photomodulation following ultraviolet exposure.

The particular set of parameters employed by this version of LED photomodulation device produces changes that have a skin rejuvenation effect clinically and histologically.

Using many of the pulsing sequence parameters developed in our laboratory, a multicenter clinical trial was conducted, with 90 patients receiving a series of eight LED treatments over 4 weeks.[6,10–12] This study showed very favorable results, with over 90% of patients improving by at least one Fitzpatrick photoaging category and 65% of patients demonstrating global improvement in facial texture, fine lines, background erythema, and pigmentation. The results peaked at 4 to 6 months following completion of a series of eight treatments.[12] Another study demonstrated similar results, which were confirmed by digital microscopy.[13]

By combining different techniques of photorejuvenation, improved results are possible. Our initial experience and observations confirm that combinations of thermal nonablative photorejuvenation and nonthermal LED photomodulation have a synergistic effect. LED photomodulation is delivered immediately subsequent to the thermal-based treatment for its anti-inflammatory effects, which may reduce the thermally induced erythema of nonablative treatments. Clinical trials are now ongoing to substantiate these observations.

Although controlled clinical trials will be required, pilot trials for atopic eczema indicate that there is potential to further use the anti-inflammatory properties of LED photomodulation. As improved wound healing has been reported with other low-level light sources, particularly red,[14,15] this novel yellow wavelength of LED appears to be very promising. Based on the preliminary work, further investigation on the yellow LED array for use as a light source for photodynamic therapy is also warranted. Preliminary data from DNA microarray analysis of the entire human genome of certain skin cell lines after LED photomodulation and after UV injury and subsequent LED therapy are currently being analyzed and support a multifaceted role for LED photomodulation in enhancing cellular energy production and diverse effects on gene expression.

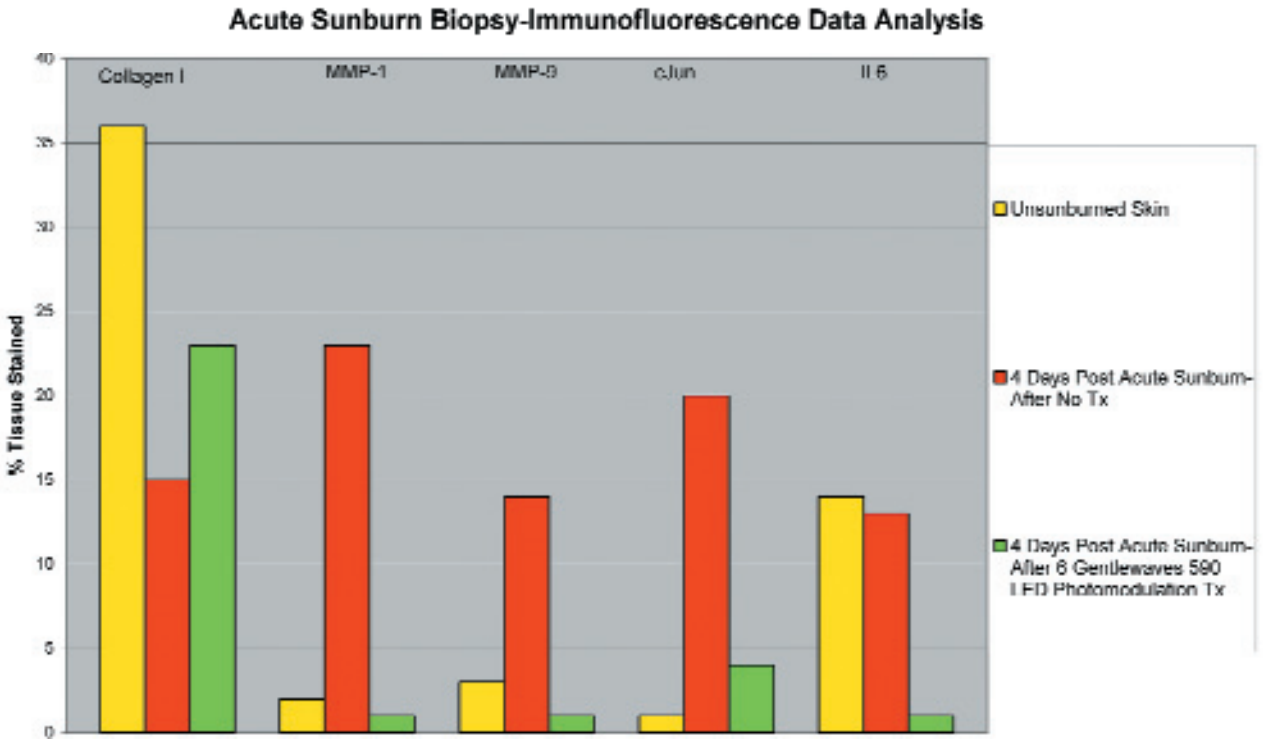


Figure 4. Changes in inflammatory mediators and the dermal matrix. LED = light-emitting diode.

