

# Low-Level Laser Therapy as a Non-Invasive Approach for Body Contouring: A Randomized, Controlled Study

Robert F. Jackson, MD,<sup>1†</sup> Doug D. Dedo, MD,<sup>2†</sup> Greg C. Roche, MD,<sup>3†</sup> David I. Turok,<sup>4†</sup> and Ryan J. Maloney, BS<sup>5\*</sup>

<sup>1</sup>River View Surgery Center, Marion, Indiana 46952

<sup>2</sup>Garden Cosmetic Center, West Palm Beach, Florida 33406

<sup>3</sup>Bloomfield Laser and Cosmetic Surgery Center, Bloomfield, Hills, Michigan 48032

<sup>4</sup>Fox River Surgery Center, Fox River Groove, Illinois, 60021

<sup>5</sup>Erchonia Medical Inc., McKinney, Texas 75069

**Background and Objective:** Transmission electron microscopic images have demonstrated the formation of transitory pores in adipocyte cell membranes followed by the collapse of adipose cells subsequent to laser irradiation of 635 nm. The objective is to evaluate the application of a 635 nm and 17.5 mW exit power per multiple diode laser for the application of non-invasive body contouring of the waist, hips, and thighs.

**Study Design/Patients and Methods:** Double-blind, randomized, placebo-controlled trial of a 2-week non-invasive laser treatment conducted from May 2007 to June 2008 across multiple-private practice sites in the United States of America. Sixty-seven volunteers between the ages of 18–65 with a body mass index (BMI) between 25 and 30 kg/m<sup>2</sup> and who satisfied the set inclusion criteria participated. Eight of the 67 subjects did not have circumference measurements recorded at the 2-week post-procedure measurement point. Participants were randomly assigned to receive low-level laser treatments or a matching sham treatment three times per week for 2 weeks. Reduction in the total combined inches of circumference measurements of the waist, hip and bilateral thighs from baseline to the completion of the 2-week procedure administration phase was assessed.

**Results:** Participants in the treatment group demonstrated an overall reduction in total circumference across all three sites of –3.51 in. ( $P < 0.001$ ) compared with control subjects who revealed a –0.684 reduction ( $P < 0.071745$ ). Test group participants demonstrated a reduction of –0.98 in. ( $P < 0.0001$ ) across the waist, –1.05 in. ( $P < 0.01$ ) across the hip, and –0.85 in. ( $P < 0.01$ ) and –0.65 in. ( $P < 0.01$ ) across the right and left thighs from baseline to 2 weeks (end of treatment). At 2 weeks post-procedure, test group subjects demonstrated a gain of 0.31 total inches collectively across all three sites.

**Conclusion:** These data suggest that low-level laser therapy can reduce overall circumference measurements of specifically treated regions. *Lasers Surg. Med.* 41:799–809, 2009. © 2009 Wiley-Liss, Inc.

**Key words:** adipocyte; adipose panicle; emulsification; photobiomodulation; transitory pore

## INTRODUCTION

The emergence of non-invasive modalities targeting subcutaneous fat to achieve a slimming effect continues to gain interest amongst physicians and patients. Numerous delivery mechanisms have been developed to achieve adipocyte destruction including, ultrasound, infrared, and radio frequency [1–5]. The external application of photonic energy at high intensities can generate significant adverse events if not properly utilized; therefore, all parameters must be properly explored in order to identify which delivery mechanism yields the most desirable results while minimizing adverse events.

In recent years, there has been an upsurge in the application of low-level laser therapy (LLLT) across myriad neurologic, dental, ophthalmic, dermatologic disorders, and injuries [6–10]. LLLT has been proven to be a safe and effective therapeutic option in clinical and histological trials; yet, a great deal of skepticism still remains regarding the efficacy of this modality at the clinical level.

Numerous studies have exhibited laser therapy's ability to induce an assortment of cellular reactions in non-photosynthetic cells. Laser therapy has been shown to preserve the membrane and genetic material of cells that are nutritionally starved [11]; regenerate erythrocytes enhancing their oxyphoric function [12]; enhance fertilization potential of spermatozoa [13]; stimulate the differentiation of satellite stem cells [14–16]; reduce the extent of myocardial infarctions and ischemic strokes [17]; and improve wound healing and modulate chronic inflammation [18]. A continually growing body of evidence suggests that laser therapy can alter cell bioenergetics, consequentially influencing the functional biochemical properties intracellularly, culminating in an observable diverse clinical effect.

<sup>†</sup>Private Practice Physician.

\*Correspondence to: Ryan J. Maloney, BS, Medical Director, McKinney, TX 75069; 1172 E. Buffalo St., Gilbert, AZ 85295.

E-mail: ryanmasu11@msn.com

Accepted 11 September 2009

Published online 15 December 2009 in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/lsm.20855

Understanding the photobiomodulatory principles of laser therapy, Neira et al. [19] applied laser therapy at 635 nm to cultured adipocytes and revealed an ability to emulsify the targeted tissue. In a separate study, Neira et al. [20] examined the effect of LLLT at 635 nm with 10 mW intensity on human adipose tissue taken from lipectomy samples. Tissue samples were irradiated for 6 minutes and compared with non-irradiated samples. Utilizing scanning and transmission electron microscopy (SEM and TEM), more than 180 images were collected, and revealed that 99% of the cellular content including fat was released from the adipocyte, a phenomenon not observed within the control samples [20]. Further, TEM images of the adipose tissue were taken at 60,000 $\times$  and revealed the formation of a transitory pore and complete deflation of adipocytes [20]. The cells within the interstitial space and capillaries remained intact demonstrating that the photochemical event was unique to the adipocytes [20]. It was concluded that the disruption of the adipocyte membrane is what enabled the liberation of the stored fatty material; thus, prompting the collapse of the adipocyte [19–21].

To confirm the histological findings and assess the depth of penetration of LLLT within the subcutaneous layer, Neira et al. [22] assessed T1 and T2 MRI sequences to evaluate any radiological changes subsequent to laser irradiation. The T2 sequence following 6 minutes of laser irradiation exhibited a less defined superficial adipose layer, less defined septae, and a much more coalescent adipose tissue. The study confirmed a change in fatty density and organization of both superficial and deep fat while supporting Neira's histological work. The morphologic changes of deep subcutaneous fat cannot be attributed to direct photostimulation; however, studies have revealed a systemic effect associated with LLLT in which non-irradiated adjacent cells become stimulated via intercellular communicators [23–25]. Therefore, the observable changes within the deep subcutaneous layers may be based upon the system effect found subsequent to LLLT.

Based upon the histological evidence, Jackson et al. [25] applied LLLT externally several minutes prior to the aspiration phase of lipoplasty in order to evaluate the impact adipocyte disruption could have on the procedure and for patient recovery. Jackson et al. [25] noted that for those patients receiving LLLT a greater volume of fat was able to be extracted and reduction in post-operative edema and pain was observed. Blinded physicians were asked to rate on a visual analog scale (VAS) from 1 to 100 their assessment of ease of extraction with 100 being the hardest to extract. Dr. Jackson noted that non-irradiated patients averaged an ease of extraction score of 73.84 compared with laser-treated patients averaging an extraction score of 12.88 [25]. Jackson concluded that laser-induced emulsification was observable at the clinical level based upon the ease of extraction scores for laser-treated subjects.

Although multiple studies have been published highlighting adipocyte modifications subsequent to laser therapy and its ability to serve as an adjunctive tool for liposuction, the purpose of this institutional review board study was to evaluate the clinical use of LLLT as an

independent modality in reducing total combined circumference measurements of waist, hip, and thighs. This investigation attempts to position LLLT as a safe and effective modality for non-invasive body contouring building upon numerous histological studies. The device utilized in this investigation possesses the same wavelength and a similar intensity to the instruments analyzed by Neira and Jackson.

## METHODS

### Participants

Seventy-seven individuals were evaluated for study suitability; all 77 qualified and were enrolled. Sixty-seven of the qualified and enrolled subjects attended the initial pre-treatment phase and completed study participation through the study endpoint.

All subjects deemed eligible for participation in this clinical study satisfied each of the following inclusion criteria: subject is candidate for liposuction of the waist, hips and bilateral thighs; willing and able to abstain from partaking in any treatment other than the study procedure to promote body contouring and/or weight loss throughout the course of study; willing and able to maintain regular diet and exercise regimen without effecting significant change in either direction during study participation; and were between the ages of 18–65 years.

Subjects had none of the following exclusionary conditions: body mass index (BMI) of 30 kg/m<sup>2</sup> or greater; diabetes mellitus dependent on insulin or oral hypoglycemic medication; known cardiovascular disease such as cardiac arrhythmias and congestive heart failure; history of cardiac surgery such as coronary artery bypass, heart transplant surgery, and pacemakers; excessive alcohol consumption (more than 21 alcoholic drinks per week); prior surgical intervention for body sculpting/weight loss, such as liposuction, abdominoplasty, gastroplasty, lap band surgery, etc.; medical, physical, or other contraindications for body sculpting/weight loss; current use of medications known to affect weight levels and/or to cause bloating or swelling and for which abstinence during the course of study participation is not safe or medically prudent; medical condition known to affect weight levels and/or to cause bloating or swelling; diagnosis of, and/or taking medication for, irritable bowel syndrome; active infection, wound or other external trauma to the areas to be treated with the laser; pregnant, breast feeding, or planning pregnancy prior to the end of study participation; serious mental health illness such as dementia or schizophrenia; psychiatric hospitalization in past 2 years; developmental disability or cognitive impairment that would preclude adequate comprehension of the informed consent form and/or ability to record the necessary study measurements; involvement in litigation and/or a worker's compensation claim and/or receiving disability benefits related to weight-related and/or body shape issues; and participation in a clinical study or other type of research in the past 90 days.

All subjects were recruited from the assessment investigators' patient base: who presented for liposuction

consultation, signed the informed consent form, and satisfied all of the study eligibility criteria. Subjects were not offered any form of compensation to participate in the clinical trial, nor were they charged for the cost of the laser procedure or related evaluations.

