Seminars in Cutaneous Medicine and Surgery

Body Contouring Using 635-nm Low Level Laser Therapy

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Noninvasive body contouring has become one of the fastest-growing areas of esthetic medicine. Many patients appear to prefer nonsurgical less-invasive procedures owing to the benefits of fewer side effects and shorter recovery times. Increasingly, 635-nm low-level laser therapy (LLLT) has been used in the treatment of a variety of medical conditions and has been shown to improve wound healing, reduce edema, and relieve acute pain. Within the past decade, LLLT has also emerged as a new modality for noninvasive body contouring. Research has shown that LLLT is effective in reducing overall body circumference measurements of specifically treated regions, including the hips, waist, thighs, and upper arms, with recent studies demonstrating the long-term effectiveness of results. The treatment is painless, and there appears to be no adverse events associated with LLLT. The mechanism of action of LLLT in body contouring is believed to stem from photoactivation of cytochrome *c* oxidase within hypertrophic adipocytes, which, in turn, affects intracellular secondary cascades, resulting in the formation of transitory pores within the adipocytes' membrane. The secondary cascades involved may include, but are not limited to, activation of cytosolic lipase and nitric oxide. Newly formed pores release intracellular lipids, which are further metabolized. Future studies need to fully outline the cellular and systemic effects of LLLT as well as determine optimal treatment protocols.
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Striving for a youthful appearance has become so important in Western society that even small imperfections on the body are now scrutinized. Tissue laxity and generalized and localized subcutaneous fat deposits are increasingly common complaints among cosmetic patients. As a result, the number of procedures performed for body contouring has increased exponentially. Chronologic aging, photoaging, or substantial changes in body dimensions experienced during pregnancy or weight loss can all contribute to the formation of localized and generalized fat deposits as well as lax skin.[1,2] Additionally, over the past 10 years, the population as a whole has become increasingly overweight, and at the same time, have become more accepting of advances in esthetic technology, including nonsurgical management of fat and body contouring.[3]

From the advent of liposuction in the late 1970s and early 1980s, the practice of body contouring has seen the growth of more effective and less risky liposuction techniques, and has evolved in the direction of minimally invasive procedures. Noninvasive body contouring is one of the most appealing aspects of cosmetic surgery today owing to the demand for safer and less-invasive procedures that offer a quicker recovery, fewer side effects, and less discomfort. Helping drive noninvasive body contouring are new therapeutic modalities that offer patients a less-invasive alternative. Accordingly, cosmetic patients are becoming more reluctant to undergo surgical procedures that involve hospitalizations, anesthetics, pain, swelling, longer recovery periods, and, in general, the risks involved with surgery.[3]

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Although liposuction is the number one invasive cosmetic plastic surgery procedure performed worldwide, noninvasive body contouring technology is the fastest-growing segment of the esthetic capital equipment space.[4] A variety of delivery mechanisms have been approved by the U.S. Food and Drug Administration (FDA) to achieve body slimming without surgery; these include endermology, ultrasonography, infrared, radiofrequency, cryolipolysis, and low level laser.[3,5,6] Endermology uses a suction/massage device to pass over fatty areas of the body and cellulitic regions; is often combined with increased exercise, dieting, and increased water intake; and yields mild clinical effectiveness.[3] Radiofrequency energy devices have been FDA-approved for the reduction of the appearance of cellulite as well as circumference reduction through infrared light and suction coupling. Optical infrared energy targets dermal water causing thermogenesis, whereas radiofrequency energy targets the hypodermis by controlled thermal stress. As a result, dermal tightening and contraction occur, as well as stimulation and promotion of collagen formation. Other radiofrequency devices use monopolar radiofrequency waves for skin tightening and the improvement of cellulite. Additionally, high-frequency focused ultrasound energy devices cause noninvasive adipocyte death, rather than amplification of fat cell metabolism, which is observed using other technologies.[3] Furthermore, this system uses mechanical (nonthermal) energy to disrupt fat cells without damaging adjacent tissues.[2]

Some noninvasive devices and techniques, such as radiofrequency and high-frequency focused ultrasound, were developed to provide concurrent circumference reduction as well as treatment of skin laxity. The concurrent therapeutic benefit stems from a thermogenic effect within the dermal and subdermal layers after the application of energy to the skin surface. As a result, thermogenesis triggers collagen denaturation and neocollagenesis while increasing adipocyte metabolism. Thermogenic skin tightening was originally noted with ablative laser resurfacing; however, noninvasive technologies have evolved over time to induce similar tightening effects.[2,7-10]

