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The Use of Low-Level Laser Therapy for Noninvasive Body Contouring

39

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39.1 Introduction

Photomedicine is an interdisciplinary therapy that employs light energy as its primary means to generate a beneficial clinical outcome. A well-established faction of photomedicine is the use of low-level laser therapy (LLLT), which yields a valuable response without generating a photothermal or photoacoustic means. Specifically, LLLT operates within the parameters of photochemistry, a discipline of science dedicated to exploring the interactions between light energy and atomic and molecular structures as well as the influence that exists on cell performance via the modulation of numerous intracellular biochemical reactions [1]. Within the past decade, LLLT has emerged as an accepted form of therapy within the cosmetic medical community, serving as an adjunct to the most frequently performed procedures: breast augmentation and lipoplasty [2, 3]. Additionally, laser therapy has illustrated utility as an independent therapeutic approach for noninvasive body slimming, an application that has been histologically and clinically validated.

LLLT is categorized by two distinctive phases: (1) a primary phase that describes the absorption of light energy by a photoabsorbing molecule and (2) a secondary phase that is characterized by a biological cascade responsible for beneficial clinical results. A detailed understanding of photosynthetic organisms is known regarding how light is responsible for energy production and organism life sustainability, but less is known about the modulatory capacity light holds within nonphotosynthetic cells. Although obvious distinctions can be made between photosynthetic and nonphotosynthetic organisms, the primary reaction that is observed and the biological structures used to absorb light energy are structurally very similar. Emission of light along a selection of nonphotosynthetic tissue promotes electron excitation within photoabsorbing structures, altering cell bioenergetics and influencing diverse downstream cascades [4–24]. An identified target of laser therapy is the terminal enzyme residing in the inner mitochondrial membrane, cytochrome *c* oxidase (Fig. 39.1), which serves an important responsibility in supporting cell bioenergetics.

Structurally, cytochrome *c* oxidase is a multicomponent membrane protein that contains a binuclear copper center (Cu_A) along with a heme binuclear center (a_3-Cu_B), both of which facilitate the transfer of electrons from water-soluble cytochrome *c* to oxygen [5–7]. Based on the presence of transition metals, this respiratory chain enzyme has been shown to absorb photonic energy, which modulates the mitochondrial membrane potential and proton gradient. This, in turn, influences changes in mitochondria optical properties by upregulating the rate of adenosine diphosphate/adenosine triphosphate (ADP/ATP) exchange [9]. Based on numerous studies, it is postulated that laser irradiation increases the rate at which cytochrome *c* oxidase transfers electrons from cytochrome *c* to dioxygen [10, 11] and reduces the catalytic center of cytochrome *c* oxidase, allowing more electrons to be made available for the reduction of dioxygen [12, 25].

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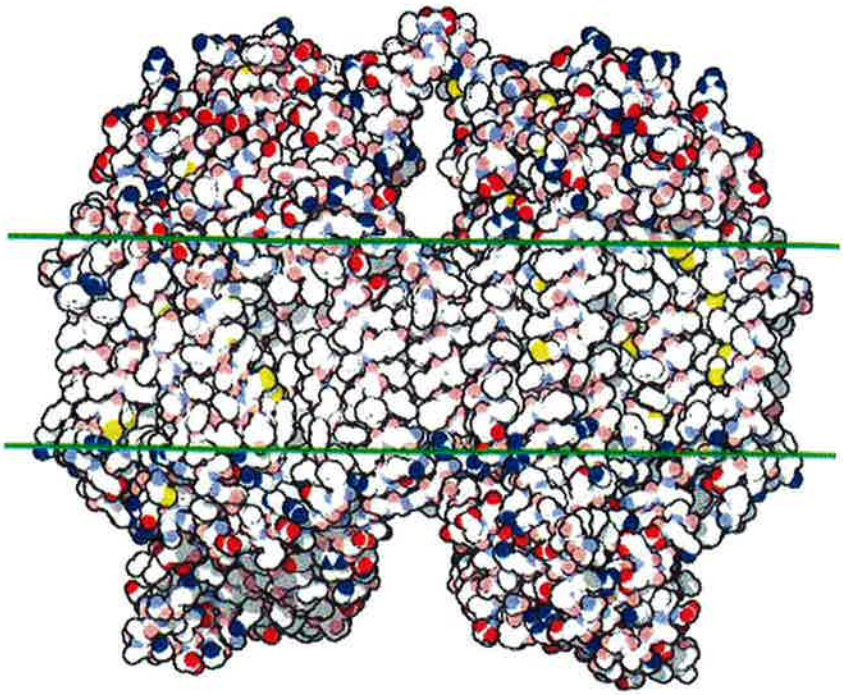

