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RESEARCH ARTICLE

HIGH-INTENSITY FOCUSED ULTRASOUND WITH SURFACE COOLING NON-INVASIVE ABDOMINAL SUBCUTANEOUS ADIPOSE TISSUE REDUCTION

***Hector Leal Silva, Esther Carmona Hernandez, Angel Perez Blanco, Mariana Grijalva Vazquez, Sugun Lee and Sebastian Leal Delgado**

Universidad de Monterrey, Mexico

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ABSTRACT

Background: High-intensity focused ultrasound (HIFU) quickly raises local temperature of subcutaneous adipose tissue, resulting in instantaneous cell death within the targeted area; higher temperatures can be safely applied using contact cooling.
Objective: Evaluate safety and performance efficacy of HIFU with surface cooling for Non-Invasive reduction of the subcutaneous adipose tissue (SAT)in the abdomen.
Methods: A new HIFU device (LIPOcel™, Jeisys Medical, Inc. Seoul, Republic of Korea) with contact cooling was used to reduce abdominal circumference adipose tissue in 3 treatment modalities.
Results: 30 subjects, mean age of 35.4 years underwent one or 2 HIFU treatments. Mean total energy dose was 509.4 J/cm^2, 495 J/cm^2, and 374 J/cm^2 for Groups A, B, and C respectively; whole study mean total fluence was 459.47 J/cm^2. Mean waist circumference reduction was 2.95 cm, 2.4 cm, and 3.8 cm for Groups A, B, and C respectively. A significant mean waist circumference reduction of 3.05 cm from baseline was observed. Most subjects (63.3%) reported being satisfied or very satisfied with the results; 80% of the investigators reported satisfactory results.
Conclusions: HIFU with surface cooling using high fluence, assessed by standardized waist circumference measurement, is safe and effective for abdominal SAT reduction and noninvasive body sculpting.

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INTRODUCTION

Non-invasive Procedures for fat reduction are becoming increasingly popular. (Sarwer and Crerand, 2004) The demand for cosmetic procedures targeting subcutaneous adipose tissue (SAT) has rapidly increased over the past decade. Nowadays, more than half of individuals interested in cosmetic procedures are most interested in "body sculpting". (Friedmann *et al*., 2014) The greater willingness of individuals to seek out cosmetic treatments, advances in technology and limited adverse events have contributed in this development. (http://www.asds. net/_Media.aspx?id=7204) SAT deposits in the abdominal region are a particularly common area of aesthetic concern for male and female patients of all demographic groups. Currently, many therapeutic options are available for the aesthetic treatment of the abdomen. (Lian and Avram, 2012) Existing procedures rely on either ablation (cooling, heating, or adipocyte disruption or dissolution), non-ablative effects (adipocyte lipolytic stimulation or ultrastructural modification), and physical removal (liposuction) of SAT. (Kennedy *et al*., 2015) High-intensity focused ultrasound (HIFU) is a recent, safe and effective non-invasive therapeutic option. It uses high-frequency acoustic energy (2 MHz, >1,000 W/cm^2) to ablate focal areas of SAT, sparing any damage to surrounding connective tissues, blood vessels, nerves, and overlying skin. (Fatemi, 2009) The thermal effects of HIFU rapidly raise adipose temperature above 55°C, producing coagulative necrosis, whereas the mechanical (cavitational) effects of this technology lead to adipocyte membrane disruption secondary to negative acoustic pressure. (Haar and Coussios, 2007; Kyriakou *et al*., 2011) There is currently one HIFU device cleared by the Food and Drug Administration (August 16, 2011) for noninvasive waist circumference reduction (LipoSonix™, Solta Medical, a division of Valeant Pharmaceuticals North America, LLC. Quebec, Canada), it targets SAT at a focal depth of 1.3 cm. Several studies (Solish *et al*., 2012; Shek *et al*., 2014; Jewell *et al*., 2011; Robinson *et al*., 2014; Jewell *et al*., 2011; Gadsden

****Corresponding author: Hector Leal Silva***
Universidad de Monterrey, Mexico.

et al., 2011; Fatemi and Kane, 2010) have confirmed the safety and efficacy of HIFU for central abdominal SAT reduction using 2 to 3 passes to deliver a mean total energy dose of 128 to 177 J/cm^2. Post-treatment adverse events with HIFU are transient and limited to tenderness, edema, focal induration, and ecchymosis. (Nassar *et al*., 2015; Shalom *et al*., 2013) Bony areas, such as the lateral margin of the lower abdomen overlying the anterior superior iliac spine, are best avoided to prevent wave reflection and subsequent cutaneous injury. (Saedi and Kaminer, 2013) This study evaluates the safety and performance efficacy of a new HIFU device, the LIPOcel™ system (Jeisys Medical, Inc. Seoul, Republic of Korea), incorporating a surface cooling technology, for Non-Invasive reduction of the subcutaneous adipose tissue in the abdominal area.

MATERIALS AND METHODS

Study Design

This single-center, prospective, randomized, baseline-controlled, unblinded, three armed clinical study was conducted at UltraLaser Center, Monterrey, Mexico. Every participant underwent one or two treatments with the HIFU LIPOcel device following randomly one of the three possible treatment protocols: A) 2 treatment sessions one month apart, one *by grid* pattern, one *by caliper* thickness; B) One treatment, grid pattern; and C) One treatment session, "pyramidal" approach, based on caliper thickness. The study proposal was granted Institutional Review Board approval, and was performed in compliance with international guidelines for Good Clinical Practice. All participants met all the inclusion criteria and none of the exclusion criteria, and signed an informed consent form.

Patients

Eligible subjects were male or female between 18 and 65 years of age, with presence of abdominal fat measured with caliper of at least 2.0 cm or more, BMI<35, in general good health, who agreed to maintain their weight within 5% by not making any major changes in their diet or lifestyle during the course of the study and signed an informed consent form. Subjects were excluded if they had any history of hypertension, heart disease, diabetes mellitus, metal plate in the treatment area, HIV positive status, previous liposuction or body contouring procedures in the treatment area, skin lesions, pregnancy, breastfeeding or any condition which might make it unsafe for the subject to participate in this study.

Device Description

The *LIPOcel system* is intended for use in non-invasive waist circumference reduction. It uses ultrasound energy to disrupt subcutaneous adipose tissue at a focal point of 13 mm. The device consists of a base, an arm, and a hand piece that contains the ultrasound transducer. The contact surface of the hand piece is cooled by a constant flow of cold water around the scanner during ultrasound treatment, intended to protect the skin from potential treatment related adverse events. Surface cooling does not affect focal point depth (13 mm) or energy dose.

Technology

The *LIPOcel* system accomplishes its intended purpose through precisely targeted HIFU energy that produces cellular disruption via thermal coagulative necrosis within the subcutaneous adipose tissue. The thermal energy also causes surrounding collagen to eventually contract, eliciting a dual tissue response, fat reduction and tissue tightening. The disrupted adipose tissue is subsequently cleared via an inflammatory response by macrophages that transport cellular debris via the lymphatic drainage system to the liver. The device used in this study functions by using a mechanical scanner that moves the ultrasound transducer over a square area that measures 9 cm^2 (3 X 3 cm), heating the SAT with the thermo-acoustic energy generated to promote adipocyte apoptosis. The entirety of a scan performed over a square is called a stack; the device can be programmed to repeat several scans over the same square site. This is done by modifying the stacking time. For example, if the stacking time is set to two, the device will complete two stacks in the same square.