Conversely, low level laser therapy (LLLT) uses a mechanism devoid of thermogenesis, and instead activates adipocyte lipolysis without damaging the adipocyte. Originally, LLLT emerged as an effective adjunct therapy for breast augmentation and lipoplasty, improving the ease of extraction during liposuction as well as reduced postsurgical pain. After numerous multisite, randomized, controlled, double-blinded studies, LLLT has developed into a substantial therapeutic option for circumferential reduction of the waist, hips, thighs, and upper arms.[11]

Low Level Laser Therapy

LLLT administers treatment with a dose rate of laser energy that causes no immediate detectable temperature rise of the treated tissue and no macroscopically visible changes in tissue structure.[12] For decades, low level lasers have been used in physical therapy to reduce pain and inflammation. Recently, they have been increasingly used in the treatment of a broad range of conditions, including the treatment of nonhealing wounds, edema, and pain of various etiologies.

In vitro data suggest that LLLT facilitates collagen synthesis,[13] keratinocyte cell motility,[14] and growth factor release,[15] as well as transforms fibroblasts to myofibroblasts.[16] Hopkins et al[17] assessed the effects of LLLT in partial-thickness wounds and demonstrated that those subjects treated with LLLT had greater wound contraction than the control group. The authors postulated that LLLT may produce an indirect healing effect on surrounding tissues. Bjordal et al[18] conducted a systematic review of all studies using LLLT for the treatment of joint capsule pain and inflammation. The authors assessed 11 trials and determined that LLLT significantly reduces pain and improves the overall health status in patients suffering with chronic joint disorders.

Some novel medical uses for LLLT under investigation include treating onychomycosis and herpes simplex infection, stimulating bone growth, and reducing the severity of burn scars.[19-22] Within the past year, there were 2 case reports of pemphigus vulgaris in which patients received systemic treatment with LLLT for oral and cutaneous lesions. The results showed prompt analgesic effect and accelerated healing of the oral and cutaneous wounds. Specifically, the patients experienced an immediate decrease of approximately 70% of oral pain after the first laser treatment and complete resolution of oral pain after the third session.[23]

The overall dosage for LLLT is based on a combination of wavelength, energy level, and time. Karu et al[24] determined that cytochrome *c* oxidase, the primary phototarget for LLLT, has a peak absorption of 632.8 nm, and therefore delivery of that wavelength is necessary for photobiomodulation. Furthermore, power density and exposure time results show that laser power <2.9 mW could enhance cell proliferation, whereas higher power has no effect. Stimulation is most pronounced at irradiation times between 0.5 and 6 minutes, based on the Arndt-Schultz biological law in which weak stimuli excite physiological activity, moderately strong stimuli empower it, strong stimuli retard it, and very strong stimuli inhibit activity.[25]

The mechanism of action by which LLLT functions appears to occur at the molecular level through a photochemical-induced cascade rather than a photothermal mechanism. LLLT is proposed to promote photoexcitation of certain reaction centers in the cytochrome *c* oxidase molecule, thereby influencing the redox state of these molecules, and thus the rate at which electrons flow across the molecule.[26,27] As a result, photoactivation of cytochrome *c* oxidase increases the mitochondrial membrane potential and electrochemical gradient, resulting in a higher exchange of adenosine diphosphate/adenosine triphosphate (ATP).[28,29] Additionally, LLLT has been reported to cause photodissociation of nitric oxide (NO) from cytochrome *c* oxidase. NO displaces oxygen from cytochrome *c* oxidase when the cell is stressed, causing a downregulation of cellular respiration and a decrease in ATP production. This dissociation of NO from cytochrome *c* oxidase triggered by LLLT prevents the displacement of oxygen from cytochrome *c* oxidase, which promotes unrestricted cellular respiration.[28,30,31] Overall, increased ATP synthesis triggers secondary signal cascades by phosphorylating secondary messengers like cyclic adenosine monophosphate. Specifically in adipocytes, activation of cyclic adenosine monophosphate triggers a secondary cascade that culminates with the stimulation of cytosolic lipase, which converts triglycerides into fatty acids and glycerol, which can pass through pores formed in the cell membrane.[32,33]

LLLT and Body Contouring

In 2000, Neira et al[34] presented a new liposuction technique that demonstrated liquefaction of fat using a low level laser device during a liposuction procedure. They specifically examined whether 635-nm, 10-mW low level lasers had an effect on adipose tissue in vivo and how it would be implemented as a lipoplasty or liposuction technique. Microscopic results showed that without laser exposure, the normal adipose tissue appeared as a grape-shaped node. After 4 minutes of laser exposure, 80% of the fat was released from the adipose cells, and at 6 minutes, 99% of the fat was released from the adipocytes. Transmission electron microscopic images of the adipose tissue showed a transitory pore and complete deflation of the adipocytes. The researchers concluded that the laser-induced formation of transitory pores within adipocyte membranes resulted in the release of intracellular fatty acids, glycerol, and triglycerides, and subsequent collapse of hypertrophic adipocytes.[25] It is further presumed that triglyceride and fatty acid oxidization occurs within the extracellular space.[33]