Fig. 39.1 Three-dimensional structure of cytochrome *c* oxidase. Protein data bank 2001

An upregulation in cellular respiration is also coupled with a transient rise in the reactive oxygen species (ROS), a product of oxidative phosphorylation, which participates in intracellular signal transduction [1, 26]. The modulation of cellular metabolism and signal transduction has been found to promote a shift in cell redox potential in the direction of greater oxidation [1], with these cytosolic responses influencing gene expression [27] via transcription factor modulation. It becomes quickly apparent how laser therapy can promote a diverse biological response following light absorption as numerous pathways regulating protein and growth factor synthesis, inflammatory cytokine production, and cell proliferation are responsive to the intracellular redox state. The modulatory capacity of laser therapy has enabled this application to seamlessly transition into cosmetic medicine as it illustrates utility in postsurgical pain management, accelerated recovery, and downregulation of inflammation. However, another phenomenon has been identified transpiring within the adipocyte, a response that has been histologically proven to promote the degeneration of the bilipid membrane, enabling the liberation of stored fatty material including triglycerides, fatty acids, and glycerol.

This discovery initiated the adoption of laser therapy as an adjunct to liposuction and later as a standalone for noninvasive body contouring, applications that have been scientifically validated through histological trials and placebo-controlled, randomized, double-blind, multicenter studies.

39.2 Histology

Subsequent to cytochrome *c* oxidase light absorption, cell metabolism is influenced, thus encouraging cell behavior, a progression that is believed to occur within the adipocyte. Possessing mitochondria, adipocytes contain the ability to absorb light energy and are subject to light-induced intracellular change. Although the exact mechanism remains unidentified, histological evidence reveals that subsequent to light absorption at 635 nm (Zerona, manufactured by Erchonia Medical), the observable outcome is the formation of transitory pores within the bilipid membrane (Fig. 39.2) [28–30].

A separate investigation acquired human adipose tissue from lipectomy samples and exposed the tissue to irradiance at 635 nm with an output intensity of 7.0 mW for 6-min [29]. Utilizing scanning and transmission electron microscopy (SEM and TEM), more than 180 images were collected, and these revealed that 99% of the intracellular content, including stored fat, was released from the adipocyte, an occurrence not observed within the control samples (Fig. 39.3) [29].

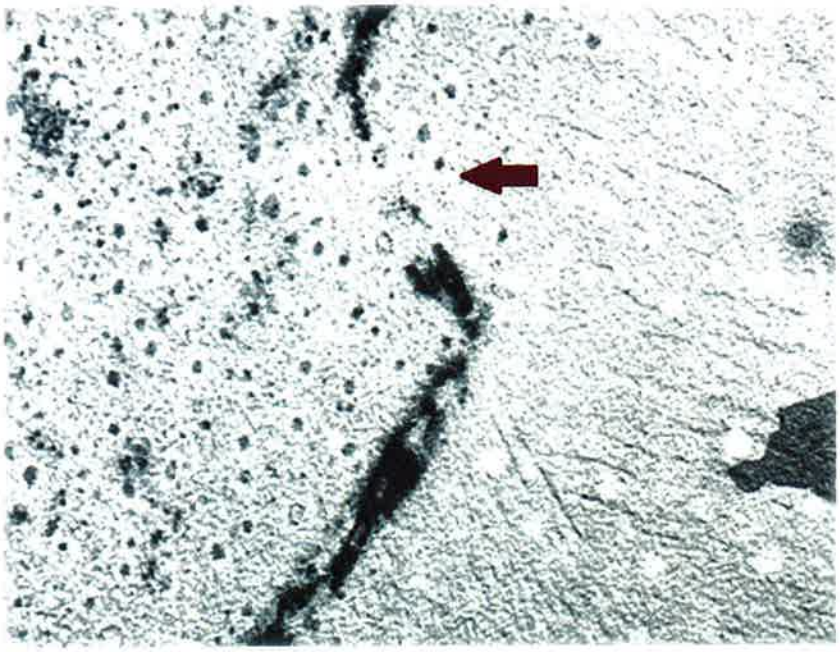

Fig. 39.2 The *arrow* indicates formation of transitory pore subsequent to laser therapy at 635 nm. Image capture at stimulation at 60,000× magnification