### Randomization and Blinding

The clinical study was a prospective, controlled double-blind parallel group three-center design. Sixty-seven participating subjects, 35 were randomized to the active treatment group and 32 were randomized to the sham-treatment group. Subject randomization was performed by a third party and was computer generated.

### Intervention

Subjects assigned to the test group were treated with a multiple head low-level diode laser consisting of five independent diode laser heads each with a scanner, each emitting 635 nm (red) laser light with each diode generating 17 mW output (The Erchonia® LipoLaser, manufactured by Erchonia Medical, Inc.). Sham-treatment group participants were treated with a multiple head non-laser red light-emitting diode (LED) consisting of five independent red diode light heads each with a scanner, each emitting 635 nm (red) light with each diode generating 2.5 mW power. Both the sham treatment light and real laser devices were designed to have the same physical appearances, including the appearance of any visible light output.

### Study Design

The circumference in inches (in.) of the subject's waist, hip, and each of the left and right thighs were measured and recorded across all time points. The hip circumference measurement was made such that both hip bones were encircled. The waist circumference measurement was the distance in inches from the top of the hip bone to the point at which the circumference of the waist was measured (the subject's natural waist formation). Finally, bilateral thigh circumference was the distance in inches from the hip bone down the point at which the circumference of the thighs were measured. Furthermore, the same individual at each test site was responsible for all circumference measurement recordings for all subjects at that test site to preserve study consistency removing the potential of inter-investigatory variability.

The circumference in inches for participant's waist, hips, and each of the left and right thighs along with their BMI's were measured at four different times: pre-procedure; end of first procedure week; end of second procedure week; and 2 weeks post-procedure.

The treatment phase of the study commenced immediately following the pre-procedure circumference measurements. The treatment phase extended over two consecutive weeks, with each subject receiving six total treatments with the laser or sham light scanning device across the consecutive 2 weeks; three procedures per week, each treatment two days apart. Each procedure took place at the investigators' test sites.

The procedure protocol required that subjects entered the procedure room and were placed in a comfortable supine position upon the treatment table. Subjects were fitted with blindfolds. The center diode of the laser or sham light scanning device was positioned at a distance of 6.00 in. above the participant's abdomen, centered along the body's midline and focused on the navel. The four remaining diodes were positioned 120° apart and tilted 30° off the center light source of the center diode. The scanner device was activated for 20 minutes.

Following anterior stimulation, the participant was then placed in a prone position upon the treatment table. The center diode of the laser scanner was positioned at a distance of 6.00 in. above the subject's back, centered along the body's midline and focused on the equivalent spot to the navel's location on the stomach. The four remaining diodes were positioned 120° apart and tilted 30° off the center light source of the center diode. The scanner device was activated for 20 minutes. The total laser energy that the subjects randomized to actual laser treatment received, front and back treatments combined, was approximately 6.60 J/cm<sup>2</sup>.

### Data Analysis

The primary efficacy outcome measure was defined as the change in total combined inches in circumference measurements (waist, hips, and bilateral thighs) from baseline (pre-procedure) to following completion of the 2-week procedure administration phase (end of week 2).

Individual subject success criteria was defined as at least 3.0 in. reduction in combined circumference measurements for the waist, hip, and bilateral thighs from baseline to after completion of the 2-week study procedure administration protocol phase. The overall study success criterion, established by Food and Drug Administration (FDA), was defined as at least a 35% difference between treatment groups, comparing the proportion of individual successes in each group. It was determined by the FDA that a reduction of at least 3.0 in. was clinically meaningful. In addition to the analysis of circumferential reduction as a means to determine a clinically meaningful outcome, participants were asked to assess their level of satisfaction pertaining to their overall change in body shape at the completion of the treatment administration phase. Patients were asked to record a rating on a 5-point scale of very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, not very satisfied, not at all satisfied.

Data were analyzed according to the intention-to-treat principle, including all subjects who had been randomized to treatment groups were included provided they had circumference measurements recorded at baseline. Drop-outs, terminated subjects, and so forth were included by carrying forward the last observation for all time points following Last Observation Carried Forward (LOCF) method. Eight of the 67 subjects did not have circumference measurements recorded at the 2 week post-procedure measurement point: 4 of these subjects who had been randomized to the test group and 4 of these subjects who had been randomized to the sham-treatment group. For these eight subjects, the (LOCF) method was employed,



**TABLE 1. Pre-Procedure Body Mass Index Measurements for Treatment Groups ( $n = 67$ )**

BMI (kg/m <sup>2</sup> )	Test group ( $n = 35$ )	Control group ( $n = 32$ )	Difference
Mean	25.74	26.05	0.31

BMI, body mass index.

such that the subject's week 2 circumference measurement was carried forward as the 2 weeks post-procedure measurement.

## RESULTS

At baseline, the differences in subject pre-procedure BMI recordings between experimental groups were not found to be statistically significant ( $t = -0.48$ ;  $df = 64$ ;  $P = 0.647$  [ $P > 0.05$ ]) (Table 1). Moreover, the differences in subject pre-procedure body circumference measurements between treatment groups were not found to be statistically significant for any body area or for the total number of inches of all body areas combined ( $t = -1.18$ ;  $df = 65$ ;  $P = 0.240$  [ $P > 0.05$ ]) (Table 2).

Of the 32 sham light treated group participants, 6.38% (2 subjects), demonstrated a total decrease in combined circumference measurements from pre-procedure to study endpoint of  $-3.0$  in. or greater, while 22 (62.9%) of the 35 enrolled test group participants demonstrated a reduction of  $-3.0$  in. or greater, a significant difference between both groups ( $P < 0.0001$ ).

Fifty-seven percent more test group participants than sham light treated group participants showed a total decrease in combined circumference measurements from pre-procedure to study endpoint of  $3.0$  in. or greater (Table 3). This outcome exceeded the pre-established target of 35% difference between treatment groups by 22%.

Comparison of the two independent group means for the continuous variable of mean change in total combined circumference (total number of inches) from study baseline to endpoint demonstrated a mean difference of  $-2.837$  (Table 4). The difference was found to be statistically significant ( $t = -7.30$ ;  $df = 65$ ;  $P < 0.0001$ ).

Compared with baseline, the total combined circumference measurements for test subjects were significantly

**TABLE 2. Pre-Procedure Circumference Measurements Between Treatment Groups ( $n = 67$ )**

Mean circumference (in.)	Test group ( $n = 35$ )	Control group ( $n = 32$ )	<i>P</i> -value
Waist	33.94	34.95	$> 0.05$
Hip	38.99	39.88	$> 0.05$
Right thigh	23.80	24.12	$> 0.05$
Left thigh	23.59	24.14	$> 0.05$
Total	120.31	122.99	$> 0.05$

In., inches.

**TABLE 3. The Total Number and Percentage of Treatment Group Participants Meeting the Individual Success Criteria ( $n = 67$ )**

	Test subjects ( $n = 35$ )	Control subjects ( $n = 32$ )
Number of participants meeting success criteria	22	2
% Meeting success criteria	62.86%	6.25%

lower at all three subsequent evaluation points:  $-2.06$  in. at week 1 ( $P < 0.01$ ),  $-3.52$  in. at week 2 ( $P < 0.01$ ), and  $-3.21$  in. at 2 weeks post-procedure ( $P < 0.01$ ). Sham light treated group subjects from baseline to 2 weeks post-procedure produced an overall reduction in total combined circumference measurements of  $-0.62$  in. ( $P > 0.05$ ). Moreover, sham light treated group participants compared with baseline demonstrated statistically insignificant changes in total combined circumference measurements across all three subsequent evaluation points ( $P > 0.05$ ) (Fig. 1).

Test group participants from week 2 to 2 weeks post-procedure revealed an overall gain in total circumference measurements of  $+0.30$  in., which was not statistically significant ( $P > 0.05$ ).

Compared with baseline, the changes in total circumference measurements between groups were statistically significant at all three subsequent evaluation points:  $-1.794$  in. at week 1 ( $t = -3.83$ ;  $df = 65$ ;  $P = 0.00029$  [ $P < 0.0005$ ]),  $-2.838$  in. at week 2 ( $t = -7.30$ ;  $df = 65$ ;  $P < 0.0001$ ), and  $-2.593$  in. at 2 weeks post-procedure ( $t = -6.66$ ;  $df = 65$ ;  $P < 0.0001$ ) (Table 5).

Participants in the test group demonstrated an overall reduction in circumference of  $-0.98$  in. across the waist from baseline to week 2 ( $P < 0.0001$ ). Compared with baseline, circumference measurements of the waist were significantly lower at all three subsequent evaluation points:  $-0.56$  in. at week 1 ( $P < 0.01$ ),  $-0.98$  in. at week 2 ( $P < 0.0001$ ), and  $-1.08$  in. at 2 weeks post-procedure ( $P < 0.001$ ). Subjects assigned to the sham light treated group revealed insignificant changes in waist circumference measurements across all evaluation points ( $P > 0.05$ ) (Fig. 2).

For test group participants, compared with baseline, circumference measurements for the hip were significantly lower at all three subsequent evaluation points:  $-0.73$  in.

**TABLE 4. Mean Change in Total Combined Circumference Measurements From Baseline to Endpoint for Treatment Groups ( $n = 67$ )**

	Test group ( $n = 35$ )	Control group ( $n = 32$ )
Mean reduction in total circumference (in.)	$-3.521$	$-0.684$

In., inches.

