Maximus™ TriLipo™ Technology for Cellulite treatment and Circumference reduction: assessment by objective non-invasive optical tests

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Running Title: TriLipo Maximus cellulite and circumference reduction - optical assessment

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Abstract

Introduction

A wide variety of devices based on monopolar or bipolar Radiofrequency (RF) technologies are available in the market. The Maximus device, based on TriLipo RF combined with simultaneous Dynamic Muscle Activation (DMA), is becoming one of the first choices for cellulite treatment and circumference reduction.

Currently, evaluations of improvement in cellulite and circumference reduction following various aesthetic treatment modalities have been based mainly on subjective and manual measurement methods, as accepted methods providing objective measurements were not commonly available. The current, randomized comparative study aims to assess the efficacy of the Maximus device based on the TriLipo technology for treatment of cellulite and circumference reduction, using non invasive non-contact optical measuring methods providing objective quantification.

Material and Methods

28 subjects with cellulite stage II - III (Nurnberger – Muller classification) were recruited. The Maximus treatment course consisted of six weekly treatments on one thigh while the untreated thigh served as a control.

Fast Optical In vivo Topography of human Skin (FOITS), a 3D advanced-optical measuring system was used to asses skin topography/texture, nodules and dimples ("orange peel" appearance), thigh volume and skin firmness at baseline, and at follow-up visits (one and 4 weeks after last treatment).

High Frequency Ultrasounds was used for assessment of changes in connective tissue.

Additionally, manual circumference measurements were performed weekly as a conventional objective evaluation method.

Photographs of thighs (treated and untreated) taken at base line and at follow up visits were evaluated by uninvolved physician to assess improvement of cellulite and skin texture

Results

No significant weight loss was recorded during the study. Statistically significant average difference of circumference reduction in treated versus untreated thigh was 1.2 cm with a maximum difference of 4.5 cm. Objective observation of photographs showed satisfactory significant improvement results at different levels in 80% of subjects. Results obtained using 3D texture analysis demonstrated a significant decrease in the amount of dimples and their size. The firmness measurements showed an increase in skin firmness consistent with the high frequency ultrasound measurements, where a dermis thickening as well as a reduction of hypodermis thickness was observed. 3D volume evaluation of the thigh showed a volume reduction and a correlation with the circumference measurement was found. Consistent results could only be observed on the treated thigh, the control thigh did not show any significant trend of change.

Discussion

Optical methods for tissue evaluation are based on mathematical models influenced by several internal and external factors. Judgment of the results should be based on trend analysis. Several factors were measured for each end point. We focused on the specific factor(s) considered the main reference to assess each end point.

Results demonstrated a trend of increase of skin firmness and volume reduction of the treated thigh. These results indicate that skin tightening was induced by the TriLipo RF that might have been enhanced by the muscle activation. The texture improvement is probably the result of this tightening combined with an increase of collagen manifested by the dermis thickening. Volume reduction is most probably the result of the tightening and the massage provided by the DMA.

The optical and ultrasound methods enabled obtaining 3D images of tissue changes and objective assessment of tissue thickening for better understanding the evolution of skin and cellulite change, following treatments.

Introduction

Cellulite or more correctly “gynoid lipodystrophy” is a multi-causal disorder affecting mostly post-pubertal women (85%). Cellulite is often described as an "orange peel," "mattress" or "dimpling" appearance on the thighs, buttocks and sometimes lower abdomen and upper arms of otherwise healthy women and rarely in men.

To better understand cellulite, a review of skin microanatomy is helpful. The outermost skin layer is the epidermis, immediately below is the dermis, rich with connective tissue. The next layer is the first of two layers of the subcutaneous (beneath the skin) fat. The prevailing evidence-based understanding is that cellulite originates in this first region of the subcutaneous fat (called the areolar layer), where cell chambers -or lobules - fat are arranged vertically in females[1,2,3]. According to this explanation, cellulite is caused by small protrusions of fat (called papillae adiposae) into the dermis, giving the skin the bumpy appearance referred to as cellulite. This theory has been confirmed using magnetic resonance imaging, ultrasonography and skin biopsy[4,5,6].

The skin irregularity is proportional to the subcutaneous fat projected into the upper dermis. The fibrous septae sequester fat in discrete packets and the vertically oriented bands are anchored to the deep fascia, causing the skin surface to pucker[7].

According to a second theory, cellulite results from a laxity (or weakening) of the connective-tissue bands in the dermis, with the fat protrusions occurring as a consequence[8].

Cellulite, excessive localized fat and lax skin are typically related to the weakening and thinning of dermal connective tissue and the enlargement of hypodermal fat cells. Significant clinical improvement may be achieved through surgical procedures, however these approaches may be associated with some risk, and therefore there is a growing demand for pain-free, non-invasive solutions that offer effective body shaping.