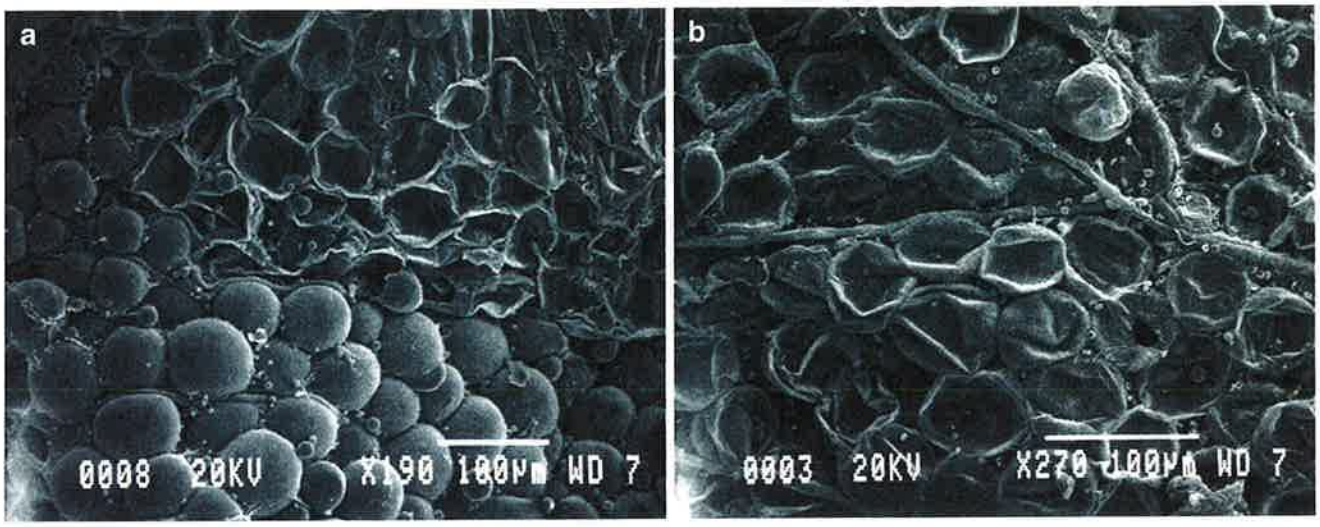

Fig. 39.3 Scanning electron microscopy of laser-treated adipocytes revealing collapsed state

To understand the effect at a deeper level, TEM images of individual adipocytes were taken at 60,000× magnification, and these illustrated the formation of an invagination or transitory pore within the membrane, which is believed to be the cause of adipocyte deflation [29].

It was recorded by the authors that adjacent nonadipocyte cells within the treated interstitial space and capillary structures remained intact, highlighting a unique result distinct to adipocytes [29]. Collectively, histological evidence supports the notion that disruption of the adipocyte membrane perhaps serves as the primary grounds for fatty material release [28–30].

Often, the transition from bench to bedside or from in vitro to in vivo cannot replicate the histological findings, and in the case of laser therapy, light attenuation through vascular-rich skin can perhaps impede a subdermal stimulation. To confirm the histological findings and assess the depth of penetration of LLLT within the subcutaneous layer, Neira et al. [31] assessed T1 and T2 weighted MRI sequences, observing any radiological changes subdermally following laser irradiation. T2 weighted sequences subsequent to 6 min of laser stimulation displayed a less defined superficial adipose layer, septae, and a homogenous or coalescent effect within the