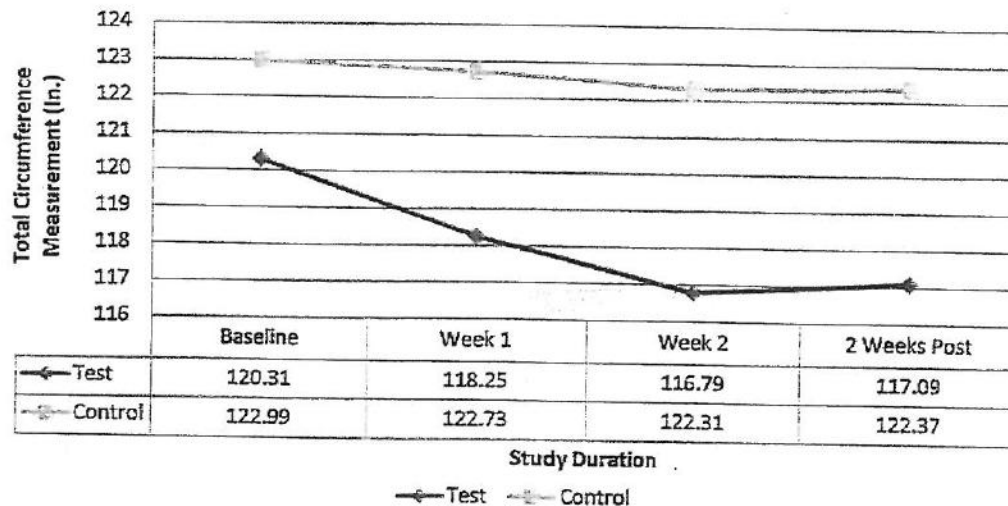


Fig. 1. Total circumference measurements across study duration for all participants ( $n = 67$ ).

at week 1 ( $P < 0.01$ ),  $-1.05$  in. at week 2 ( $P < 0.01$ ), and  $-0.70$  in. at 2 weeks post-procedure ( $P < 0.01$ ). Sham light treated group participants demonstrated insignificant changes in hip circumference measurement across all evaluation points ( $P > 0.05$ ) (Fig. 3).

Compared with baseline, circumference measurements of the right thigh for test subjects were significantly lower at all three subsequent evaluation points:  $-0.49$  in. at week 1 ( $P < 0.01$ ),  $-0.85$  in. at week 2 ( $P < 0.01$ ), and  $-0.78$  in. at 2 weeks post-procedure ( $P < 0.01$ ). Participants of the sham light treated group revealed insignificant changes in right thigh circumference measurements across all measurement points ( $P > 0.05$ ) (Fig. 4).

Compared with baseline, circumference measurements of the left thigh for test subjects were significantly lower at all three subsequent evaluation points:  $-0.29$  in. at week 1 ( $P < 0.05$ ),  $-0.65$  in. at week 2 ( $P < 0.01$ ), and  $-0.67$  in. at 2 weeks post-procedure ( $P < 0.01$ ). For subjects assigned to the sham light treated group, the changes in left thigh circumference measurement across all measurement points were not statistically significant for any interval ( $P > 0.05$ ) (Fig. 5).

Of the total 67 study participants, 61 responded to the satisfaction survey. Thirty of the 35 test subjects and 31 of the 32 sham light treated subjects assessed their satisfac-

tion level subsequent to the treatment administration phase. Twenty-one test group participants (70%) and eight sham light group participants (26%) recorded a "satisfied" rating. (Fig. 6) Moreover, 1 test group participant and 11 control group participants recorded a "dissatisfied" rating (Fig. 6). The difference of the rating score between the two treatment groups was found to be statistically significant ( $P < 0.0005$ ).

## DISCUSSION

In this double-blind, controlled, randomized trial, we observed that low-level laser of the appropriate wavelength applied three times per week for 2 weeks can significantly reduce the circumference at specifically targeted tissue sites due to reduction in the adipose layer. To fully appreciate these results, further scientific exploration is required to gain a better understanding of the role the lymphatic and circulatory systems may play in the absorption of the released triglycerides, fatty acids, and other adipocyte stored material evacuated following the laser induced formation of the transitory pore. Further, a study must be conducted to assess the long-term maintenance of the circumferential loss. A non-randomized, non-controlled study assessing the alteration of serum triglyceride and cholesterol levels using the same

TABLE 5. The Difference in Change in Total Circumference Measurements Between Evaluation Time Points Between Treatment Groups ( $n = 67$ )

Mean reduction (in.)	Test group ( $n = 35$ )	Control group ( $n = 32$ )	Difference between groups
Baseline—week 1	-2.06	-0.27	-1.794
Baseline—week 2	-3.52	-0.68	-2.838
Baseline—2 weeks post	-3.21	-0.62	-2.953
Week 1—week 2	-1.46	-0.42	-1.044
Week 1—2 weeks post	-1.15	-0.36	-0.799
Week 2—week 4	+0.31	+0.06	+0.245

In., inches.

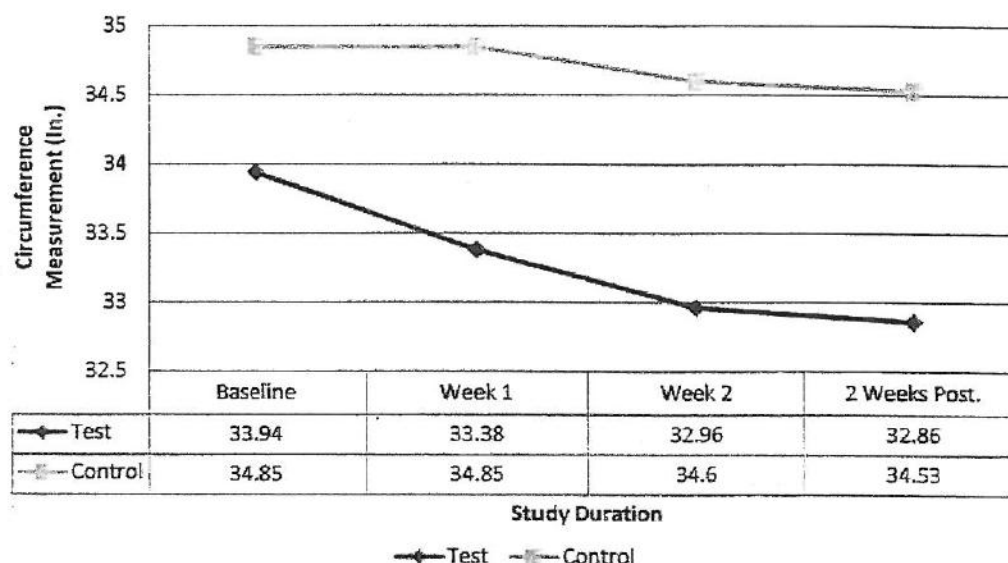


Fig. 2. Circumference measurements of the waist at each evaluation point for all participants ( $n = 67$ ).

treatment parameters as used in this study was recently completed, the study will be published with preliminary results revealing an overall reduction in both triglyceride and total cholesterol levels following 2 weeks of laser therapy [26]. Further, no adverse events were reported in this clinical investigation. Punch biopsies were not performed during this clinical investigation as the mechanism of adipose tissue reduction has been previously demonstrated in the literature by Neira's work which provided compelling evidence that the application of laser therapy at 635 nm with output intensity between 7 and 20 mW consistently induces the formation of a transitory pore within the membrane of adipocytes provoking their collapse.

This ability to modulate cellular metabolism and provoke diverse biologic responses is strongly dependent on the intensity, wavelength, and frequency of light being emitted. Moreover, the very same biological response induced by a specific wavelength can be further optimized or inhibited depending whether the radiation characteristic is pulsatile or constant wave (CW) [27]. The parameters of laser light are important in the emulsification of adipocytes. Dr. Neira [20] noted that greater intensities of laser light did not achieve the same biological response that lower energy output devices did. Across multiple laser applications, studies indicate a greater induction of cellular modulation is readily attained utilizing low-energy laser devices [18,28].

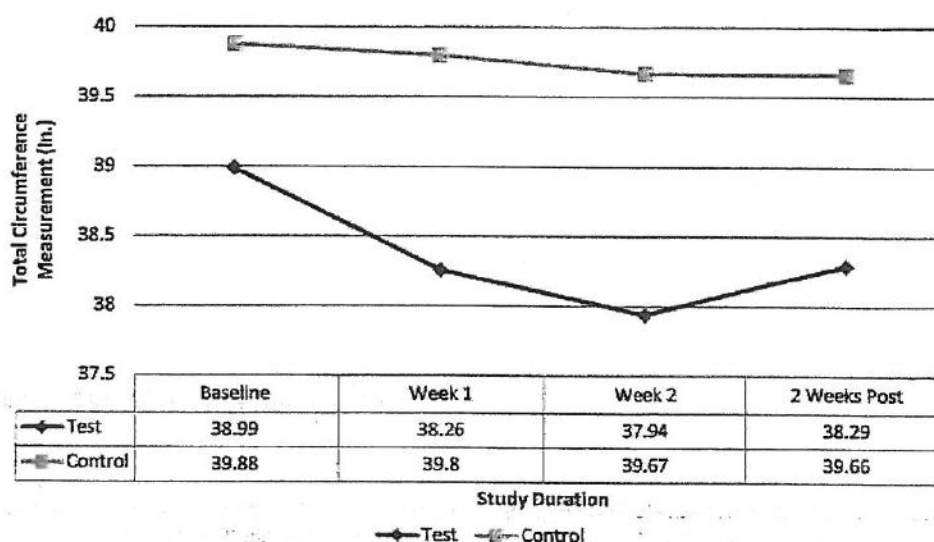


Fig. 3. Circumference measurements of the hip at each evaluation point for all participants ( $n = 67$ ).

the positive motivation of rapid circumferential reduction should be performed. Although a concerted effort must exist amongst multiple medical practitioners to properly educate the patient on the importance of healthy choices, non-invasive body-contouring tools like LLLT, may play a vital role in encouraging patients to adhere to new lifestyle changes.