Device Safety

The LIPOcel system conforms to its essential specifications, thermal, electrical, electromagnetic and mechanical safety, in accordance to medical device safety international harmonized standards.

Subject safety

Initial preclinical studies performed in animals with the LIPOcel system showed results comparable to those achieved using the LipoSonix system. (Jewell *et al*., 2011) The safety of treatment with the *LipoSonix* system was assessed throughout 24 weeks post-treatment. The AEs resulting from treatment with this device during this study were mostly mild, short-lived in duration, and resolved without incident. There were no serious adverse events (SAEs) or unanticipated adverse device effects (UADEs) related to treatment with the investigational device. (Jewell *et al*., 2011 Clinical safety in humans was evaluated and assessed throughout this study with the investigational LIPOcel system device.

Substantial Equivalence

The device used in this study is substantially equivalent to the *LipoSonix* system. Both devices have the same intended use, performing a non-invasive treatment to achieve a desired aesthetic effect. The *LIPOcel* system uses the same technology and principles as the *LipoSonix* system: HIFU, to thermally coagulate soft tissue which results in subcutaneous adipose tissue reduction. The mechanism of action for both devices is essentially the same as well: coagulated adipose tissue is removed by normal healing processes of the body. Both devices can deliver more than one energy dose at 13 mm depth within the subcutaneous soft tissue of the body.

Treatments

The LIPOcel treatments were performed on 30 patients divided randomly in 3 groups of 10 patients each, named Group A, B

and C. Three treatment schemes or protocols, one for each group, were designed based on the level of tolerance of the patient in order to use the higher tolerable energy in each patient. The treatment started with an average fluence of 85 J/cm^2 and the energy dose was lowered or elevated in increments of 5 J/cm^2 according to the patient´s tolerance. Once the energy was set, the treatment was performed using that fluence, unless the patient complained of excessive pain, in which case, the energy dose was lowered again by 5 J/cm^2 before proceeding with the remaining treatment. The time required to complete one treatment session was approximately 60 to 90 minutes. Two different methods were used to determine the treatment area. The first method (*By Grid*) consisted in following a grid provided by the device manufacturer to determine the area to be treated (Figure 1) and thus the number of squares to be used per treatment; the grid was used for the first treatment session of group A and for the treatment of group B. The second method (*By Caliper*) involved the use of a caliper to measure the size, limits and thickness of the adipose panniculus to be treated, squares were marked in areas within a thickness ≥2cm; this method as described was used for the second treatment session of group A, and was also used as the basis for the "pyramidal" treatment scheme used with group C; where the region limited by caliper ≥2cm constituted the first pass area, same as in group A, but inside that area, a new limit was set as an intermediate region (the limits of this area were established at the midpoint between the edge of the original area and the thickest SAT deposit measured by caliper), which received a second pass; and finally, the innermost region, determined around the thickest SAT deposit measured by caliper, received a third pass (Figure 2).

For Group A, each subject received two unblinded treatments, separated by four weeks. This group was assessed before treatment, before second treatment, corresponding to the 4-weeks follow-up (FU) visit, 4 weeks after the second treatment (8-weeks FU), and 8 weeks after the second treatment (12-weeks FU). The fluence of both treatments ranged from 65 to a maximum of 100 J/cm^2 per pass. The maximum fluence tolerated by the majority of patients was between 80 and 90 J/cm^2. The number of treatment squares per pass ranged between 16 and 28. In the first treatment session, the area to be treated was established *by grid*, following the one provided by the device manufacturer. For the second treatment session in this group, the area to be treated was determined *by caliper* measurements ≥2.0 cm thickness. The entirety of the area determined for treatment received one pass with a stacking time of 3 (equal to 3 passes). The sum of the 2 treatment sessions was then equivalent to 6 single passes.

For Group B, each subject received one treatment. The patients were assessed at follow-up visits 4, 8 and 12 weeks post treatment. In this group, every patient received two passes with a stacking time of 3, equivalent to 6 single passes. The fluences ranged from 60 to 95 J/cm^2 per pass. Most patients were able to tolerate a fluence between 80 and 90 J/cm^2 per pass. In six patients fluence was set ≥90 J/cm^2. The minimum amount of squares was 16, up to a maximum of 26 treatment squares in the abdominal area per pass. The area treated was established *by grid*. For Group C, each subject received one treatment, with multiple staggered passes, depending on caliper measurements. The subjects were assessed at 4, 8 and 12 weeks post treatment. In this group, every patient received a stacking time of 2for the first pass in all the abdominal region, a second pass also with stacking time of 2 in the intermediate region and finally, a third pass, with a stacking time of 2 in the area around the thickest fat point of the abdomen measured by caliper. The treatment was performed in a staggered way as in a pyramid, in which areas with less fat received less passes. Thicker areas received a total of 4passes and the area around the thickest point received the equivalent to 6 passes (3 passes with stacking of 2). The fluence in this group ranged from 65 to 110 J/cm^2 per pass. The fluence set for treatments was between 90 and 100 J/cm^2 for the majority of the treatments. During the first pass almost all of the patients tolerated a fluence between 90 and 100 J/cm^2. The minimum amount of squares were 13, up to a maximum of 86 treatment squares in all the abdominal area for the first pass. The number of HIFU shots for the whole treatment ranged from 38 to 172. The single patient that received 172 shots, was treated in the abdominal area and the flanks to assess the technology impact in an almost circumferential abdominal treatment.

In all three groups, the treatment scanner shot was stopped when patients experienced excessive pain, therefore some shots were lost. The shots lost were between 2 and 6 per patient. To reach the tolerated fluence the treatment started with a fluence of 85 J/cm^2 in groups A and B and with 95 J/cm^2 in group C, and moved it up or down (five by five) according to each patient's tolerance to pain. Pain was assessed during and immediately after each treatment through a Numeric Rating Scale (NRS) pain scale (Farrar *et al*., 2001) ranging from 0 to 10 in which 0 represents no pain at all and 10 represents intolerable pain.