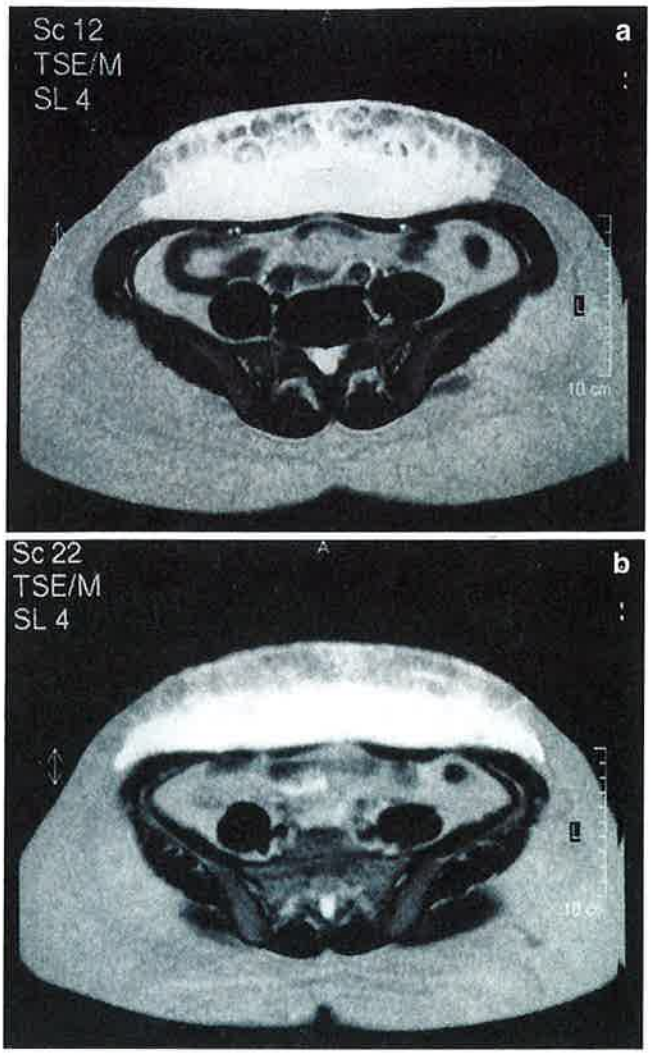

Fig. 39.4 MRI T2 sequence comparison. (**a**) Pretreatment MRI depicting fat characterized by defined septae borders. (**b**) Six minutes following laser therapy at 635 nm revealing fat homogeneity and coalescence of tissue

Table 39.1 Average ease of the process of fat extraction VAS rating by treatment group and treatment area

	Test group		Placebo group	
	n	Mean VAS rating	*n*	Mean VAS rating
Right stomach	30	12.07	28	71.43
Left stomach	30	12.23	28	71.5
Right thigh	22	12.27	18	75.17
Left thigh	22	12.59	18	76.67
Right hip	22	12.5	21	74.43
Left hip	22	15.64	21	73.86

Anatomical region represents area undergoing liposuction

treated adipose tissue. Transdermal delivery of 635 nm at 7.0 mW illustrated a structural change in fat density and organization of both superficial and deep fat (Fig. 39.4).

Photobiomodulation via an external light delivery system represents a unique and misunderstood sector of medicine; yet, studies continually affirm that light has the capacity to penetrate the skin barrier and engender a positive response within the targeted tissue [32, 33].

The transition from an in vitro setting to an in vivo environment for laser therapy within the cosmetic medical community was first established as an adjunct to liposuction. A placebo-controlled, randomized, double-blind, multicentered clinical study was conducted assessing the ease of extraction and reduction in visual analog scale (VAS) rating following a single application of laser therapy (Zerona, manufactured by Erchonia Medical) during the tumescent phase [2]. Jackson et al. [2] noted that blinded physicians, when asked to assess the ease of extraction using a scale from 0 to 100, with 100 being the hardest, recorded a significantly higher score was recorded for control subjects at a mean of 73.84 as compared to the average score of 12.88 for the test subjects (Table 39.1). Ease of extraction is based on the surgeon's perception cannula mobility through subcutaneous fat tissue.

In addition to the ease of extraction, patients were asked to rate on a VAS from 1 to 100 with "active" treatment subjects, revealing a significant reduction in pain at 24 h postoperatively as compared with the control (Table 39.2).