## ACKNOWLEDGMENTS

Mr. Maloney had full access to the clinical data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; however, Mr. Maloney was not at any time involved in the collection and analysis of data. Mr. Maloney was provided the full clinical data from an independent regulatory firm. Mr. Maloney takes responsibility that the data provided to him from the independent regulatory firm was not altered, manipulated, or changed in any way. Ryan Maloney is the Medical Director for Erchonia Medical, Inc., the sponsor and provider of the low-level laser device utilized in the clinical study. Mr. Maloney had no contact with the study participants, clinical investigators, or the independent regulatory firm responsible for processing and analyzing the clinical data. Mr. Maloney is a paid consultant for Erchonia Medical, Inc., and shares the patent with Erchonia for the test device utilized in the study. Statistical analysis of all collected clinical data was performed by an independent regulatory consulting firm, Regulatory Insight, Inc. Elvira Walls, MS, was the independent statistician for this clinical investigation. Elvira Walls was compensated for her time. At no time did she communicate with any of the participants of the clinical trial or with Ryan Maloney. Elvira Walls had full access to the clinical data and takes responsibility for the integrity of the data and the accuracy of the data analysis. The sponsor of the clinical trial, Erchonia Medical, Inc., was the manufacturer of the device used in the clinical trial. The role of the sponsor was simply to provide the real treatment device and the placebo device. No patients or investigators were provided funding for their participation in this clinical investigation. No employed member of Erchonia Medical, Inc., was involved in the recruitment or the clinical investigator process. Dr. Robert Jackson, MD, was the primary clinical investigator. Dr. Robert Jackson was involved in the assessment phase of the clinical trial. Dr. Jackson was not aware of patient group assignments nor during any part of the clinical trial was he made aware of a patient's group assignment. Dr. Jackson was not provided any compensation for his participation in the clinical trial. Dr. Jackson was not involved in the writing of this manuscript; he however did read and edit this piece. Dr. Greg Roche served as an investigator for this study and was directly involved in the assessment phase of the clinical trial. Dr. Roche was not aware of patient group assignments nor during any part of the clinical trial was he made aware of a patient's group assignment. Dr. Roche was not provided any compensation for his participation in the clinical trial. Dr. Roche was not involved in the writing of

this manuscript; he however did read and edit this piece. The same applies for Dr. Dedo, he served as an investigator and was involved in the assessment phase of the clinical trial.

## REFERENCES

1. Wanner M, Avram M, Gagnon D, Mihm MC, Zurakowski D, Watanabe K, Tannous Z, Anderson RR, Manstein D. Effects of non-invasive, 1,210 nm laser exposure on adipose tissue: Results of a human pilot study. *Lasers Surg Med* 2009; 41(6):401-407.
2. Kim KH, Geronemus RG. Laser lipolysis using a novel 1,064 nm Nd:YAG laser. *Dermatol Surg* 2006;32:241-248.
3. O'Dey DM, Prescher A, Poprawe R, Gaus S, Stanzel S, Pallua N. Ablative targeting of fatty-tissue using a high powered diode laser. *Lasers Surg Med* 2008;40:100-105.
4. Moreno-Moraga J, Valero-Altes T, Martinez-Riquelme A, Isarria-Marcosy MI, De La Torre JR. Body contouring by noninvasive transdermal focused ultrasound. *Lasers Surg Med* 2007;39:315-323.
5. Narins RS, Tope WD, Pope K, Ross EV. Overtreatment effects associated with radiofrequency tissue tightening device: Rare, preventable, and correctable with subcision and autologous fat transfer. *Dermatol Surg* 2006;32:115-124.
6. Stonecipher KG, Kezirian GM. Wavefront-optimized versus wavefront-guided LASIK for myopic astigmatism with the ALLEGRETTO WAVE: Three-month results of a prospective FDA trial. *J Refract Surg* 2008;24(4):S424-S430.
7. Zins JE, Alghoul M, Gonzalez AM, Strumbe P. Self-reported outcome after diode laser hair removal. *Ann Plast Surg* 2008;60(3):233-238.
8. Katz B, McBean J. The new laser liposuction for men. *Dermatol Ther* 2007;20(6):448-451.
9. Zouari L, Bousson V, Hamze B, Roulot E, Roqueplan F, Laredo JD. CT-guided percutaneous laser photocoagulation of osteoid osteomas of the hands and feet. *Eur Radiol* 2008; May 24.
10. Posten W, Wrona DA, Dover JS, Arndt KA, Silapunt S, Alam M. Low-level laser therapy for wound healing: Mechanism and efficacy. *Dermatol Surg* 2005;31(3):334-340.
11. Carnevali CM, Soares CP, Zangaro RA, Pinheiro ALB, Silva NS. Laser light prevents apoptosis on Cho K-1 cells line. *J Clin Laser Med Surg* 2003;21:193-196.
12. Siposan DG, Lukacs A. Relative variation of the received dose of some erythrocyte and leukocyte indices of human blood as a result of low-level laser irradiation: An in vitro study. *J Clin Laser Med Surg* 2001;19:89-103.
13. Cohen N, Lubart R, Rubinstein S, Breitbart H. Light irradiation of mouse spermatozoa stimulation of in vitro fertilization and calcium signals. *Photochem Photobiol* 1998; 68:407-413.
14. Ben-Dov N, Schefer G, Irintchev A, Wernig A, Oron U, Halevy O. Low-energy laser irradiation affects satellite cell proliferation and differentiation in vitro. *Biochem Biophys* 1999;144:372-380.
15. Shefer G, Oron U, Irintchev A, Wernig A, Halevy O. Skeletal muscle cell activation by low-energy laser irradiation: A role for the MAPK/ERK pathway. *J Cell Physiol* 2001;187:73-80.
16. Shefer G, Barash I, Oron U, Halevy O. Low-energy laser irradiation enhances de novo protein synthesis via its effects on translation-regulatory proteins in skeletal muscle myoblasts. *Biochem Biophys* 2003;159:131-139.
17. Streeter JD, Taboada L, Oron U. Mechanisms of action of light therapy for stroke and acute myocardial infarction. *Mitochondrion* 2004;4:569-576.
18. Tafur J, Mills PJ. Low-intensity light therapy: Exploring the role of redox mechanisms. *Photomed Laser Surg* 2008; 26(4):323-328.
19. Neira R, Solarte E, Isaza C, et al. Effects of the electric laser diode beam on in vitro human adipose tissue culture. *Congreso Bolivariano de Cirugía Plástica Reconstructiva* 2001.