Several non-invasive treatments are available nowadays for body shaping, improved cellulite appearance and circumference reduction. These include professional devices based on optical energy or RF, devices based on vacuum and massage, devices based on electrical muscle stimulation and devices based on combined technologies. The mechanism of operation of such procedures involves stimulating the natural metabolic processes and increasing collagen regeneration in a gradual, safe, painless ‘lunch time’ clinical process [9-15].

The Maximus system, powered by the TriLipo technology, is a novel system developed and marketed by Pollogen™ Ltd.

The Maximus system combines TriLipo RF and Dynamic Muscle Activation (commercially termed TriLipo DMA). The TriLipo RF component of the system is identical to Pollogen’s Apollo™ system which uses a multiple-electrode, TriPollar design at RF frequency of 1 MHz and maximum power of 50 Watts. The TriPollar design is based on three or more electrodes. Published clinical studies confirm the safety and efficacy of the TriPollar technology[16-20].

The TriLipo DMA component of the Maximus system, uses the same multiple electrode array to deliver low frequency pulsed currents to underlying skin muscles.

The Maximus system is indicated for non-invasive body shaping, skin tightening, reduction of cellulite and treatment of wrinkles. The TriLipo RF energy generates heat through resistance in both the dermal and subcutaneous layers. Selective and focused electro-heating of the skin is intended to stimulate collagen remodeling and to increase fat metabolism. Simultaneously, muscle activation through the TriLipo DMA may increase circulation, venous return and lymphatic drainage thus resulting in effective oxygenation and removal of waste products.

In the current study we evaluated the safety and efficacy of the Maximus system, based on the TriLipo technology for non invasive improvement of thigh cellulite appearance and circumference reduction, using unique optical measuring methods for objective quantification.

Materials and Methods

Before the main study, a pilot test was carried out at Centro Medico Teknon, to assure safety and efficacy of the Maximus™ system and also to evaluate the accuracy of the optical tests selected for the trial. Following the supportive outcome of this pilot study, it was decided to conduct a larger scale study.

The study was approved by the Centro Médico Teknon Ethical Committee (Barcelona-Spain) and conformed to the guidelines of the 1975 Declaration of Helsinki. Informed Consent was obtained from all the patients. Exclusion criteria included pregnancy or expectation of pregnancy, active systemic or local skin infections, skin diseases affecting the area to be treated, having metal stents, implants, or any surgery in the treatment area, taking medications that might cause impaired skin healing such as steroid therapy, heparin, or related drugs. No other treatment of cellulite or body shaping procedure was allowed during the study.

Twenty eight (28) healthy female subjects, between the ages of 25 to 60 and with cellulite stages II - III (according to the Nurnberger – Muller 4 stages cellulite scale[6]), were enrolled in the study. Subjects were instructed to adhere to their regular diet, exercise program and lifestyle.

Subjects underwent six (6) weekly treatments for cellulite improvement and circumference reduction of one thigh. The other thigh was not treated and served as a control. Treated thighs were randomized among subjects.

Two follow-up visits were scheduled at one and four weeks after the last treatment for evaluation of treatment efficacy and safety results.

The treatment area was cleaned and lubricated with medical grade glycerin. Patients were provided with a ‘bio-feedback control’ which allowed them to stop the treatment in case significant discomfort was felt. The overall treatment time for one thigh was typically 30 minutes.

Treatment started with device default parameters of RF and DMA and continued with gradual increase of parameters, following treatment guidelines and according to each subject’s needs and tolerance. The treatment goal was to raise the patient’s skin temperature to an endpoint of 42^{O}C, while the patient simultaneously experienced muscle activation. The heating was usually accompanied with erythema and some variable-level edema while muscle activation was usually accompanied by a feeling of muscle contraction and slight tingling.

A non-contact, infrared thermometer was used to monitor external skin temperature during treatment which was maintained at a temperature of 40-42^{o}C.

Assessments and Evaluations:

Safety evaluation was based on observations of treated area by the investigators.

Efficacy evaluation included conventional methods such as photography and manual circumference measurements and more sophisticated optical measurements.

Thigh photographs (treated and untreated sides) were taken using a high resolution digital camera placed on a tripod. Photos were taken under standard settings such as: distance, angle, position, background and lighting. Uniform disposable underwear was used and the subject crossed the arms in front of the chest.

Baseline and follow-up photos were taken using the same conditions and settings.

Subjects' photographs were evaluated by a staff member who was not performing the treatments, thus permitting an objective evaluation of treatment visual efficacy.

Circumference measurements of treated and untreated thighs were taken using two methods: a conventional standardized manual measurement and Light Optical Topography non-contact measurements.

Standardized manual circumference measurements were taken at the beginning of each visit. Measurement was performed at the upper third of the thighs.

A height measuring and patient positioning device was used to define a fixed reference point (relative to the floor or other location) for the location of the measurements on each subject's thighs. The height of reference points for each subject was recorded. At least three marks of the same height at the front, back and sides of each thigh were made, and a measuring tape (with tension control) was placed across all marks creating a straight, horizontal and continuous line between the marks.