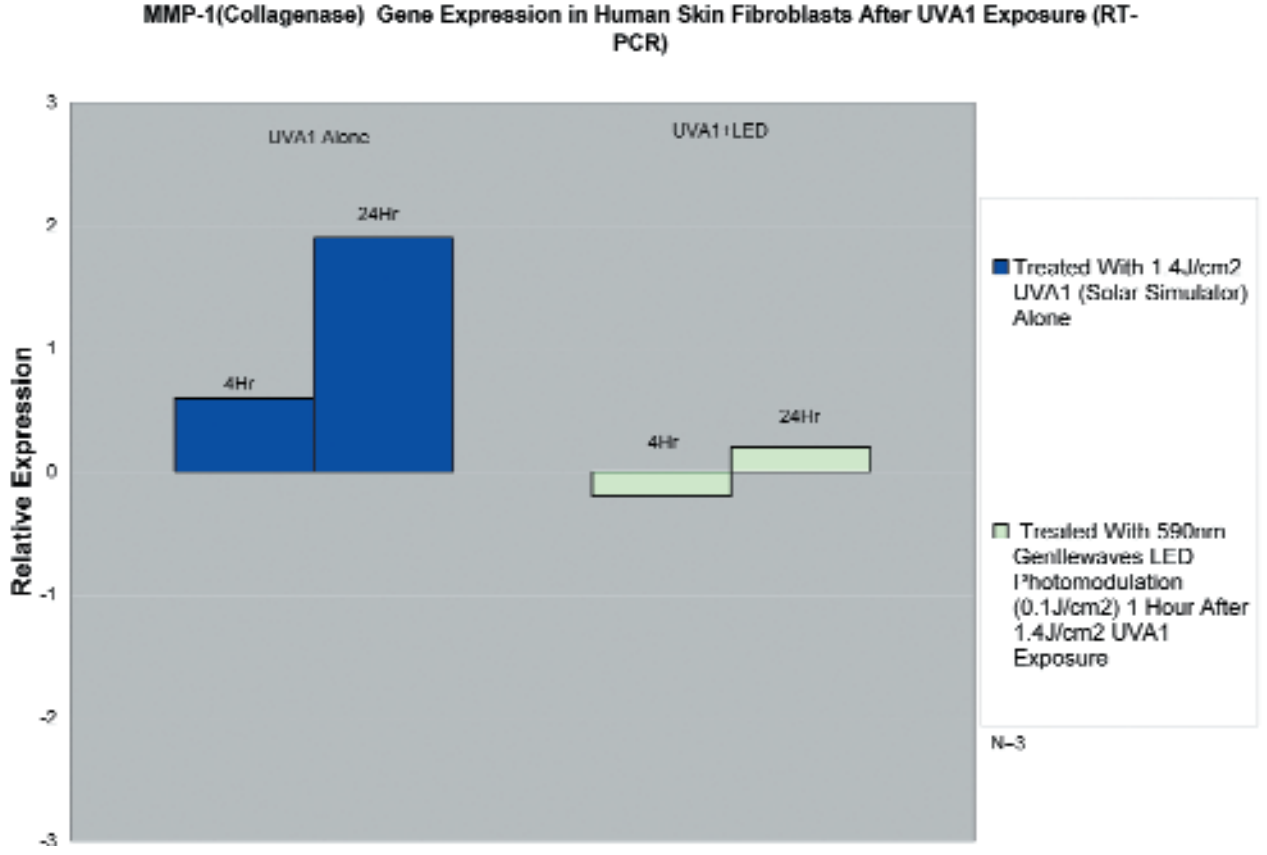


Figure 5. Changes with light-emitting diode (LED) exposure after ultraviolet exposure. RT-PCR = reverse transcriptase–polymerase chain reaction; UVA = ultraviolet A.