20. Neira R, Arroyave, Ramirez H, et al. Fat liquefaction: Effect of low-level laser energy on adipose tissue. *Plast Reconstr Surg* 2002;110:912-922.
21. Neira R, Arroyave J, Solarte E, et al. In vitro culture of adipose cells after irradiating them with a low-level laser device. *Congreso Bolivariano de Cirugia Plastica Reconstructiva* 2001.
22. Neira R, Jackson R, Dedo D, Ortiz CL, Arroyave A. Low-level-laser assisted lipoplasty: Appearance of fat demonstrated by MRI on abdominal tissue. *Am J Cosmet Surg* 2001;18(3):133-140.
23. Rochkind S, Rousso M, Nissan M, Villarreal M, Barr-Nea L, Rees DG. System effects of low-power laser irradiation on the peripheral and central nervous system, cutaneous wounds, and burns. *Lasers Surg Med* 1989;9(2):174-182.
24. Schindl A, Heinze G, Schindl M, Pernerstorfer-Schon H, Schindl L. Systemic effects of low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvasc Res* 2002;64:240-246.
25. Jackson R, Roche G, Butterwick KJ, Dedo DD, Slaterry K. Low-level laser-assisted liposuction: A 2004 clinical trial of its effectiveness for enhancing ease of liposuction procedures and facilitating the recovery process for patients undergoing thigh, hip, and stomach contouring. *Am J Cosmet Surg* 2004;21(4):191-198.
26. Maloney R, Shanks S, Jenney E. The reduction in cholesterol and triglyceride serum levels following low-level laser irradiation: A non-controlled, non-randomized pilot study. *Laser Surg Med* 2009;21S:66.
27. Karu T. *Ten lectures on basic science of laser phototherapy*. Grangesberg, Sweden: Prima Books AB; 2007.
28. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg* 2005;23(1):3-9.
29. Tsukihara T, Aoyama H, Yamashita E, Tomizaki T, Yamaguchi H, Shinzawa-Itou K, Nakashima R, Yaono R, Yoshikawa S. Structures of metal sites of oxidized bovine heart cytochrome c oxidase at 2.8 Å. *Science* 1995;269:1069-1074.
30. Tsukihara T, Aoyama H, Yamashita E, Tomizaki T, Yamaguchi H, Shinzawa-Itou K, Nakashima R, Yaono R, Yoshikawa S. The whole structure of the 13-subunit oxidized cytochrome c oxidase at 2.8 Å. *Science* 1996;272:1136-1144.
31. Iwata S, Ostermeier C, Ludwig B, Michel H. Structure of 2.8 Å resolution of cytochrome c oxidase from *Paracoccus denitrificans*. *Nature* 1995;376:660-669.
32. Karu TI, Afanasyeva NI. Cytochrome oxidase as primary photoacceptor for cultured cells in visible and near IR regions. *Doklady Akad. Nauk (Moscow)* 1995;342:693-695.
33. Alexandratou E, Yova D, Handris P, Kletsas D, Loukas S. Human fibroblast alterations induced by low power laser irradiation at the single cell level using confocal microscopy. *Photochem Photobiol Sci* 2002;1:547-552.
34. Terenin AN. Photochemistry of dyes and other organic compounds. Moscow, Leningrad. Acad Sci Publ 1947.
35. Marcus RA, Sutin N. Electron transfer in chemistry and biology. *Biochem Biophys* 1985;81:265-322.
36. Konev SV, Beljanovich LM, Rudenok AN. Photoreactivations of the cytochrome oxidase complex with cyanide: The reaction of heme a3 photoreduction. *Membr Cell Biol (Moscow)* 1998;12:743-754.
37. Byrnes KR, Wu X, Waynant RW, Ilev IK, Anders JJ. Low power laser irradiation alters gene expression of olfactory ensheathing cells in vitro. *Lasers Surg Med* 2005;37:161-171.
38. Snyder SK, Byrnes KR, Borke RC, Sanchez A, Anders JJ. Quantification of calcitonin gene-related peptide mRNA and neuronal cell death in facial motor nuclei following axotomy and 633 nm low power laser treatment. *Lasers Surg Med* 2002;31:216-222.
39. Bradley C, Bradley KN, Disimone G, Reinisch L, Davidson JM. Low energy helium-neon laser irradiation and the tensile strength of incisional wounds in the rat. *Wound Rep Reg* 1995;3:512-517.
40. Allendrof JDF, Bessler M, Huang J, Kayton ML, Laird D, Nowygrod R, Treat MR. Helium-neon laser irradiation at fluences of 1, 2 and 4 J/cm<sup>2</sup> failed to accelerate wound healing as assessed by both wound contracture rate and tensile strength. *Lasers Surg Med* 1997;20:340-345.
41. Lowe AS, Walker MD, O'Byrne M, Baxter GD, Hirst DG. Effect of low intensity monochromatic light therapy (890 nm) on a radiation impaired, wound-healing model in murine skin. *Lasers Surg Med* 1998;23:291-298.
42. Walker MD, Rumpf S, Baxter GD, Hirst DG, Lowe AS. Effect of low-intensity laser irradiation (660 nm) on a radiation-impaired wound-healing model in murine skin. *Lasers Surg Med* 2000;26:41-47.
43. Lubart R, Wollman Y, Friedman H, Rochkind S, Laulicht I. Effects of visible and near-infrared lasers on cell culture. *J Photochem Photobiol* 1992;12:305-310.
44. Moore P, Ridgway TD, Higbee RG, Howard EW, Lucroy MD. Effect of wavelength on low-intensity laser irradiation-stimulated cell proliferation in vitro. *Lasers Surg Med* 2005;36:8-12.
45. Alexandratou E, Yova D, Handris P, Kletsas D, Loukas S. Human fibroblasts alterations induced by low power laser irradiation at the single cell level using confocal microscopy. *Photochem Photobiol Sci* 2002;1:547-552.
46. Grossman N, Schneid N, Reuveni H, Halevy S, Lubart R. 780 nm low power diode laser irradiation stimulates proliferation of keratinocyte cultures: Involvement of reactive oxygen species. *Lasers Surg Med* 1998;22:212-218.
47. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg* 2005;1:3-9.
48. Lin Y, Berg AH, Iyengar P, Lam TKT, Giacca A, Combs TP, Rajala MW, Du X, Rollman B, Li W, Hawkins M, Barzilai N, Rhodes CJ, Fantus IG, Brownlee M, Scherer PE. The hyperglycemia-induced inflammatory response in adipocytes: The role of reactive oxygen species. *J Biol Chem* 2005;280:4617-4626.
49. Lubart R, Friedman H, Levinshal T, Lavie R, Breitbart H. Effect of light on calcium transport in bull sperm cells. *J. Photochem Photobiol* 1992;15:337-341.
50. Tong M, Liu YF, Zhao XN, Yan CZ, Hu ZR, Zhang ZH. Effects of different wavelengths of low level laser irradiation on murine immunological activity and intracellular Ca<sup>2+</sup> in human lymphocytes and cultured cortical neuroglialocytes. *Lasers Med Sci* 2000;15:201-206.
51. Gordon SA, Surrey K. Red and far-red action on oxidative phosphorylation. *Radiat Res* 1960;12:325-339.
52. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, Cingolani A. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 1984;175:95-99.
53. Geiger PG, Korytowski W, Lin F, Girotti AW. Lipid peroxidation in photodynamically stressed mammalian cells: Use of cholesterol hydroperoxides as mechanistic reporter. *Free Radic Biol Med* 1997;23(1):57-68.
54. Klebanov GI, Chichuk TV, Osipov AN, Vladimirov YA. The role of lipid peroxidation products in the effect of He-Ne laser on human blood leukocytes. *Biofizika* 2005;50:862-866.
55. Vladimirov IuA, Klebanov GI, Borisenko GG, Osipov AN. Molecular and cellular mechanisms of the low intensity laser radiation effect. *Biofizika* 2004;49(2):339-350.
56. Geiger PG, Korytowski W, Girotti AW. Photodynamically generated 3-beta-hydroxy-5 alpha-cholesterol-6-ene-5-hydroperoxide: Toxic reactivity in membranes and susceptibility to enzymatic detoxification. *Photochem Photobiol* 1995;62:580-587.
57. Gius D, Botero A, Shah A, Curry HA. Intracellular oxidation/reduction status in the regulation of transcription factors NF- $\kappa$ B and AP-1. *Toxicol Lett* 1999;106:93-106.
58. Sun Y, Oberley LW. Redox regulation of transcriptional activators. *Free Radic Biol Med* 1996;21:335-348.
59. Calkhoven CF, Ab G. Multiple steps in the regulation of transcription factor level and activity. *Biochem J* 1996;317:329-342.
60. Haddad JJ. Oxygen-sensing mechanisms and the regulation of redox-responsive transcription factors in development and pathophysiology. *Respir Res* 2002;3:26-53.



61. Zhang Q, Piston DW, Goodman RH. Regulation of corepressor function by nuclear NADH. *Science* 2002;295:1895-1897.
62. Karu TI, Kalendo GS, Letokhov VS, Lobko VV. Dependence of biological action of low-intensity visible light upon HeLa cells on irradiation parameters: Coherence, dose, wavelength, and irradiation mode. *Sov J Quantum Electron* 1982;12:1134-1138.
63. Sazonov AM, Romanov GA, Portnoi LM, Odinkova VA, Karu TI, Lobko VV, Letokhov VS. Low intensity noncoherent red light in the complex treatment of peptic ulcers. *Sov Med* 1985;12:42-45.
64. Karu TI, Kalendo GS, Letokhov VS, Lobko VV. Biostimulation of HeLa cells by low intensity visible light. Stimulation of DNA and RNA synthesis in a wide spectral range. *Nuovo Cimento* 1984;3:309-318.



## A Double-Blind, Placebo-Controlled Randomized Trial Evaluating the Ability of Low-Level Laser Therapy to Improve the Appearance of Cellulite

Robert F. Jackson, MD,<sup>1</sup> Gregory C. Roche, DC,<sup>2</sup> and Steven C. Shanks<sup>3\*</sup>

<sup>1</sup>Surgeon's, Inc., Marion, Indiana 46952

<sup>2</sup>Bloomfield Laser and Cosmetic Surgery Center, Bloomfield Hills, Michigan 48302

<sup>3</sup>Erchonia Corporation, McKinney, Texas

**Background and Objective:** Cellulite is present in 90% of post-adolescent women. Several technologies have been developed for treating cellulite; however, they all involve some degree of massage or mechanical manipulation. The purpose of this study was to assess the effectiveness of a low-level laser light device employing green 532 nm diodes as a stand-alone procedure without massage or mechanical manipulation for improving the appearance of cellulite in the thighs and buttocks.

**Study Design/Materials and Methods:** This double-blind study randomized subjects to undergo treatment with the LLLT device ( $N = 34$ ) or sham treatment ( $N = 34$ ). During a 2-week treatment phase, each subject received three weekly treatment sessions 2–3 days apart. During each session, the front and back of the hips, thighs, and waist were exposed for 15 minutes (30 minutes total).

**Results:** Nineteen subjects in the LLLT group achieved a decrease of one or more stages on the Nurnberger–Muller grading scale (55.88%) versus three subjects (8.82%) in the sham-treated group ( $P < 0.0001$ ). Two LLLT-treated subjects achieved 2-stage improvements on the Nurnberger–Muller Scale at the 2-week study endpoint and four did at the 6-week follow-up evaluation versus none of the sham-treated subjects at either time point. Subjects treated with LLLT achieved a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation (for each,  $p < 0.0001$  vs. baseline) versus no change for sham-treated subjects. LLLT-treated subjects also showed significant decreases in mean baseline body weight ( $P < 0.0005$ ), BMI ( $P < 0.001$ ), and percent BSA affected by cellulite ( $P < 0.0005$ ) versus no change for any parameter among sham-treated subjects. Most LLLT-treated subjects (62.1%) were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received versus 25.8% of sham-treated subjects. There were no reports of adverse events.

**Conclusions:** Low-level laser therapy using green 532 nm diodes is safe and effective for improving the

appearance of cellulite in the thighs and buttocks. In contrast with other technologies, LLLT is effective as a stand-alone procedure without requiring massage or mechanical manipulation. Future studies will assess the long-term benefits of LLLT for the treatment of cellulite. *Lasers Surg. Med.* 45:141–147, 2013.

© 2013 Wiley Periodicals, Inc.

**Key words:** 532 nm wavelength; aesthetic therapy; green diode; gynoid lipodystrophy; noninvasive therapy

### INTRODUCTION

Gynoid lipodystrophy, or cellulite, refers to superficial pockets of trapped fat which causes the skin to have an uneven dimpling or “orange peel” appearance. Although rarely seen in men, it is present in 90% of post-adolescent women [1]. Cellulite is most commonly located on the thighs, buttocks, and lower abdomen but is unrelated to obesity which is due to an increase in the number and size of adipocytes.

The cause of cellulite appears to be multifactorial and not universally agreed upon, but is likely due to alterations in the intercellular matrix of subcutaneous tissue and changes in vascular and lymphatic microcirculation

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: [Steven Shanks is owner of the company that manufactures the Erchonia laser used in this study. He also holds patents on the laser and patent pending application for the procedure. Mr. Shanks collaborated with a regulatory consultant during the design of the treatment protocol used in the study; however, at no time did Mr. Shanks have access to the clinical data until the study was completed or have any contact with the patients enrolled in the study].