The reduction in pain was evident when assessing the dose-dependency for postsurgical pain management, which was significantly lower in patients within the active group [2]. Further, the average emulsification of extracted fat was assessed utilizing a VAS scale, elucidating a significant difference ($p<0.0001$) between treatment groups regarding the quantity of emulsified subcutaneous fat (Table 39.3).

It is important to note that a preceding study reviewed 700 cases and documented an improved contour, skin retraction, with an improved overall postoperative recovery [34]. The authors in both studies concluded that the transdermal delivery of laser therapy at 635 nm induced adipocyte collapse and was observable at the clinical level based upon the ease of extraction scores and accelerated patient recovery for laser-treated subjects.

Table 39.2 (A) Degree of discomfort and degree of swelling rating across study duration by treatment group and (B) mean degree of swelling by treatment group and anatomical region

(A)				
		Test group		Placebo group
Time after operation	*n*	Mean VAS rating	*n*	Mean VAS rating
24 h	36	24.56	34	47.41
7 days	36	12.19	34	26.15
2 weeks	35	7.23	34	22.15
4 weeks	34	3.15	34	12.32
(B)				
		Test group		Placebo group
	n	Mean VAS rating	*n*	Mean VAS rating
Right stomach	30	14.4	28	62.71
Left stomach	30	13	28	62.67
Right thigh	22	14.83	18	66.83
Left thigh	22	14.65	18	65.56
Right hip	22	12.68	21	69.95
Left hip	22	12.68	21	70.86

Table 39.3 Preprocedure circumference measurements by treatment group

Circumference (in.)	Test (n=35)	Placebo (n = 32)	All (n = 67)
Waist			
Mean	33.94	34.85	34.37
SD	3.63	3.83	3.72
Hip			
Mean	38.99	39.88	39.41
SD	2.87	3.77	3.33
Right thigh			
Mean	23.80	24.12	23.95
SD	1.52	2.04	1.78
Left thigh			
Mean	23.59	24.14	23.85
SD	1.40	1.95	1.70
Total inches			
Mean	120.31	122.99	121.59
SD	7.96	10.55	9.31

39.3 Noninvasive Body Contouring

As an adjunct to liposuction, laser therapy's primary utility was practical for postoperative pain management and accelerated recovery, a possible outcome based on the fundamental principle that electromagnetic energy at 635 nm promotes the liberation of stored intracellular fat. This secondary outcome was the foundation for the noninvasive body technique, the Zerona, manufactured by Erchonia Medical. Release of intracellular fat would shift into the interstitial space. This is regulated by the lymphatic system and possesses the capacity to hydrolyze triglycerides into nonesterified free fatty acids (NEFAs), which is important for fat catabolism. No dissention lies from the idea that fat catabolism is a fundamental element of the body's natural metabolic system; however, uncertainty still remains regarding the fate of laser-liberated fatty debris. Since the test participants within the aforementioned study demonstrated a circumferential reduction, the intracellular aspects released must have been eliminated from the treated area. When released, the fatty debris would enter the interstitial space, a region of the body regulated by the lymphatic system, an anastomosing network of lymphatic vessels that funnel toward lymph nodes transporting fluids, pathogens, and cellular debris [35]. The flow of lymph, which originates in connective tissue, eventually is deposited into the circulatory system primarily through the thoracic duct, which empties into the subclavian vein. As the fluid passes through the lymph nodes, the extraneous materials are filtered out via macrophages, which contain enzymes capable of degrading triglycerides and cholesterol. It is postulated that the fatty debris released postlaser therapy is transported to lymph nodes where lysosomal acid lipase (LAL) hydrolyzes the released triglycerides to generate NEFAs [36].