To further investigate the usefulness of LLLT in liposuction, Jackson et al[11,26] applied LLLT externally several minutes before the aspiration phase of lipoplasty to evaluate the impact adipocyte disruption could have on the procedure and for patient recovery. They noted that for those patients receiving LLLT, a greater volume of fat was able to be extracted, and a reduction in postoperative edema and pain was observed ($P < .001$). The conclusion was that laser-induced emulsification was beneficial and observable at the clinical level.

Caruso-Davis et al[35] conducted a study to examine the clinical effectiveness by which 635-680-nm LLLT acts as a noninvasive body contouring intervention method. Results showed a statistically significant cumulative girth loss of −2.15 cm after eight 30-minute treatments over 4 weeks ($P < .05$). As a secondary objective, in vitro assays were conducted to determine cell lysis and glycerol and triglyceride release. Three separate experiments were performed to evaluate whether fat loss was induced by irradiation with LLLT due to: (1) laser activation of the complement cascade, (2) laser-induced adipocyte death, or (3) laser-induced increased triglyceride release or lipolysis from adipocytes. Obtained from subcutaneous fat during abdominal surgery, human adipose-derived stem cells were plated and differentiated to form adipocytes. In the first experiment, results showed that serum complement lysed fat cells in both irradiated and nonirradiated adipocytes. Consequently, it was determined that LLLT does not activate the complement cascade to induce fat loss from adipocytes. In the second experiment,

Figure 1 Zerona 635 nm LLLT Body Device.

researchers found that irradiation with LLLT does not kill adipocytes, as in both irradiated and nonirradiated groups, the adipocytes maintained intact metabolic functions and the number of viable cells, as measured by the propidium iodide assay, remained the same. Furthermore, calcein levels, a dye injected into both groups, were lower in the laser-treated group, suggesting reduction of cell-trapped calcein due to leakage. Finally, results of the last experiment showed that irradiation with LLLT increased triglyceride release, but not lipolysis from adipocytes. The findings from these 3 in vitro experiments are consistent with the theory that LLLT creates pores in adipocytes through which fat leaks into the interstitial space without inducing cell lysis and further confirms the ability of the laser to influence fat loss.

Clinically, LLLT is one of the newest noninvasive modalities for body contouring. The LLLT device (635-nm Zerona, Erchonia Corporation, McKinney, TX) was cleared by the FDA in 2010 as a noninvasive dermatologic esthetic treatment for the reduction of the circumference of hips, waist, and thighs (Fig. 1). Jackson et al[26] evaluated the clinical use of LLLT as an independent modality in reducing total combined circumference measurements of waist, hips, and thighs. Their results showed a statistically significant overall reduction in total circumference across all 3 sites of −3.51 inches ($P < .001$) compared with sham-treated subjects, who revealed a −0.684-inch reduction. Specifically, from baseline to 2 weeks, subjects showed a reduction of −0.98 inches ($P < .0001$) in the waist, −1.05 inches ($P < .01$) in the hips, and −0.85 inches ($P < .01$) and −0.65 inches ($P < .01$) in the right and left thighs, respectively. In total, 57% more of the LLLT-treated group, compared with the control group, demonstrated a decreased combined circumference measurement of ≥3.0 inches from baseline to end point. The

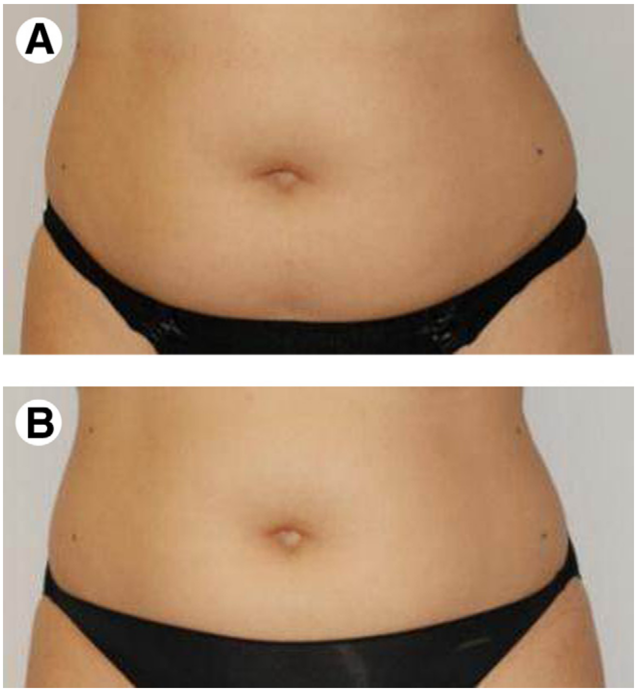

Figure 2 (A) Before treatment abdomen. (B) Immediately post 5 daily 40 minute treatments over one week: 2.0 inch total reduction.