ClinicalTrials.gov Identifier: NCT01702259.  
\*Corresponding to: Steven C. Shanks, Erchonia Corporation, 2021 Commerce Drive, McKinney, TX 75069.  
E-mail: ssshanks@erchonia.com

Accepted 14 January 2013  
Published online in Wiley Online Library  
(wileyonlinelibrary.com).  
DOI 10.1002/lsm.22119



[2]. The formation of cellulite is also due to differences in the structural anatomy of subcutaneous tissue in women with a possible influence of estrogen [2,3]. Regardless of the underlying cause, herniation of subcutaneous fat occurs within fibrous connective tissue results in the characteristic appearance of cellulite.

Cellulite does not represent a disease state and there is no cure for it; however, numerous treatments have been developed to improve the appearance of cellulite. Among individuals with poor venous return, vigorous massage may enhance the removal of interstitial fluid by increasing circulation and lymphatic drainage and also break down adhesions [1]. A device consisting of rollers purportedly reduces cellulite by improving venous return and stimulating lipolysis and the production of collagen and elastin [4,5].

Other noninvasive systems have been developed which combine massage or mechanical manipulation with various technologies including bipolar radiofrequency, ultrasound energy, laser or infrared light, and suction [6-13]. Clinical studies performed with all of these devices have reported varying degrees of improvement in the visual improvement in cellulite and skin texture. Numerous topical cosmeceuticals are also promoted as treatments for cellulite which contain caffeine or methylxanthines, retinoids, alpha hydroxy acids, or a variety of herbal extracts [1]. While a few of these report beneficial results [14,15], there is little clinical evidence that the majority of these products can improve the appearance of cellulite [16].

In contrast to noninvasive treatments, mesotherapy involves microinjections of various combinations of drugs, vitamins, and natural extracts into the mesoderm where they reportedly provide beneficial effects by causing lipolysis [17,18]. The safety and efficacy of this procedure have not been established through randomized, double-blinded controlled studies. Consequently, there are no FDA-approved mesotherapy preparations. The use of mesotherapy for the treatment of cellulite has been associated with toxicity and other adverse effects [19,20].

The purpose of this randomized, double-blind, sham-controlled study is to determine the effectiveness of a low-level laser light device employing green 532 nm diodes for improving the appearance of cellulite in the thighs and buttocks. Unlike other technologies, low-level laser therapy will be used as a stand-alone procedure without massage or mechanical manipulation.

## METHODS

### Study Subjects

The study enrolled healthy subjects who were 18-55 years of age and expressed a desire to improve the appearance of their cellulite. Study subjects were rated as 1 or 2 on the American Society of Anesthesiologists Physical Status Classification System and had moderate bilateral thigh and buttock cellulite graded as Stage II or III on the Nurnberger-Muller scale. Each subject expressed their willingness to abstain from participating in any treatment designed to improve cellulite appearance, promote weight loss or improve body contouring during the study

including but not limited to cellulite creams, lotions and gels; over-the-counter and prescription medications including dietary/herbal supplements/minerals and appetite suppressants; weight loss, diet, or exercise programs; light or heat treatments; mesotherapy; surgical procedures such as liposuction, abdominoplasty, stomach stapling, or lap bands; and alternative therapies such as acupuncture, body wraps, hypnotherapy, or massage. Each subject agreed to maintain their normal pre-study diet and exercise regimen.

Reasons for exclusion from the study included cellulite on their thighs or buttocks graded as Stage 0 or 1 on the Nurnberger-Muller scale; weight fluctuation >10 pounds during the prior month; prior attempts to reduce cellulite in the planned treatment areas during the previous 6 months; current use of any medication known to affect body weight or cause bloating or swelling which could not be safely discontinued during the study; a medical condition known to affect body weight levels or cause bloating or swelling; a history of irritable bowel syndrome; active infection, dermatitis, significant scarring, or trauma in the planned treatment areas; photosensitivity or contraindications to light therapy; diabetes mellitus requiring the use of insulin or oral hypoglycemic agents; cardiovascular disease or a history of cardiac surgery, deep venous thrombosis, or arterial disease of the legs; pregnancy, breast feeding, or planned pregnancy prior to the end of study; mental illness, developmental disability, or cognitive impairment that could prevent providing informed consent or jeopardize the study objectives; or participation in another clinical study during the prior 30 days.

### Low-Level Laser Device

The LLLT device used in this study (Erchonia® GL Scanner; Erchonia Corporation, McKinney, TX; GLS) is fundamentally the same as a LLLT device described in previous studies [21] but utilizes six 532-nm green diodes instead of five 635-nm red diodes (Fig. 1). Four mounted diodes in the scanner device are positioned 120° apart from one another and tilted at a 30° angle. The remaining two diodes are positioned 4" from the center and tilted at a 15° angle. Internal mechanics of the GLS collect the laser light emitted from each diode and processes it through a proprietary lens which redirects the beam with a line refractor. The refracted light of each diode is bent into a random, spiraling pattern that is independent of the other diodes. The overlapping patterns of light ensure total coverage of the treatment area. The target area is approximately 8" x 10" in. (80 in.<sup>2</sup> or approximately 516 cm<sup>2</sup>). Each diode has a mean power output of 17 mW and the total output of the six diodes is 102 mW.

The LLLT device used in the clinical trial could be activated with two buttons: based on the randomization schedule, the Investigator would push the button which activated the actual 17 mW, 532 nm laser or the button which activated a sham 1.25 mW, 532 nm green light-emitting diode (LED). When activated, the sham LED light is indistinguishable from green laser light. Subjects were provided with safety goggles during each procedure.

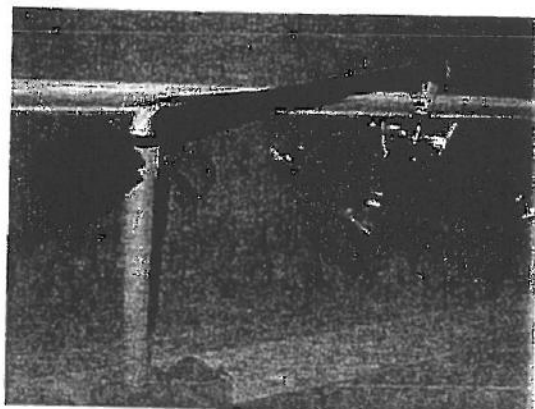


Fig. 1. The prototype LLLT device used in this study utilized six 532 nm green diodes. Each diode had a mean power output of 17 mW and the total output of the six diodes was 102 mW. Based on the randomized treatment for each patient, the Investigator pushed one button on the device which turned on the active 17 mW, 532 nm laser or the button which activated a sham 1.25 mW, 532 nm green light-emitting diode (LED). When activated, the sham LED light is indistinguishable from green laser light.

### Procedure

Using a computer-generated sequence methodology, subjects were randomized to undergo LLLT or sham treatment. During the 2-week treatment phase, each subject received three weekly treatment sessions at least 2 days but not more than 3 days apart. Lying on their back, each subject was comfortably positioned on the treatment table. The center diode of the GLS was positioned 4 in. above the abdomen, centered along the body midline and focused on the navel. The device was activated for 15 minutes. Afterward, the subject turned over onto their stomach and the GLS was again positioned 4 in. above the back, centered along the body midline and focused above the navel. The GLS was again activated for 15 minutes.

### Primary Outcome Measure

During pre-investigational device exemption (IDE) discussions, representatives of the Food and Drug Administration determined the primary efficacy outcome measure for this study should be the difference in the proportion of LLLT- and sham-treatment subjects achieving a bilateral decrease of one or more stages on the Nurnberger-Muller grading scale, a widely used tool for measuring cellulite [12,22]:

- Stage 0: No dimpling or apparent visible alterations to the skin surface upon standing or lying down or upon pinching the skin.
- Stage I: No dimpling or apparent visible alterations to the skin surface upon standing or lying down. Dimpling appears with the pinch test or muscular contraction.

- Stage II: Dimpling appears spontaneously when standing but not when not lying down. The orange peel appearance of the skin is evident to the naked eye, without need for manipulation.
- Stage III: Dimpling is spontaneously present when both standing and lying down, evident to the naked eye without need for manipulation. Orange peel skin surface appearance with raised areas and nodules.

In addition to classifying cellulite severity, the Nurnberger-Muller scale can be used to assess changes in severity following treatment intervention. Assessments using the Nurnberger-Muller scale were made at baseline, 2 weeks (following the last treatment session) and 6 weeks (4 weeks after the last treatment session).

### Other Assessments

Other pre- and post-treatment assessments included circumferential measurements of the right and left thigh, body mass index (BMI), and the body surface area (BSA) covered by cellulite [23,24]. Thigh circumference measurements were made while the subject stood erect with their weight evenly distributed on both feet with legs slightly parted. The circumference of each thigh was measured 1 cm below the gluteal line or fold (buttock crease). The pressure-sensitive tape measure recorded circumference to within 1 mm. All measurements were made by the blinded Investigator.

Other assessments included the presence and location of existing irregularities on the thighs and buttocks such as scars, asymmetries, stretch marks, discoloration; clinical features associated with cellulite including the severity of "orange peel," sub-cyanotic white spots, pain upon skin palpation, hypothermic skin, paresthesias, and telangiectasias; or seroma formation. Enrolled subjects were queried about any changes in routine OTC and prescription medication use or other therapies and diet and exercise regimens reported during baseline assessments.

At the completion of the Week 2 study procedures, each subject was asked to rate how satisfied they were with any overall change in the appearance of the cellulite in their thighs and buttocks areas using the following five-point scale:

- Very Satisfied
- Somewhat Satisfied
- Neither Satisfied nor Dissatisfied
- Not Very Satisfied
- Not at All Satisfied

### Safety

Safety assessments consisted of adverse events reported by subjects during the study and any adverse effect in the treatment area observed by the investigators.

### Statistical Analysis

The primary endpoint was the proportion of subjects achieving a decrease of  $\geq 1$  grades of the right and left

thigh and buttocks on the Nurnberger-Muller Scale. Fisher's exact test was used to compare the LLLT- and sham-treated groups. A one-tailed test was applied with an alpha value of 0.05. Changes in secondary outcome measures were assessed across and between treatment groups using *t*-test, ANOVA, ANCOVA and linear regression analysis.