Assessments

Weight, clinical photographs (S5 Pro, Fujifilm, Tokyo, Japan), 3D images (VECTRA 3D, Canfield Scientific, Inc. Fairfield, NJ, USA), BMI and body fat% using impedance device (InBody Co. Ltd, Seoul, Korea), waist circumference (WC) and caliper measurements were assessed in every patient before treatment and in every follow up visit. Caliper measurements, 4 measurements, corresponding to each of the 4 abdominal quadrants, were assessed before treatment and at the last follow up visit. Caliper measurements were obtained by professional caliper (Lange Skinfold Caliper, Beta Technology, Santa Cruz, CA) always by the same staff member, with the patient in standing position. The abdomen was assessed searching for the point with the thickest caliper measurement and marked, the patient was then measured from the floor to this point. This same mark was later used to measure waist circumference, ensuring circumference was measured at the same level where the greatest SAT deposit was located. Caliper measurements, height to thickest point, and waist circumference were documented initially and in every follow-up visit. The abdominal area was assessed for areas with caliper measurements< 2 cm, to define the treatment region for patients in the second treatment of Group A and for the treatment of group C. Waist Circumference measurements were

recorded using a standardized validated technique: a calibrated tape was used, subjects were instructed to be in a standing position, cross their arms and tuck their hands under the axillae, to relax their abdominal muscles, exhale, and hold their exhalation throughout each measurement. (Benritter *et al*., 2011) Computerized axial tomography scan (CAT scan) of the abdomen in a fixed horizontal position, were performed before first treatment and at 12 weeks FU visit in 4 patients; only 3 slices per subject per scan were taken to minimize exposure and risk to the patients. Computerized Axial Tomography Scan images were all obtained in a Brilliance 16 CT scanner (Koninklijke Philips N.V., Amsterdam, Netherlands) with the patient comfortably resting in supine position. The CAT scan single image per subject at the thickest point level was used to assess, at least in a sample sub-group, how fat thickness by caliper correlates with the subcutaneous fat layer with the subject in supine position, same position used to perform treatments (Figure 3). A second CAT scan image was obtained of each patient during the 12 week follow up visit, but irregularities in the height of the scan rendered the images useless for comparison with the baseline. A complete abdominal magnetic resonance imaging (MRI) study could have great value for this purpose in future studies.

Objective

The objective of this trial was to evaluate the efficacy and safety of a novel High Intensity Focused Ultrasound (HIFU) with surface cooling procedure (LIPOcel), for abdominal subcutaneous adipose tissue non-invasive reduction in 3 treatment modalities: A) 2 treatment sessions one month apart, one *by grid* pattern, one *by caliper* thickness; B) One treatment, grid pattern; and C) One treatment session, "pyramidal" approach, based on caliper thickness.

Primary Efficacy Endpoint: Statistically significant post treatment reduction at 12 weeks follow-up versus baseline in subjects who underwent LIPOcel treatment in one of the three Arms: A, B or C.

Secondary Efficacy Endpoints: a) Statistically significant post treatment circumference and caliper reduction at 2 weeks, 4 weeks and 8 weeks follow-up versus baseline. b) Comparison of the abdominal circumference and caliper reduction, Arm A versus Arm B, versus Arm C post LIPOcel procedure. c) Evaluate investigator satisfaction score using a 5-point Likert scale at all follow-up visits (4-weeks FU, 8-weeksand 12-weeks FU).d) Evaluate subject satisfaction score using a 5-point Likert scale at all follow-up visits (4-weeks FU, 8-weeksand 12-weeks FU).e) Evaluate subject comfort/pain during treatment using NRS scale.

Primary Safety Endpoint: To evaluate the safety of the treatment while analyzing the number, severity and type of any adverse event (anticipated or not) recorded throughout the study and post treatment (immediate and delayed response).

Statistical Analysis: All analyses were performed using SPSS v 21 (SPSS, IBM, Armonk, New York, USA). ANOVA one way test, t student for unpaired samples and statistical descriptive tests were performed for this study.

RESULTS

Subject and Treatment Characteristics

For this study population, 20 of the subjects enrolled were female and 10 were male. The subject ages ranged from 22 to 54, with a mean of 35.4 years. There was no weight specification in the eligibility criteria. Weight ranged from 48.7 to 116.1 kg, with a mean of 78.16 kg. Body Mass Index (BMI) ranged from 20.8 to 34.7, with a mean BMI of 30.46. No weight or BMI significant change was recorded throughout the course of the study in any of the participants. The mean total energy dose in Group A considering two treatments of one pass and 3 stacking each, 4 weeks apart (equivalent to a total of 6 single passes), was of 509.4 J/cm^2. For group B, considering a single treatment of 2 passes and 3 stacking (equivalent also to 6 single passes), the mean total energy dose was of 495 J/cm^2. And for group C, giving one complete pass with 2 stacking, then one semi complete pass of 2 stacking and a very concentrated one pass on the thickest area (equivalent to a treatment of 2 full passes and 2 stacking) resulting in a mean energy dose of 374 J/cm^2. The mean total dose energy of the whole cohort population was of 459.47 J/cm^2.

Efficacy

The primary effectiveness end point was abdominal fat reduction at the 12-week follow-up visit versus baseline measured by WC and by caliper (Figures 4, 5 and 6). In this study, Group A, using a mean total energy dose of 509.4 J/cm^2 had a mean waist circumference reduction of 2.95 cm and a mean caliper measurement reduction of 0.83 cm. Group B, using a mean total energy dose of 495 J/cm^2 had a mean waist circumference reduction of 2.4 cm and a mean caliper measurement reduction of 0.6 cm. And Group C, using a mean total energy dose of 374 J/cm^2 had a mean waist circumference reduction of 3.8 cm and a mean caliper measurement reduction of 0.85 cm. There were no statistically significant differences between groups in fat reduction measured either by waist circumference or by caliper. A statistically significant mean waist circumference reduction for all subjects of 3.05 ± 5.95 cm (p<.0001) from baseline was observed at 12 week follow up, with no significant differences in results between protocols including total fluence (394 vs 495 vs 509.4 J/cm^2), immediate versus delayed pulse stacking, or the use of multiple (6) low-fluence (65 J/cm^2) passes vs. fewer (4) high-fluence (110 J/cm^2) passes. A statistically significant (p <.0001) mean reduction by caliper for the whole study population of 0.76 cm ± 1.34 cm was calculated from the measurements at 12 weeks FU visit from baseline. Investigators and subjects performed satisfaction surveys. At the 12 week visit most subjects in all treatment groups stated being satisfied or very satisfied with the treatment outcome. For the complete study, 50% of the patients were satisfied, 13.3% of the patients were very satisfied, 33.3% of the patients were neutral and 3.3% (one case) of the patients were unsatisfied. For the physician investigator satisfaction survey, 80% were satisfied with the results, 10% were neutral, 6.7% were very satisfied and 3.3% (one case) were unsatisfied, (coincidentally, this was the same case where the patient reported to be unsatisfied).