As the NEFAs empty into the circulatory system, its most likely fate is into hepatocytes, a site of fat metabolism; however, muscle, along with numerous other tissue structures, metabolize plasma NEFAs to generate energy. Therefore, it can be proposed that a significant portion of the laser-liberated fat undergoes enzymatic cleavage forming NEFAs, which participate in tissue metabolism. Although the fate of triglycerides and NEFAs is speculative, a nonrandomized perspective study acquired fasting lipid panels in subjects receiving LLLT (Zerona, manufactured by Erchonia Medical) for noninvasive body-slimming and the data revealed no significant transient elevations in either serum triglyceride or cholesterol concentrations, providing preliminary support that triglycerides are degraded prior to entering the circulatory system [37]. It is expected that if the triglycerides were not cleaved

along the glycerol backbone prior to entering the circulatory system, there would be a rise in serum triglyceride levels. Numerous outcomes potentially await NEFAs, including β-oxidation, phospholipidgenesis, muscle and organ metabolism, or triglyceride resynthesis and redistribution [35, 38]. The determination of the exact fortune of the laser-liberated fatty material would require various and extensive histological investigations.

Many questions regarding procedures and therapeutic interventions still remain, but one question that must be answered is the question regarding the efficacy of the therapy. In all cases, the most appropriate means to evaluate the effectiveness of an application is to perform a placebo-controlled, randomized, double-blind, multicentered clinical study, a design that was implemented by Jackson et al. [39] to assess LLLT (Zerona, manufactured by Erchonia Medical) for non-invasive body contouring. Aside from the physicians comparing the test and sham group, the study design also incorporated a patient self-examination survey in order to determine whether the results were visibly meaningful to participating individuals. Moreover, blinded physicians were asked to visually assess each patient and conjecture to which group, either "active" or "sham," the individual was assigned. Jackson and coworkers attempted to evaluate the utility of LLLT from a statistical analysis perspective as well as from a clinical viewpoint.

Sixty-seven subjects were enrolled and completed the study participation through the study endpoint. All subjects were deemed eligible for participation after satisfying extensive inclusion/exclusion criteria. A key element of the inclusion criteria was the willingness and ability 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 as well as maintenance of a regular diet and exercise regimen without affecting significant change in either direction during study participation. All patients fell within a body mass index (BMI) range of 25–30 kg/m^2.

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

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 that emitted a 635-nm (red) laser light. Each generated a 17-mW output (Zerona, manufactured by Erchonia Medical). Sham-treatment group participants were treated with a multiple head nonlaser red light emitting diode (LED) consisting of five independent red diode light heads, each with a scanner that emitted a 635-nm (red) light. Each diode generated 2.5 mW of 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.

Circumferential measurements in inches were taken along the subject's waist, hip, and each thigh. Anatomical features were documented for each patient with respect to the tape measure placement to preserve measurement accuracy and precision throughout the various time points. Circumference measurements along with the patient's BMI were measured at four different times: (1) preprocedure, (2) end of first procedure week, (3) end of second procedure week, and (4) 2 weeks postprocedure. The treatment phase commenced immediately following preprocedure circumference measurements and extended over two consecutive weeks, with each subject receiving six total treatments with the laser or sham-light scanning device. Three procedures were performed per week, each 2 days apart. Subjects received 20 min each of the anterior and posterior stimulation, treating the waist, hip, and thighs simultaneously for a total of 40 min of treatment. The total laser energy that the subjects randomized to the actual laser treatment received (front and back treatments combined) was approximately 6.60 J/cm^2.

The overall efficacy outcome measure was characterized as the change in total combined inches in circumference measurements for the waist, hip, and bilateral thighs from the baseline values (preprocedure) to following the completion of the 2-week procedure administration phase (end of week 2).

The primary success criterion was established by the Food and Drug Administration (FDA), which was defined as at least a 35% difference between treatment groups, comparing the proportion of individual successes in each group. Further, it was determined by the FDA that a reduction of at least 3.0 in. was clinically meaningful, and patients were determined successes if

Table 39.4 Comparison of the proportion of successes between treatment groups

2 × 2 table	Success met	Success not met	
Test group	22	13	35
Placebo group	2	30	32
	24	43	67

Table 39.5 Mean and standard deviation of the change in circumference by treatment group

	Test subjects ($n=35$)	Placebo subjects ($n=32$)
Mean	−3.521	−0.684
SD	1.854	1.233

that reduction was revealed in 2 weeks. Circumferential reduction aside, to assess the clinical meaningfulness of the process, 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 and approximate to which group they were assigned. Patients were asked to record a rating on a five-point scale of: very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, not very satisfied, and not at all satisfied. Additionally, blinded assessment investigators were asked to approximate into which group subjects were enrolled to determine if the reduction was visible following the 2-week treatment administration phase.