authors concluded that low level laser of the appropriate wavelength applied 3 times per week for 2 weeks can significantly reduce the circumference at specifically targeted tissue sites due to reduction in the adipose layer. Moreover, no adverse events were reported.[26] In addition, our clinical data indicate that greater than a 1-inch abdominal circumference reduction can be achieved in 1 week by delivering 5 daily treatments (Fig. 2).

Following the studies of the past decade, Jackson et al[36] sought to determine whether the results of LLLT therapy are based on simple fluid redistribution. Data were used from 689 participants to evaluate the circumferential reduction of the waist, hips, and thighs, as well as nontreated systemic regions, and significant differences were found ($P < .0001$). The authors reported that the circumferential reduction represents intracellular lipids permeated from the treated area and further suggested that these lipids are degraded in the lymphatic system before entering the circulatory system and are then further catabolized. The question was whether the liberated material and consequential body slimming could arise as a result of simple fluid redistribution. If this were the case, the remote nontreated regions, tested in their newest study, would show an increase in circumferential measurements after LLLT treatment. The results showed a mean total circumferential loss, in both treated and remote regions, of −5.17 inches, demonstrating that fluid redistribution is not the likely cause for the reduction. The authors proposed that the slimming induced by LLLT is secondary to lipid mobilization and subsequent lipid metabolism.[36]

Skepticism still remained regarding the efficacy of this modality in its clinical usefulness. The results of a study carried out by Elm et al[37] did not show a significant reduction in waist circumference after LLLT treatment ($P > .5$). However, it must be noted that this study was limited by its small sample size (n = 5) and only partial body sites were treated. Additionally, one of the authors failed to disclose a significant conflict of interest: being a shareholder in a competing company.[38]

To fully evaluate the clinical efficacy of LLLT in a clinical model without significant confounding variables, Nestor et al[39] used an upper arm circumference model, and conducted a randomized double-blind study (n = 40) in which patients received either three 20-minute LLLT (635-nm Zerona AD, Erchonia Corporation, McKinney, TX) (Fig. 3) or sham treatments each week for 2 weeks. The primary outcome measures were the number of subjects who achieved a total decrease in arm circumference ≥1.25 cm for the 3 combined measurement points after 2 weeks of 3 treatments a week for a total of 6 treatments, as well as the average difference between the combined arm circumference measurements for the active versus sham treatment groups. Their results demonstrated that after 6 total treatments in 2 weeks, 12 subjects (60%) achieved a ≥1.5-cm decrease in upper arm circumference versus 0 (0%) in the sham treatment group, and showed a combined statistically significant reduction in arm circumference of −3.7 cm ($P < .0001$) versus −0.2 cm. After the first week of treatment, which included 3 laser procedures, a 2.2-cm reduction in total circumference was observed, followed by a 3.7-cm reduction after the second week of 3 laser

Figure 3 Zerona 635 nm LLLT Arm Device.