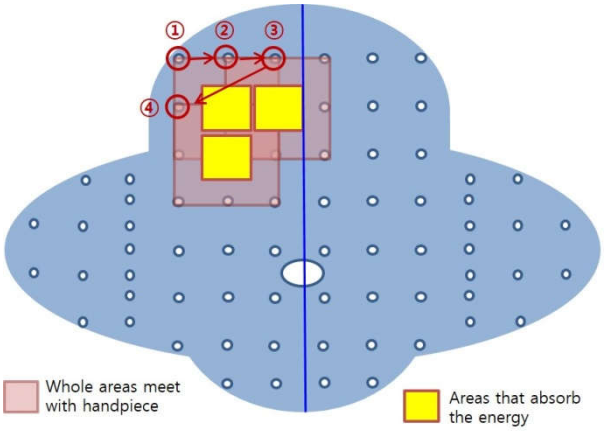

Figure 1A. Grid provided by the device manufacturer to determine the area to be treated

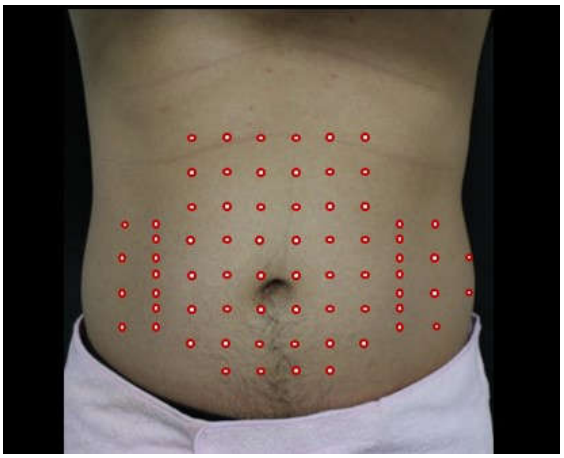

Figure 1B. Shows the abdominal area using the grid design, to be treated

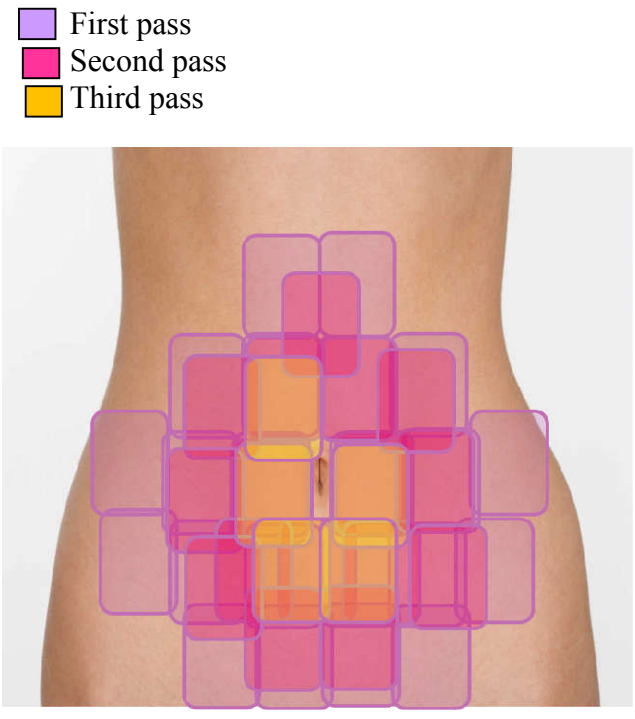

Figure 2. The "pyramidal" treatment approach

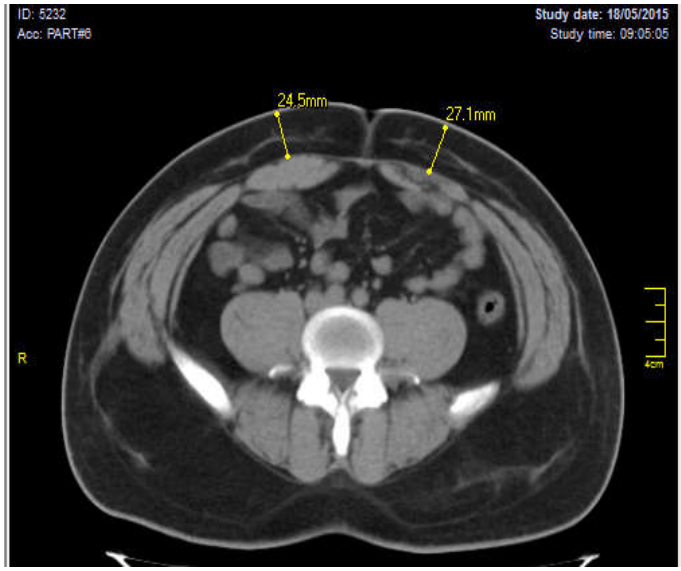

Figure 3A. Patient caliper measurement was 4 cm, related to 24.5 and 27.7 mm CT scan measurements

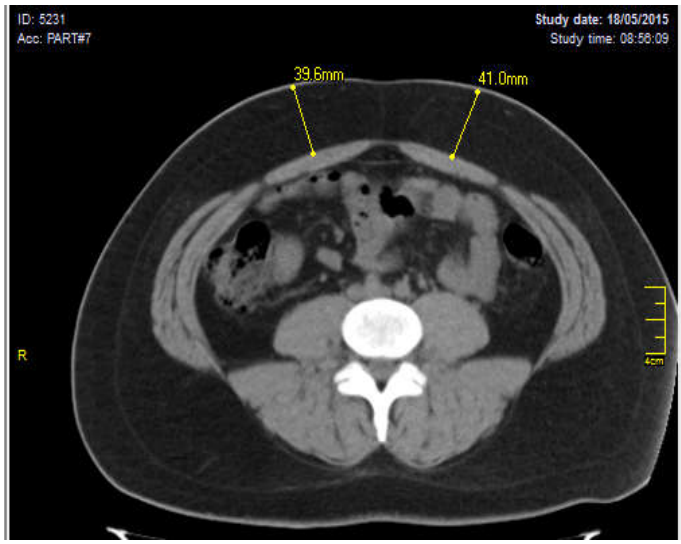

Figure 3B. Patient caliper measurement was 5.4 cm, related to 39.6 and 41 mm CT scan measurements

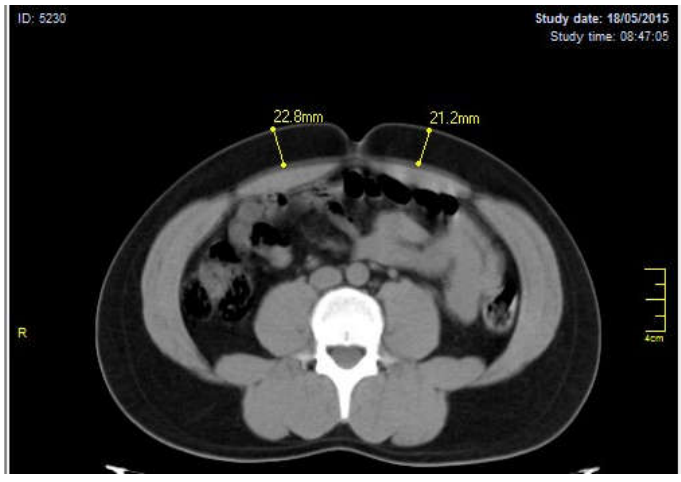

Figure 3C. Patient caliper measurement was 4.4 cm, related to 22.8 and 21.2 mm CT scan measurements.