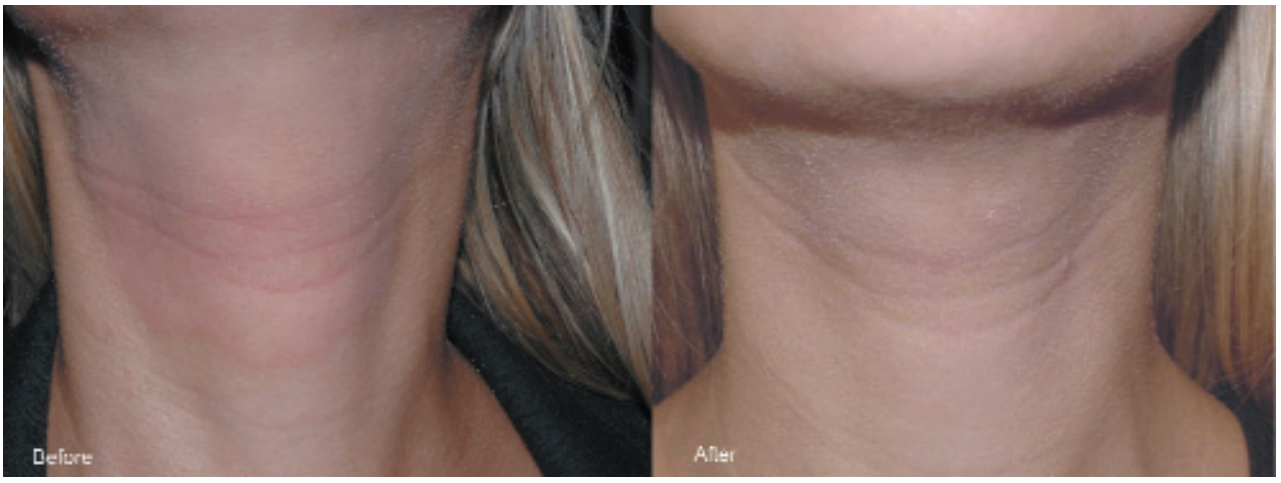


Figure 6. Atopical eczema with all topical agents withdrawn seen after two light-emitting diode photomodulation treatments.

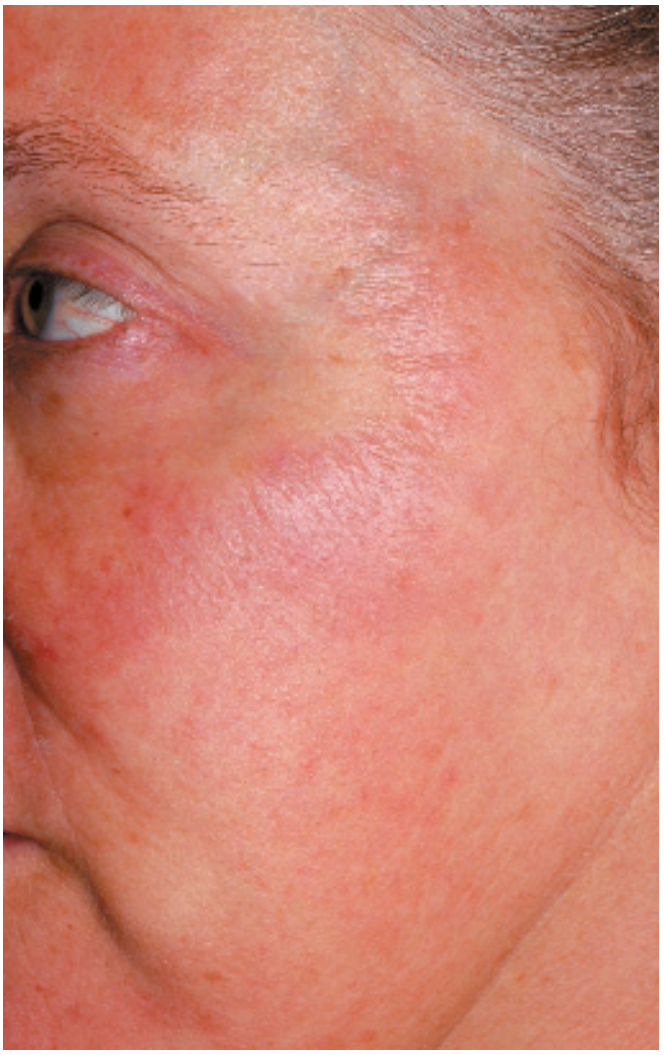


Figure 7. Skin changes induced by Levulan with a light-emitting diode (LED) array after 24 hours. Incubation with Levulan for 45 minutes; exposure to an LED array for 15 minutes continuous on (not pulsed).

Many clinical and basic science research pathways await further exploration.

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