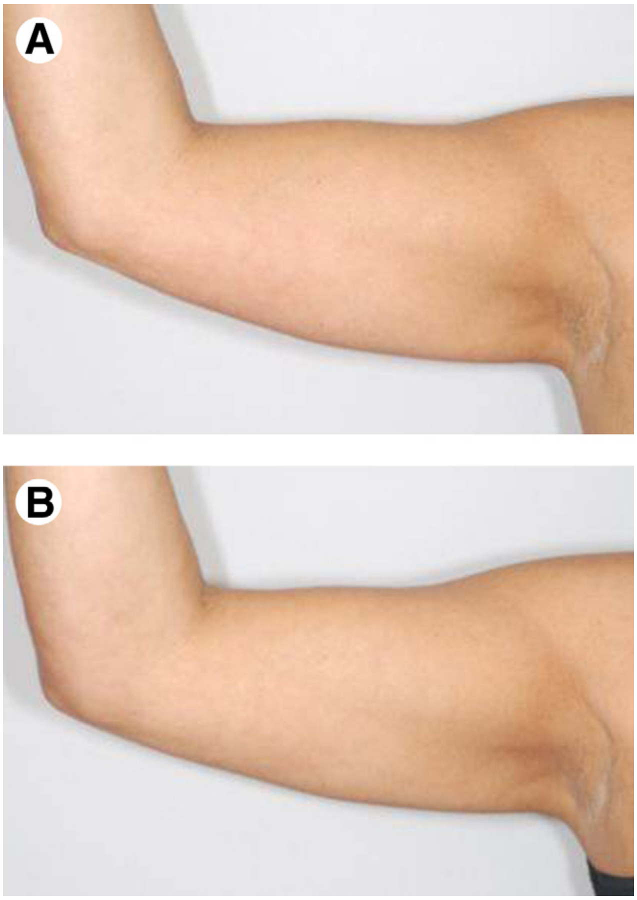

Figure 4 (A) Before treatment arm. (B) Two weeks post 6 treatments over 2 weeks: 2.5 inch total reduction.

procedures (Fig. 4). This indicated both a progressive and cumulative treatment effect of the laser.[39]

Furthermore, Nestor et al[40] extended their previous study in an attempt to demonstrate the long-term efficacy and safety of the 635-nm LLLT on reducing upper arm circumference. In this multicenter trial, additional subjects (total N = 62) received three 20-minute LLLT (n = 31) or sham treatments (n = 31) each week for 2 weeks. Upper arm circumference was initially measured at 1 week, after 3 LLLT treatments, at 2 weeks, after 6 LLLT treatments, and then at 2 weeks post-treatment. Long-term efficacy was assessed at a follow-up visit between 5 and 10 months. The combined results showed that 58% of subjects achieved study success criteria, defined as a combined reduction in arm circumference ≥1.25 cm measured at 3 equally spaced points between the elbow and shoulder. This was compared with 3% of sham-treated subjects ($P < .000005$). The average combined change in arm circumference for the LLLT treatment group was −2.01 cm after 3 LLLT treatments and −3.70 cm after 6 treatments, versus 0.11 and −0.31 cm for the sham group ($P <$ .01), which indicated a progressive and cumulative nature of the treatment effect, as previously shown. The study also investigated a subset of subjects for long-term efficacy and accessed a subgroup (n = 33) at an average of 7.6 months after treatment (range: 5-9 months) and showed similar overall reductions versus the sham group (−3.25 vs −0.15). The results appear to indicate that LLLT has long-term, if not permanent, effects on fat reduction and body contouring. Additionally, blinded subjective assessments revealed significantly greater satisfaction and improved appearance in the LLLT-treated subjects. As with previous studies, no treatment-related adverse events were reported.[40] Moreover, the use of the upper arm in body contouring studies provides both an esthetically important and nonconfounded clinical model. The use of the upper arm, as opposed to areas such as the abdomen, hips, and waist, avoids confounding variables such as water retention, bloating, abdominal muscle flexure versus laxity, fed versus fasting condition, and inhaling versus exhaling respirations.[41]

LLLT has also shown to provide further clinical benefit to patients, including a reduction in both cholesterol and leptin levels. Leptin, an adipocyte-derived hormone, influences appetite, energy expenditure, and neuroendocrine function. In a 2-week trial (n = 22), Maloney et al[42] demonstrated a 50% reduction, 29.49 to 14.60 points ($P < .0001$), in leptin levels after 6 total treatments of LLLT.

Future studies need to further define the cellular and systemic effects of 635-nm LLLT and to determine optimal treatment protocols. These should include investigating other potential health-related indications for treatment, including obesity and hyperlipidemia, as well as assessing the overall metabolic effect of LLLT. Studies also need to determine the overall beneficial systemic effects of LLLT, including possible changes to adipocyte-related hormones that give rise to both the observed reduction in nontreated remote regions of the body[36] as well as the long-term circumferential reduction.[40]

Conclusions

Noninvasive body contouring has become a popular solution to deal with unwanted fat. LLLT has previously been used for a wide variety of medical conditions that include wound healing, reduction of edema, and pain relief. Within the past decade, it has become the newest modality for noninvasive body contouring, treating a patient population that is shying away from surgical cosmetic procedures and opting for less-invasive and safer options. Research has demonstrated that LLLT can reduce overall body circumference measurements of specifically treated as well as nontreated remote regions. It has been proven effective, and cleared by the FDA for the reduction of circumference of hips, waist, thighs, and, most recently, upper arms. Recent studies indicate that the results of LLLT are long-lasting if not permanent. With no adverse events reported to date, LLLT appears to be both safe and effective for fat reduction and body slimming.

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