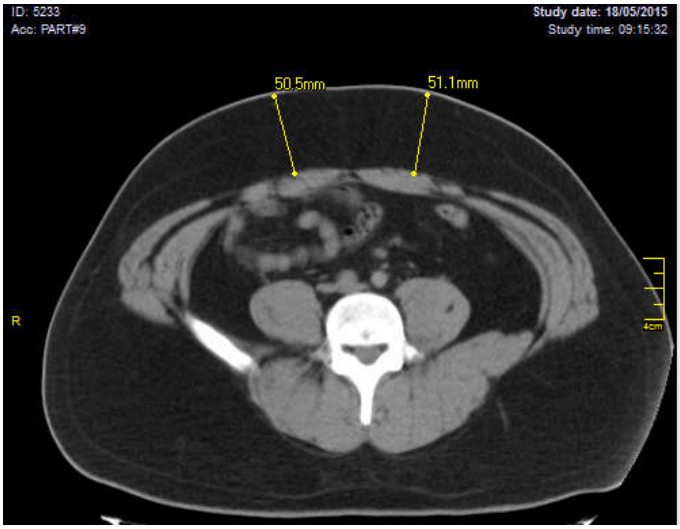

Figure 3D. Patient caliper measurement was 6.3 cm, related to 50.5 and 51.1 mm CT scan measurements