### Ethics

The protocol used in this study was approved by an independent institutional review board (Ethical & Independent Review Services, Corte Madera, CA). Each subject provided informed consent prior to participating in any treatment-related activities.

## RESULTS

### Demographics

The study enrolled 34 subjects in each treatment group (Table 1). All 68 subjects completed the study. There were no significant between-group differences in mean baseline Nurnberger-Muller Scale stage, body weight, BMI, thigh circumference measurements or the amount of BSA affected by cellulite.

### Primary Outcome Measure

Nineteen subjects in the LLLT group achieved the individual success criteria (55.88%) versus three subjects (8.82%) in the sham-treated group ( $P < 0.0001$ ; Table 2).

### Secondary Outcome Measures

The per-protocol analysis for bilateral changes in Nurnberger-Muller Scale Stage is based on 52 subjects. Two LLLT-treated subjects achieved a 2-stage improvement on the Nurnberger-Muller Scale at the 2-week study end-

**TABLE 3. Changes in Nurnberger-Muller Scale Stages, Per-Protocol Population**

	LLL- treatment (N = 23)	Sham- treatment (N = 29)
Week 2, n (%)		
Decrease of 2 stages	2 (9%)	—
Decrease of 1 stage	13 (56%)	1 (3%)
No change	8 (35%)	27 (94%)
Increase of 1 stage	—	1 (3%)
Week 6, n (%)		
Decrease of 2 stages	4 (17%)	—
Decrease of 1 stage	13 (57%)	4 (14)
No change	6 (26%)	27 (83%)
Increase of 1 stage	11	1 (3%)

point and four did at the 6-week follow-up evaluation versus none of the sham-treated subjects at either time point (Table 3). The majority of sham-treated subjects demonstrated no change in Nurnberger-Muller Scale at the 2- and 6-week evaluations (88% and 79%, respectively).

Subjects treated with LLLT demonstrated a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation (for each,  $P < 0.0001$  vs. baseline) while subjects undergoing sham treatment showed no change (Table 4; Fig. 2). Similarly, LLLT-treated subjects showed significant decreases in mean baseline body weight ( $P < 0.0005$ ), BMI ( $P < 0.001$ ) and percent BSA affected by cellulite ( $P < 0.0005$ ) while no change was observed for these parameters among sham-treated subjects (Table 5). Among the participants responding to the satisfaction survey, 62.1% of LLLT-treated subjects were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received from treatment versus 25.8% of sham-treated subjects (Table 6; Fig. 3).

### Other Assessments

None of the participating subjects reported any deviation from baseline diet, exercise or medication use during the study that would impact any study measurements. No

**TABLE 1. Subject Demographics**

	LLL-treatment (N = 30) <sup>a</sup>	Sham-treatment (N = 33) <sup>a</sup>
Female gender	30 (100%)	33 (100%)
Age, mean (SD)	39.87 (10.01)	39.94 (10.72)
Race/ethnicity, N (%)		
Caucasian	27 (90%)	31 (94%)
African American	1 (3%)	—
Middle Eastern	2 (7%)	2 (6%)

<sup>a</sup>Data were missing for four subjects in the LLLT group and one in the Sham group.

**TABLE 2. Subjects Achieving Individual Success**

	LLL- treatment (N = 34)	Sham- treatment (N = 34)	Significance <sup>a</sup>
Subjects (%)	19 (55.88)	3 (8.82)	$P < 0.0001$

<sup>a</sup>Fischer's exact test for two independent proportions.

**TABLE 4. Change in Combined Thigh Circumference, Per-Protocol Population**

	LLL- treatment (N = 23)	Sham- treatment (N = 29)
Change (in.)	Mean (SD)	Mean (SD)
Pre-treatment	47.13 (4.16)	45.59 (4.36)
Post-treatment (Week 2)	45.27 (4.34)*	45.22 (4.35)
Follow-up (Week 6)	44.77 (4.76)*	45.18 (4.44)

\* $P < 0.0001$  versus baseline.



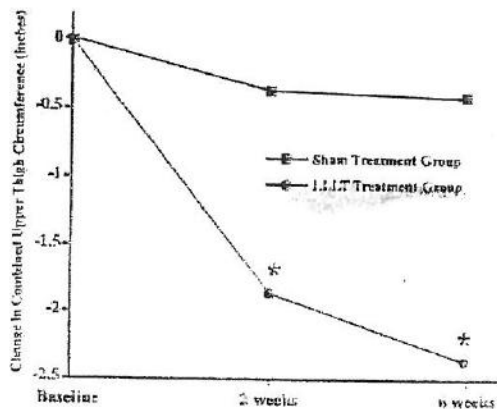


Fig. 2. Subjects treated with LLLT demonstrated a significant decrease in combined baseline thigh circumference at the 2-week study endpoint and 6-week follow-up evaluation while for subjects undergoing sham treatment showed no change. \* $P < 0.0001$  versus baseline.

changes in any of the recorded baseline skin markers at any of the three study evaluation visits were noted for any subject in the study. There were no reports of adverse events.

## DISCUSSION

The results of this study indicate LLLT using a green 532 nm diode is an effective stand-alone method for improving the appearance of cellulite. These results are in contrast with other technologies which require massage or mechanical manipulation to achieve beneficial effects. It could be argued that massage may even play a role in

TABLE 5. Changes in Body Weight, BMI, and BSA Affected by Cellulite

	LLLT-treatment (N = 23)	Sham-treatment (N = 29)
Body weight (lb), mean (SD)		
Pre-treatment (Baseline)	154.55 (25.53)	154.34 (28.78)
Post-treatment (Week 2)	153.00 (25.26)*	154.05 (28.70)
Follow-up (Week 6)	152.77 (24.86)*	153.62 (28.45)
BMI ( $\text{kg}/\text{m}^2$ ), mean (SD)		
Pre-treatment (baseline)	25.99 (3.04)	24.90 (2.69)
Post-treatment (Week 2)	25.73 (2.98) <sup>†</sup>	24.85 (2.66)
Follow-up (Week 6)	25.70 (2.95) <sup>†</sup>	24.79 (2.62)
BSA (%), mean (SD)		
Pre-treatment (baseline)	16.65 (6.23)	14.74 (6.92)
Post-treatment (Week 2)	12.76 (6.47)*	14.08 (6.55)
Follow-up (Week 6)	12.33 (6.77)*	13.58 (6.59)

\* $P < 0.0005$ , one-way ANOVA for correlated samples.

<sup>†</sup> $P < 0.001$ , one-way ANOVA for correlated samples.

TABLE 6. Subject Satisfaction Survey, Per-Protocol Population

	LLLT-treatment (N = 29)	Sham-treatment (N = 31)
Response, N (%)		
Very satisfied	10 (34.5)	2 (6.5)
Somewhat satisfied	8 (27.5)	6 (19.4)
Neither satisfied nor dissatisfied	8 (27.5)	14 (45.2)
Not very satisfied	1 (3.5)	9 (29.0)
Not at all satisfied	2 (7.0)	—

the improvements reported following the application topical products for 4 and 12 weeks [14,15]. The repeated application of a cream or gel involves repeatedly rubbing the product into the skin and the act of massaging the affected areas with topical products may be responsible for these results [1].

A large and growing body of research is revealing the unique and diverse biological response that occurs following the application of low-level laser light to living tissue. LLLT has been shown to modify gene expression [25], cellular proliferation [26–30], intracellular pH balance [31], mitochondrial membrane potentials [32], generation of transient reactive oxygen species [33–36], calcium ion levels [33,37,38], proton gradients [39], and cellular oxygen consumption [40].

While the exact mechanism remains unknown, previous work by others has shown that 532 nm lasers induce a biological cascade at the cellular level resulting in observable clinical effects that include promoting collagen synthesis [41–47]. We propose that the use of 532 nm light may correct the irregular pattern of connective tissue associated with collagen and induce skin tightening by stimulating the synthesis of new collagen. The application of green laser may therefore serve as an effective

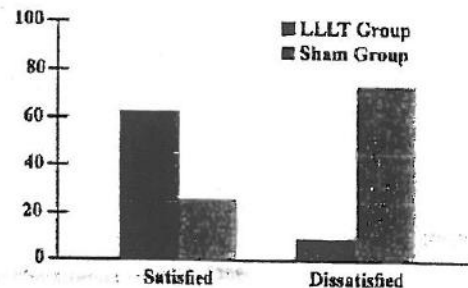


Fig. 3. Among the participants responding to the subject satisfaction survey, 62.1% of LLLT-treated subjects were Very Satisfied or Somewhat Satisfied with the improvement in cellulite they received from treatment versus 25.8% of sham-treated subjects.

method of decreasing the appearance of cellulite by tightening the skin.

The subjects in the study achieved significant improvement in the appearance of cellulite on the thighs and buttocks following six 30-minute treatment sessions over a period of 2 weeks. These improvements persisted for a minimum of 4 weeks following the last treatment. The number of subjects achieving 2-stage improvement on the Nurnberger-Muller Scale increased from two at the 2-week study endpoint to four at the 6-week follow-up evaluation suggesting clinical improvements may even continue to occur following treatment. Future studies will further assess the long-term benefits of LLLT for the treatment of cellulite.

## CONCLUSION

Low-level laser therapy using green 532 nm diodes is safe and effective for improving the appearance of cellulite in the buttocks and thighs and buttocks after 2 weeks. In contrast with other technologies, LLLT is effective as a stand-alone procedure without massage or mechanical manipulation. The results from the current study indicate the beneficial effects of LLLT on cellulite persist for 4 weeks. Future studies will assess the long-term benefits of LLLT for the treatment of cellulite.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Elvira Walls, Regulatory Insight, Inc. and Dr. Carl Hornfeldt, Apothekon, Inc. during the preparation of this manuscript.