At the start of the study, no significant differences in subject preprocedure BMI were observed between experimental groups ($t=-0.48$; $df=64$; $p=0.647$ [$p>0.05$]). Further, variation in subject preprocedure body circumference measurements were not statistically significant for any treatment region or for the total number of inches across all determined treatment areas when combined ($t=-1.18$; $df=65$; $p=0.240$ [$p>0.05$]) (Table 39.3).

Subsequent to the treatment administration phase, 22 (62.9%) of the "active" treatment participants produced a reduction of 3.0 in. or greater in 2 weeks, compared with two subjects within the sham light group revealing a similar outcome. The difference was determined to be significant at $p<0.0001$ (Table 39.4).

Fifty-seven percent more test group participants than sham light treated group participants showed a total decrease in combined circumference measurements (of 3.0 in. or greater) from preprocedure to the study endpoint, an outcome that exceeded the preestablished 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, a deviation found to be statistically significant ($t=-7.30$; $df=65$; $p<0.0001$) (Table 39.5).

Contrast to baseline, total combined circumference measurements for test subjects were significantly 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 postprocedure ($p<0.01$). In departure, sham subjects from baseline across 2 weeks postprocedure illustrated an overall reduction in total combined circumference measurements of 0.62 in. ($p>0.05$) with no significant changes. Moreover, sham light treated group participants compared with baseline recorded insignificant changes in total combined circumference measurements across all three subsequent evaluation points ($p>0.05$) (Fig. 39.5).

Importantly, test group participants from week 2 to 2 weeks postprocedure 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 postprocedure ($t=-6.66$; $df=65$; [$p<0.0001$]).

Active group participants revealed an overall reduction in circumference of −0.98 in. across the waist, 1.05 at the hip, and 0.85 and 0.65 across the right and left thighs, which were all significant (Table 39.6).

When evaluating the clinical meaningfulness of the Zerona procedure, 61 of the 67 subjects responded to the satisfaction survey. Thirty of the thirty-five test subjects and 31 of the 32 sham light treated subjects recorded their satisfaction 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. 39.6).

Moreover, one test group participant and 11 control group participants recorded a "dissatisfied" rating (Fig. 39.5). The difference of the rating score between the two treatment groups was found to be statistically significant ($p<0.0005$). Subjects were also asked to

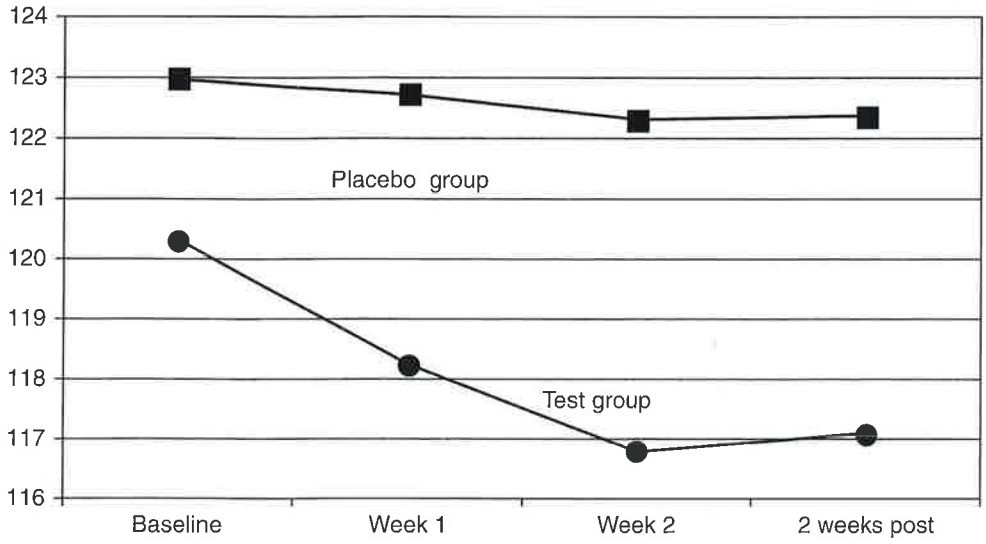

Fig. 39.5 Mean total circumference measurements by measurement time point by treatment group for the ITT population