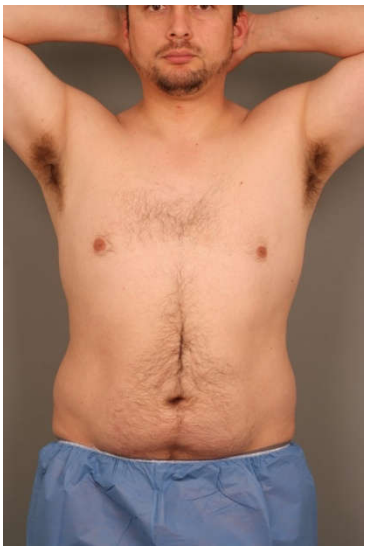

Figure 4A. Front Baseline

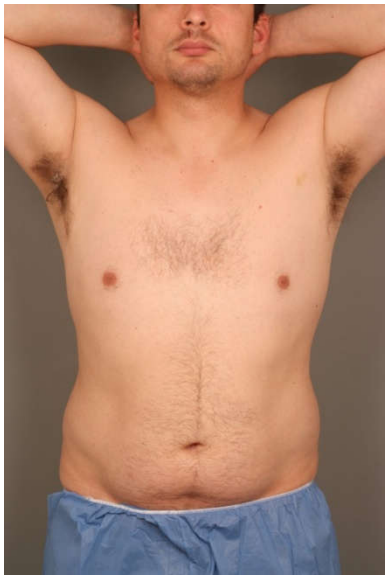

Figure 4B. Front First Follow Up

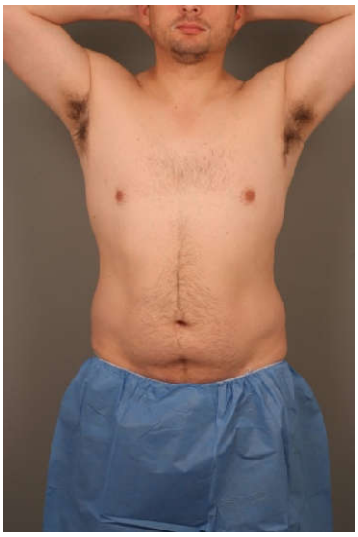

Figure 4C. Front Final Follow Up

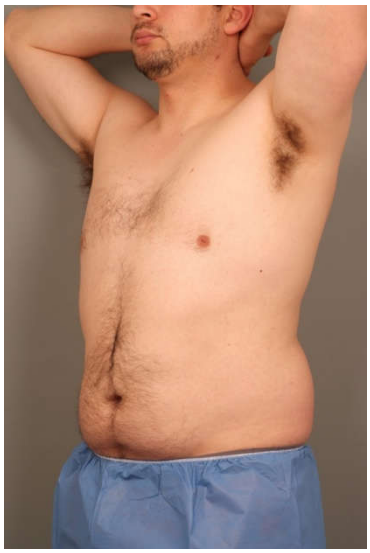

Figure 4D. Oblique Baseline

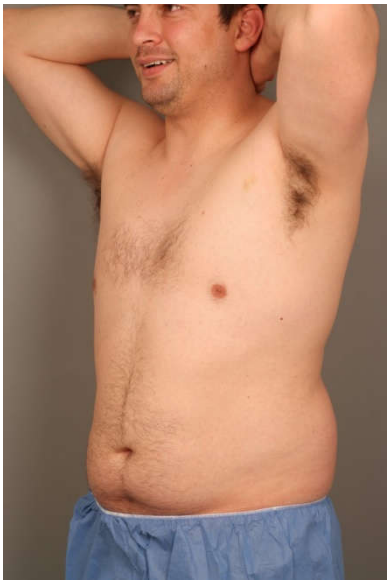

Figure 4E. Oblique First Follow Up

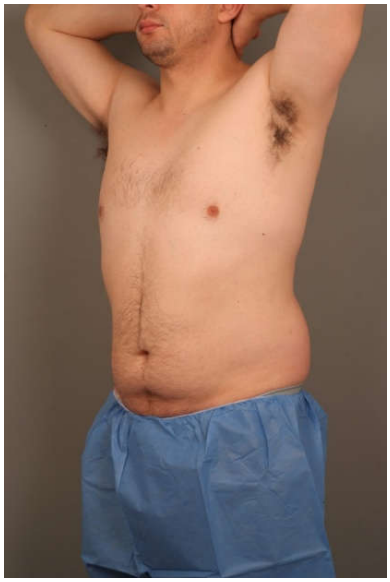

Figure 4F. Oblique Final Follow Up

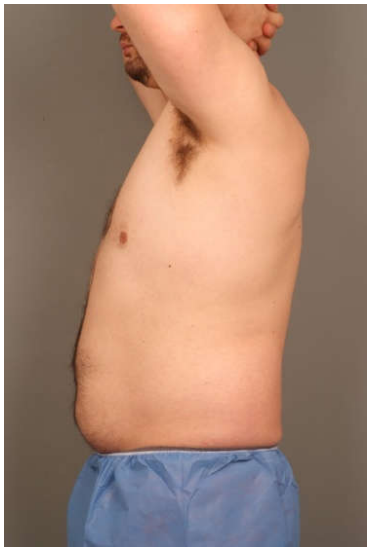

Figure 4G. Profile Baseline

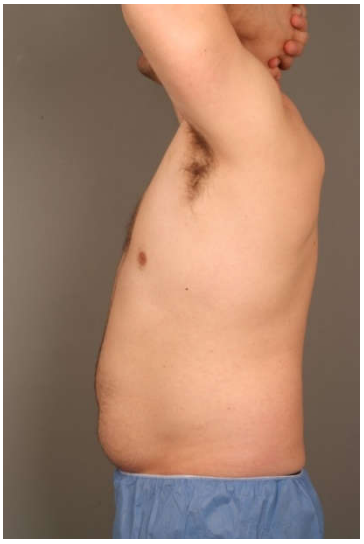

Figure 4H. Profile First Follow Up

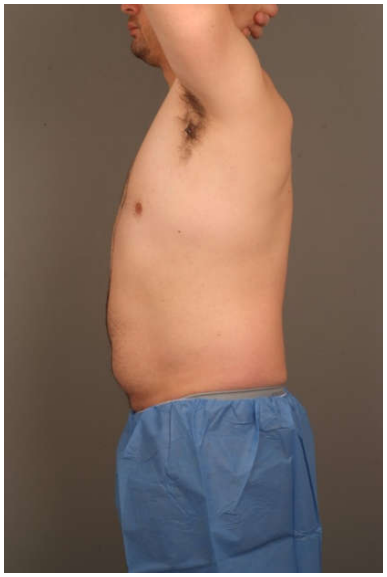

Figure 4I. Profile Final Follow Up

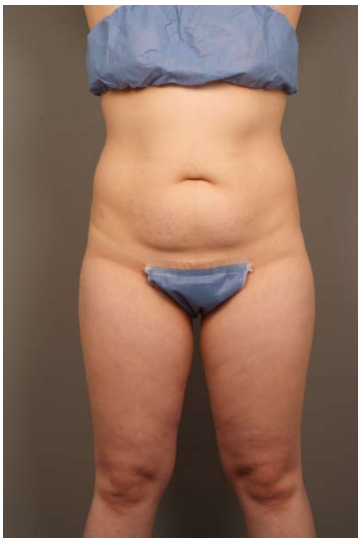

Figure 5A. Front Baseline

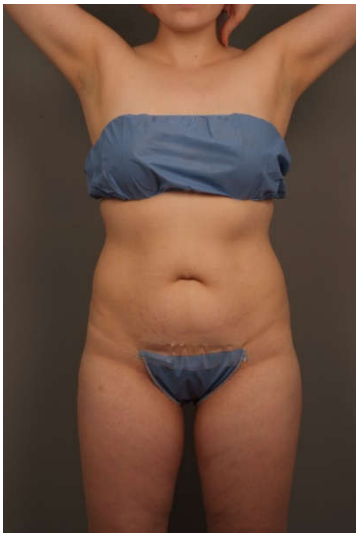

Figure 5B. Front First Follow Up

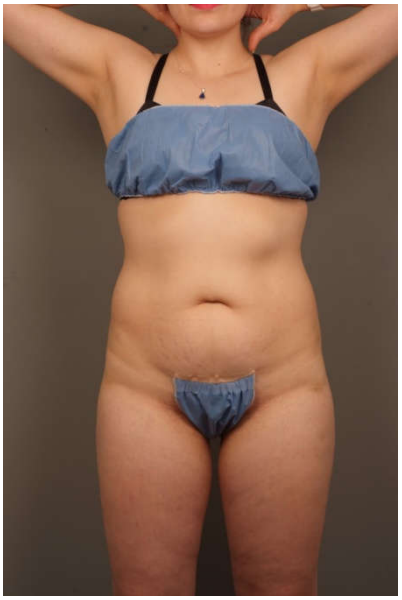

Figure 5C. Front Final Follow Up

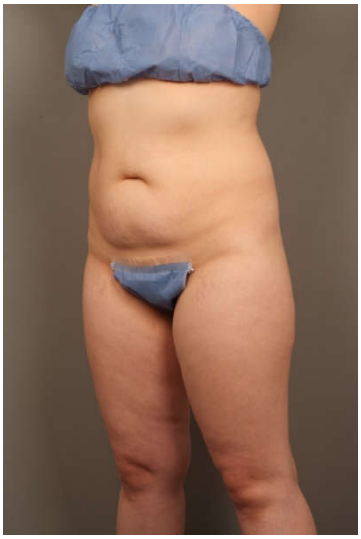

Figure 5D. Oblique Baseline

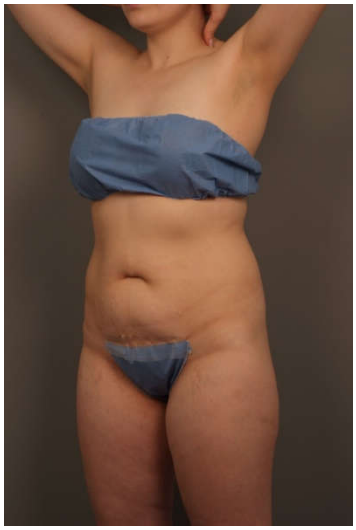

Figure 5E. Oblique First Follow Up

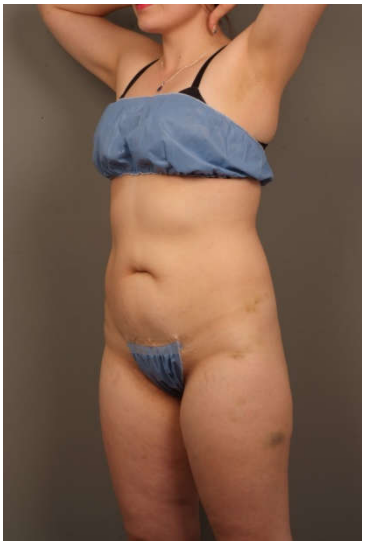

Figure 5F. Oblique Final Follow Up

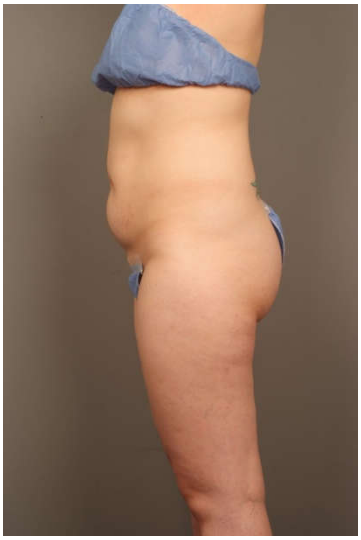

Figure 5G. Profile Baseline

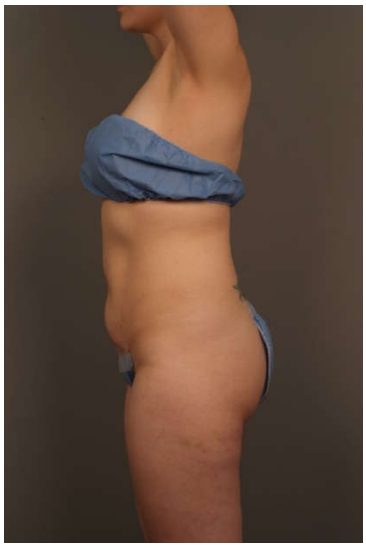

Figure 5H. Profile First Follow Up

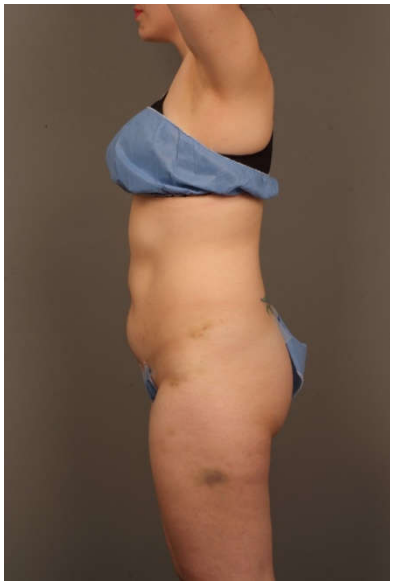

Figure 5I. Profile Final Follow Up

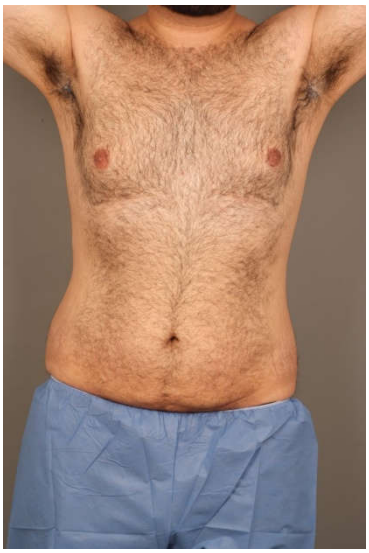

Figure 6A. Front Baseline

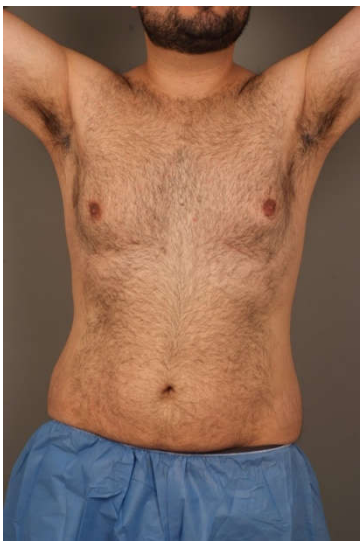

Figure 6B. Front First Follow Up

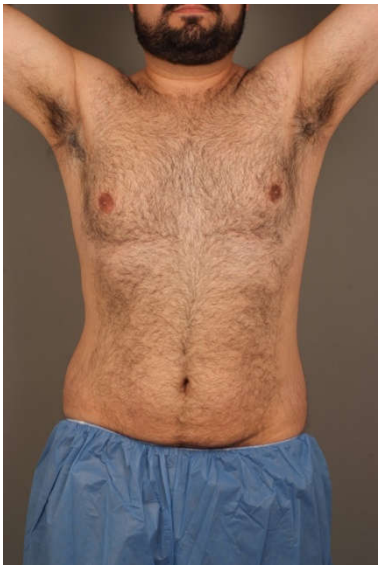