## REFERENCES

- Rawlings AV. Cellulite its treatment. *Int J Cosmet Sci* 2006;28:175-190.
- Rossi AB, Vergnanini AL. Cellulite: A review. *J Eur Acad Dermatol Venereol* 2000;14:251-262.
- Terranova F, Berardesca E, Mailbach H. Cellulite: Nature and aetiopathogenesis. *Int J Cosmet Sci* 2006;28:157-167.
- Chang P, Wiseman J, Jacoby T, Salisbury AV, Ersek RA. Noninvasive mechanical body contouring: (Endermologie) a one-year clinical outcome study update. *Aesthetic Plast Surg* 1998;22:145-153.
- Güleç AT. Treatment of cellulite with LPG endermologie. *Int J Dermatol* 2009;48:265-270.
- Sadick NS, Mulholland RS. A prospective clinical study to evaluate the efficacy and safety of cellulite treatment using the combination of optical and RF energies for subcutaneous tissue heating. *J Cosmet Laser Ther* 2004;6:187-190.
- Sadick N, Magro C. A study evaluating the safety and efficacy of the VelaSmooth system in the treatment of cellulite. *J Cosmet Laser Ther* 2007;9:15-20.
- Hexsel DM, Siega C, Schilling-Souza J, Porto MD, Rodrigues TC. A bipolar radiofrequency, infrared, vacuum and mechanical massage device for treatment of cellulite: A pilot study. *J Cosmet Laser Ther* 2011;13:297-302.
- Gold MH, Khatri KA, Hails K, Weiss RA, Fournier N. Reduction in thigh circumference and improvement in the appearance of cellulite with dual-wavelength, low-level laser energy and massage. *J Cosmet Laser Ther* 2011;13:13-20.
- Kulick MI. Evaluation of a noninvasive, dual-wavelength laser-suction and massage device for the regional treatment of cellulite. *Plast Reconstr Surg* 2010;125:1768-1796.
- Foster KW, Kouba DJ, Hayes J, Freeman V, Moy RL. Reductions in thigh and inframammary circumference following treatment with a novel device combining ultrasound, suction, and massage. *J Drugs Dermatol* 2008;7:113-115.
- Nootheti PK, Maggantay A, Yosowitz G, Calderon S, Goldman MP. A single center, randomized, comparative, prospective clinical study to determine the efficacy of the VelaSmooth system versus the Triactive system for the treatment of cellulite. *Lasers Surg Med* 2006;38:908-912.
- Bousquet-Rouaud R, Bazan M, Chaintreuil J, Echague AV. High-frequency ultrasound evaluation of cellulite treated with the 1064 nm Nd:YAG laser. *J Cosmet Laser Ther* 2009;11:34-44.
- Roure R, Oddos T, Rossi A, Vial F, Bertin C. Evaluation of the efficacy of a topical cosmetic slimming product combining tetrahydroxypropyl ethylenediamine, caffeine, carnitine, forskolin and retinol. In vitro, ex vivo and in vivo studies. *Int J Cosmet Sci* 2011;33:519-526.
- Rao J, Gold MH, Goldman MP. A two-center, double-blinded, randomized trial testing the tolerability and efficacy of a novel therapeutic agent for cellulite reduction. *J Cosmet Dermatol* 2005;4:93-102.
- Hexsel D, Soirefmann M. Cosmeceuticals for cellulite. *Semin Cutan Med Surg* 2011;30:167-170.
- Rotunda AM, Avram MM, Avram AS. Cellulite: Is there a role for injectables? *J Cosmet Laser Ther* 2005;7:147-154.
- Kutubay Z. Evaluation of mesotherapeutic injections of three different combinations of lipolytic agents for body contouring. *J Cosmet Laser Ther* 2011;13:142-153.
- Ramos-e-Silva M, Pereira AL, Ramos-e-Silva S, Piñeiro-Maceira J. Oleoma: Rare complication of mesotherapy for cellulite. *Int J Dermatol* 2012;51:162-167.
- Vukčević NP, Babić G, Segrt Z, Ercegović GV, Janković S, Adimović L. Severe acute caffeine poisoning due to intradermal injections: Mesotherapy hazard. *Vojnosanit Pregl* 2012;69:707-713.
- Nestor MS, Zarraga MB, Park H. Effect of 635 nm low-level laser therapy on upper arm circumference reduction: A double-blind, randomized, sham-controlled trial. *J Clin Aesthet Dermatol* 2012;6:42-48.
- Sasaki GH, Oberg K, Tucker B, Gaston M. The effectiveness and safety of topical PhotoActiv phosphatidylcholine-based anti-cellulite gel and LED (red and near-infrared) light on Grade II-III thigh cellulite: A randomized, double-blinded study. *J Cosmet Laser Ther* 2007;9:87-95.
- Mertens DM, Jenkins ME, Warden GD. Outpatient burn management. *Nurs Clin North Am* 1997;32:343-364.
- Lund C, Browder N. The estimation of areas of burns. *Surg Gynecol Obstet* 1944;79:352-358.
- Byrnes KR, Wu X, Waynant RW, Ilev IK, Anders JJ. Low power laser irradiation alters gene expression of olfactory ensheathing cells in vitro. *Lasers Surg Med* 2005;37:161-171.
- Snyder SK, Byrnes KR, Borke RC, Sanchez A, Anders JJ. Quantification of calcitonin gene-related peptide mRNA and neuronal cell death in facial motor nuclei following axotomy and 633 nm low power laser treatment. *Lasers Surg Med* 2002;31:216-222.
- Broadley C, Broadley KN, Disimone G, Reimsch L, Davidson JM. Low energy helium-neon laser irradiation and the tensile strength of incisional wounds in the rat. *Wound Rep Reg* 1995;3:512-517.
- Allendorf JDF, Bessler M, Huang J, Kayton ML, Laird D, Nowygrod R, Treat MR. Helium-neon laser irradiation at fluences of 1, 2 and 4 J/cm<sup>2</sup> failed to accelerate wound healing as assessed by both wound contracture rate and tensile strength. *Lasers Surg Med* 1997;20:340-345.
- Lowe AS, Walker MD, O'Byrne M, Baxter GD, Hirst DG. Effect of low intensity monochromatic light therapy (890 nm) on a radiation impaired, wound-healing model in murine skin. *Lasers Surg Med* 1998;23:291-298.
- Walker MD, Rumpf S, Baxter GD, Hirst DG, Lowe AS. Effect of low-intensity laser irradiation (660 nm) on a radiation-impaired wound-healing model in murine skin. *Lasers Surg Med* 2000;26:41-47.
- Lubart R, Wollman Y, Friedman H, Rochkind S, Laulicht I. Effects of visible and near-infrared lasers on cell culture. *J Photochem Photobiol* 1992;12:305-310.

32. Moore P, Ridgway TD, Higbee RG, Howard EW, Lucroy MD. Effect of wavelength on low-intensity laser irradiation-stimulated cell proliferation in vitro. *Lasers Surg Med* 2005;36:8-12.
33. Alexandratou E, Yova D, Handris P, Kletsas D, Loukas S. Human fibroblasts alterations induced by low power laser irradiation at the single cell level using confocal microscopy. *Photochem Photobiol Sci* 2002;1:547-552.
34. Grossman N, Schneid N, Reuveni H, Halevy S, Lubart R. 780 nm low power diode laser irradiation stimulates proliferation of keratinocyte cultures: Involvement of reactive oxygen species. *Lasers Surg Med* 1998;22:212-218.
35. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg* 2005;1:3-9.
36. Lin Y, Berg AH, Iyengar P, Lam TKT, Giacca A, Combs TP, Rajala MW, Du X, Rollman B, Li W, Hawkins M, Barzilai N, Rhodes CJ, Fantus IG, Brownlee M, Scherer PE. The hyperglycemia-induced inflammatory response in adipocytes: The role of reactive oxygen species. *J Biol Chem* 2005;280:4617-4626.
37. Lubart R, Friedman H, Levinshal T, Lavie R, Breitbart H. Effect of light on calcium transport in bull sperm cells. *J Photochem Photobiol* 1992;15:337-341.
38. Tong M, Liu YP, Zhao XN, Yan CZ, Hu ZR, Zhang ZH. Effects of different wavelengths of low level laser irradiation on murine immunological activity and intracellular  $Ca^{2+}$  in human lymphocytes and cultured cortical neurogliaocytes. *Lasers Med Sci* 2000;15:201-206.
39. Gordon SA, Surrey K. Red and far-red action on oxidative phosphorylation. *Radiat Res* 1960;12:325-339.
40. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, Cingolani A. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett* 1984;175:95-99.
41. Soaton ED, Mouser PE, Charakida A, Alam S, Seldon PM, Chu AC. Investigation of the mechanism of action nonablative pulsed-dye laser therapy in photorejuvenation and inflammatory acne vulgaris. *Br J Dermatol* 2007;152:409.
42. Rostan E, Bowes LE, Iyer S, Fitzpatrick RE. A double-blind, side-by-side comparison study of low fluence long pulse dye laser to coolant treatment for wrinkling of the cheeks. *J Cosmet Laser Ther* 2001;3:129-136.
43. Goldberg D, Tan M, Dale-Sarradet M, Gordon M. Nonablative dermal remodeling with a 585 nm, 350-microsec, flash-lamp pulsed dye laser: Clinical and ultrastructural analysis. *Dermatol Surg* 2003;29:161-164.
44. Moody Br, McCarthy JL, Hruza GJ. Collagen remodeling after 585 nm pulsed dye laser irradiation: An ultrasonographic analysis. *Dermatol Surg* 2003;29:997-999.
45. Hsu TS, Zelickson B, Dover JS, Kilmer S, Burns J, Hruza G, Brown DB, Bernstein EF. 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.
46. Michel JL. ED 2000: 585 nm collagen remodeling pulsed dye laser. *J Cosmet Laser Ther* 2003;5:201-203.
47. Bjerring P, Clement M, Heickendorff L, Lybecker H, Kiernan M. Dermal collagen production following irradiation by dye laser and broadband light source. *J Cosmet Laser Ther* 2002;4:39-43.