Table 39.6 Individual treatment area circumference measurements from baseline to study endpoint by treatment group

	Test group			Placebo group		
	n	Mean	SD	*n*	Mean	SD
Waist						
Baseline	35	33.94	3.63	32	34.85	3.83
Week 1	35	33.38	3.39	32	34.85	3.76
Week 2	35	32.96	3.51	32	34.60	3.93
Hip						
Baseline	35	38.99	2.87	32	39.88	3.77
Week 1	35	38.26	3.71	32	39.80	3.57
Week 2	35	37.94	3.60	32	39.67	3.73
Right thigh						
Baseline	35	23.80	1.52	32	24.12	2.04
Week 1	35	23.31	1.41	32	24.10	2.09
Week 2	35	22.95	1.40	32	24.07	2.10
Left thigh						
Baseline	35	23.59	1.40	32	24.14	1.95
Week 1	35	23.30	1.34	32	23.98	2.02
Week 2	35	22.94	1.27	32	23.97	2.11

record comments relating to their participation in the clinical trial while recording their daily compliance diaries on each day of the administration period. The comments for test group participants included:

"Feeling slimmer and more lean"

"Clothes fitting better, people are commenting stating looking like I' m losing weight"

"My abdomen feels like its tightening"

"The texture on my thighs feels smoother"

"I feel like I'm losing weight"

For sham group participants, no remarks regarding their body contouring changes were recorded.

Further, subjects were asked to ascertain to which group they were assigned. For test group participants, 79% were able to correctly identify their group assignment, and 78% of sham group members were able to ascertain correctly their group.

The study was designed not only to evaluate statistical analysis regarding the potential reduction observed but also to capture the clinical utility of this device as perceived by the subjects. Further, an independent observer was utilized to interpret the visual reduction and indicate subject assignment. Regarding test participants, investigators were able to determine that

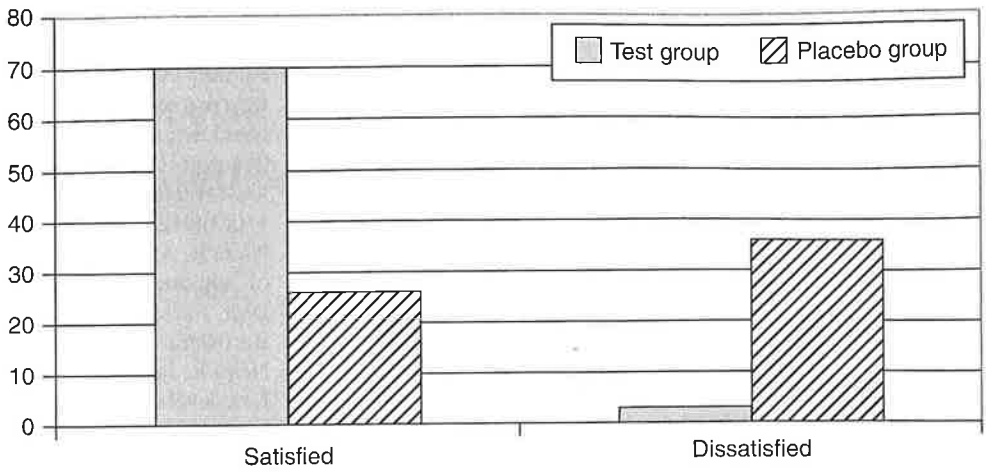

Fig. 39.6 Percentage of test and placebo group subjects who were "Satisfied" and "Dissatisfied"

83% of subjects were assigned to the active group, with an 81% rate when determining individuals belonging to the sham group.

Aesthetic medicine does not deviate from other medical disciplines in that innovation is the cornerstone for advancement in medical intervention, and Zerona represents that innovation. As a transdermal device, the modulation of adipocyte structural integrity inducing intracellular fat release without upregulating inflammation and preserving cell viability is an improvement that dramatically departs from standard cosmetic practices. Even though further studies are warranted to better understand this modality, preceding histological trials and completion of a Level 1 study highlight the efficacy of Zerona and potential benefit patients can obtain following the procedure.

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