Figure 6C. Front Final Follow Up

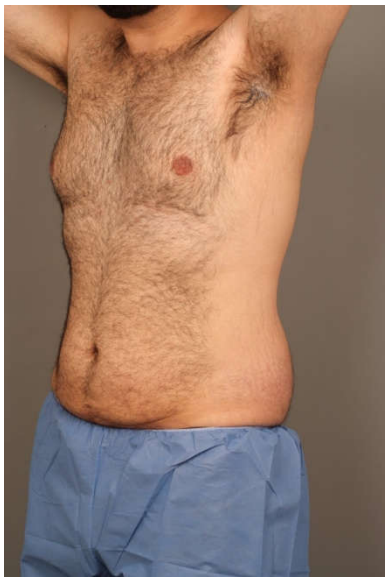

Figure 6D. Oblique Baseline

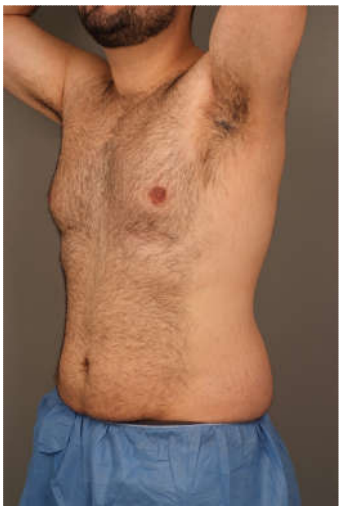

Figure 6E. Oblique First Follow Up

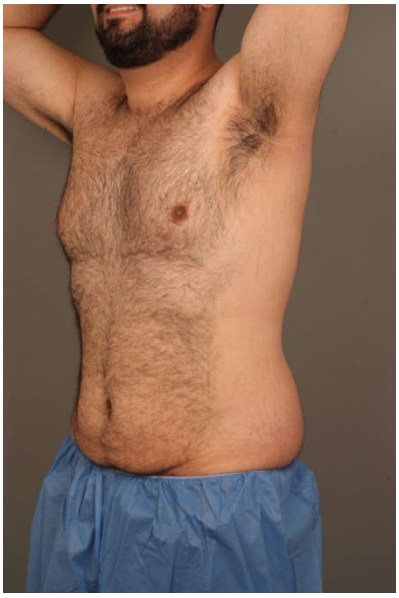

Figure 6F. Oblique Final Follow Up

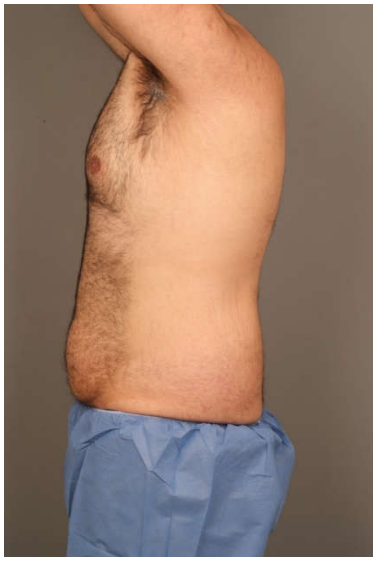

Figure 6G. Profile Baseline

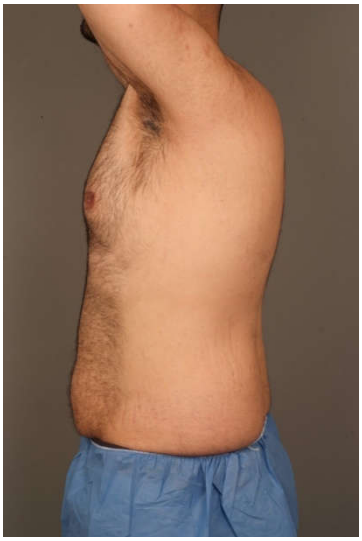

Figure 6H. Profile First Follow Up

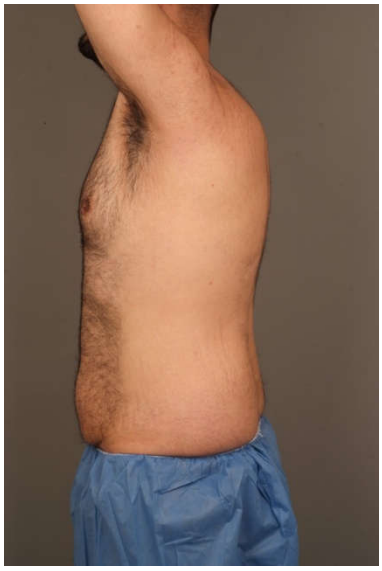

Figure 6I. Profile Final Follow Up

Safety

All adverse events occurred during treatments resolved later in the course of the study without treatment. The most common anticipated adverse events were erythema, ecchymosis and dysesthesia. One patient developed a non-anticipated urticaria-like reaction localized to treatment area, which resolved 48 hours later without treatment. Subject comfort and pain during treatment was assessed using the NRS scale immediately after the completion of treatment. The reported pain corresponds to the highest pain sensation reported post-treatment by the patient at specific points during treatment. In all treatments, less than 10 percent of the treatment squares were reported as painful, the rest were reported as completely tolerable (not painful). The mean pain score for group A was of 6.95, for group B was of 6.9 and for group C was of 8.2. The mean pain score for the whole study population was 7.35.In all cases, post-treatment pain was mild and resolved without treatment in less than two hours.

DISCUSSION

In this single center, randomized, controlled, prospective, unblinded study, one or 2 treatments of HIFU with contact cooling using one of 3 possible treatment protocols produced significant abdominal fat reduction, assessed by standardized waist circumference measurement, by caliper, and by patient and clinician scores. A number of studies (Solish *et al*., 2012; Jewell *et al*., 2011; Robinson *et al*., 2014) have confirmed the efficacy and safety of HIFU to treat abdominal SAT using 2 to 3 passes to deliver a mean total energy dose of 128 to 177 J/cm^2. The lack of a sham group constitutes a restraint in this study. The addition of a sham group would have increased the validity of the data; like Jewell *et al*, who reported significantly greater reductions in waist circumference at 141 and 159 J/cm^2 compared to sham treatments in a protocol population of 168 subjects. (Solish *et al*., 2012) Never the less, since a significant mean waist circumference reduction from baseline to the 12 week follow up with standardized measurements was the primary endpoint of this study, incorporating a sham group

probably would not have affected the results obtained. In this study, a mean total energy dose of 509.4 J/cm^2, 495 J/cm^2, and 374 J/cm^2 for groups A, B, and C respectively, was used, and despite the high dose of energy and the differences in treatment protocols, no significant differences were observed in fat reduction among groups. Subjects with fluencies set as low as 65 J/cm^2 per pass did not show significantly different fat reduction than those patients with fluences set (per patient's individual tolerance) as high as 110 J/cm^2 per pass. It is speculated that contact cooling of the system used for this study contributes to the high fluence tolerability while maintaining the incidence of adverse events low, comparable to the incidence of adverse events reported by several authors using lower fluence in devices without surface cooling. (Solish *et al*., 2012; Robinson *et al*., 2014) Part of the objective for this study was to evaluate the effectiveness of the surface cooling or contact cooling device, which theoretically allows for the safe delivery of greater energy doses. (Ikink *et al*., 2015) It is appealing to hypothesize that higher energy doses applied safely could be related to higher fat reduction. That was the basic idea behind the use of high doses of energy in this study, but contrary to the expected outcome, there were no significant differences in SAT reduction using higher energy doses. Adverse effects were more frequent in the subjects where energy was set higher, and there were no significantly improved results. The relatively high pain scores during treatments reported in this study could also imply little if any benefit to surface cooling. For the complete cohort of our study, the mean waist reduction was 3.05 cm, comparable with those results published by several authors using other HIFU technologies like Solish and colleagues, (Solish *et al*., 2012) who treated 45 blinded subjects randomized to 3 passes of either 141, 156, or 177 J/cm^2, showed no significant discrepancy between treatment arms, and obtained a mean reduction in waist circumference of 2.51 cm among all subjects in one session. In two unblinded multicenter trials, Robinson *et al*. (2014) randomized 188 subjects to multiple treatment protocols for HIFU of the abdomen and flanks. A statistically significant mean waist circumference reduction of 2.3 ± 2.9 cm (p<.0001) from baseline was observed at 12 week follow up, with no significant differences in results between protocols including total fluence (150 vs 180 J/cm^2), immediate versus delayed pulse stacking, or the use of multiple (5-6) low-fluence (30 J/cm^2) passes vs. fewer (3) high-fluence (60 J/cm^2) passes. Treated patients demonstrated clinically evident reductions in waist circumference (WC) as early as 4 weeks after treatment (1.1 ± 1.9 cm, p<.0001). In this study, analyzing waist circumference reduction at the earliest FU visit at 4 weeks, there was a significant reduction, mean 1.5 cm ± 2.5 cm (p<.0001). The best results were observed at 12 weeks post treatment, both by waist circumference measurement and by caliper. Shek *et al*. (2014) mirrored these findings with results dependent on total fluence and not the number of passes or fluence per pass, noting a WC reduction of 2.1 cm at 12 weeks after treatment, with results dependent on total fluence (150-165 J/cm^2). Therefore, using a greater number of passes with lower fluences per pass enhances the tolerability of HIFU. Robinson *et al*. (2014) observed no disparity between two treatment modalities, "grid-repeat" and "site repeat", the latter is comparable to the "stacking" functionality of the device used in this study. This study corroborates those findings, and it was observed that a stacking of two delivered similar results to a stacking of three. The majority of study subjects (90%) had some degree of abdominal circumference reduction and fat thickness by caliper measurements. The difference lies in tolerability; a stacking of three was generally too painful for the majority of patients, while a stacking of two was generally well tolerated.

Analysis by group

Group A received 2 treatments, separated by 4 weeks, each one of 3 passes (1 pass with 3 stacking) and a mean total energy dose of 509.4 J/cm2. Interestingly, the SAT reduction showed the same progression even with the first treatment (at 4-weeks FU) as the other arms; no significant differences between this group and the other arms of the study were found in terms of measurements. Even though this group received the greatest number of passes and the highest total energy dose, it was not the group that exhibited the better results, it even was the group with the only reported case of caliper (1 mm) and waist circumference (1 cm) measurements augmentations. This subject, curiously, reported to be satisfied and was assessed with satisfactory results by the investigators. The mean waist circumference reduction of this group was 2.95 cm and the mean caliper reduction was 0.83 cm. In Group B, two patients did not exhibit any waist circumference reduction and one patient reported just 1 mm of reduction in the caliper measurement. This group reported the least pain during treatment and the only patient unsatisfied with results in spite of a 2 cm waist circumference reduction and a 2 mm caliper reduction. The mean waist circumference reduction was 2.4 cm, and 0.6cm caliper reduction. Group B produced less significant results compared to the rest of the cohort. Treatments in Groups A and B were performed with a staking of 3, interestingly almost all report of excessive pain during treatment occurred during the third staking. Group C had the greatest significant (p < .0001) reduction in caliper (0.85 cm) and (3.8 cm) abdominal circumference measurements and none of the subjects in this group exhibited a reduction < 1 cm. The subject with the greatest individual reduction (9 cm), was in this group. Patients in this group reported the highest scores in the NSR pain scale (8.2), above the complete cohort's mean (7.35); although it is important to mention that high scores were directly proportional to the energy dose used. In the subject satisfaction survey at the final follow up, none of the patients reported to be unsatisfied, 2 of them reported to be very satisfied, and 3 to be neutral. In the investigators satisfaction survey, the results were satisfactory for 9 patients, and just 1 was reported to exhibit neutral results. It is important to mention that this group was treated with the lowest total mean energy dose (374 J/cm^2).

Conclusion

HIFU with surface cooling treatment using high fluence is safe and effective for abdominal SAT reduction assessed by standardized waist circumference measurement, by caliper measurement, and by subjective subject and investigator physician satisfaction scores. Although more studies are needed to validate these initial findings, it was observed that subjects treated with the "pyramidal" approach with 6 passes

(3 sequential passes with stacking time of 2) and fluences between 65 to 85 J/cm^2 per pass, tended to obtain the greatest SAT reduction with less discomfort and fewer anticipated adverse events.

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