The optical measurements performed at the baseline and follow-up visits were 3D captures of the thighs with the Fast Optical in vivo Topometry of Human Skin (FOITS) technique, a method which provides a new approach for measurement of the skin surface. With this touch-free technique, three-dimensional information may be gathered from the skin surface. Due to the relatively high depth of focus and large area that is measured, it is possible to examine complicated test areas such as areas with cellulite. The FOITS measurements were done using the Fringe projection technology of the Dermatop system (Eothech, France).

Optical measurements included:

- Circumference measurements using Light Optical Topography non-contact measurements of the FaceScan III EO for objective circumference measurements. The body station of the DermaTop FaceScan for skin and body measurements was used.

- Skin appearance and cellulite morphology changes such as dimples and nodules were measured by the FOV application of the DermaTop V3 device. Analysis included calculations of average dimples amplitudes, depth and volume and 3D representations of the measured areas.
- Skin Firmness was optically measured by the Dynaskin application of the Dermatop system, which blows air perpendicular to the area of interest. Analysis of results reflects skin firmness, sagginess and laxity.
- Ultrasound measurements were conducted using a real time ultrasound scanning device to measure the thickness of the dermal connective layer according to constant reference points (DUB-Taberna Pro Medicum-Germany).

Firmness and Texture measurements were performed on two zones: the anterolateral zone of the thigh and the posterior side of the thigh under the buttock fold (Figure 1). Ultrasound measurements were performed only on the anterolateral zone.

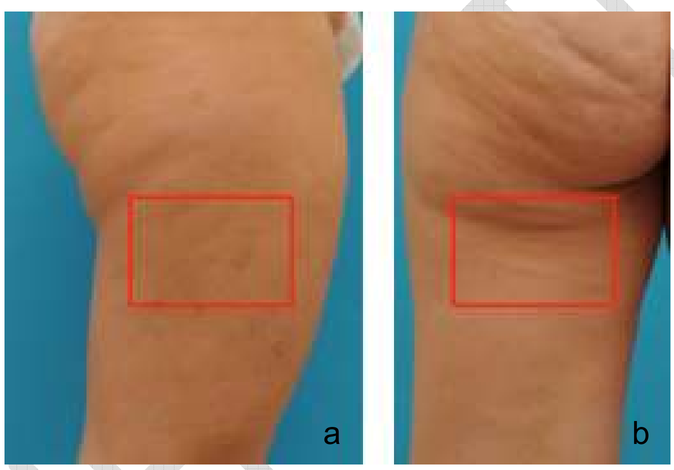

Figure 1: a - Anterolateral zone, b - Posterior Zone. The red squares indicate where the Texture and Firmness measures were taken.

Statistical analysis

The results of treated and untreated thighs as well as the treatment effects were analyzed using Paired Student t-tests and Wilcoxon W tests depending on the adjustment to a Normal distribution of the samples. The Pearson Correlation Test was used for the circumference measurements. Some trend simulations were performed in some cases where statistical significance was not found. For all the tests, a result was found statistically significant for $p<0,05$ and $p<0,01$ or even $p<0,001$ when possible.

Results

The collected data has clinical and instrumental aspects.

From a clinical point of view, the subjects' assessment was performed independently by the personnel involved in the treatments and by a blinded evaluator assessing only the photographs and the subject's file.

Out of the 28 recruited subjects, 2 were forced to quit the study for medical reasons (not related to the treatments) on week 2 and week 4 respectively. Three other subjects couldn't be present at their follow-up visit on week 10 and thus their data is only considered until week 7. Thus 26 subjects' data was used for the week 1 (baseline) to week 7 (1 week follow-up) analysis and 23 were considered for the week 1 to week 10 (4 weeks follow-up) analysis.

No unexpected adverse side effects were observed during the study. All subjects who received the full course of 6 treatments reported no pain during the treatments. Thus, the primary end-point of safety was successfully achieved according to the clinical protocol.

The personnel involved in the treatments that kept contact with the subjects throughout the whole study, assessed a general improvement of the treated thigh in most of the subjects. However, as expected, their scoring of cellulite grade according to the Nurnberger – Muller 4 stages cellulite scale did not indicate improvement at the follow-up visits as compared to baseline as this scale uses major structural differences between grades. This scale was used in the study only for purpose of subjects' classification for recruitment..

The doctors participating as observers (one of them acting as a blind evaluator), whom analyzed the photographs and the CRFs, rated 12 subjects (48%) as showing very satisfactory result, 3 (12%) as showing satisfactory result, 5 (20%) as showing slightly satisfactory results and 5 (20%) as showing no or unsatisfactory results. In all the cases they were able to correctly determine which of the two thighs had received the treatment and which one was the control thigh.

The subjects' level of satisfaction with the treatment results correlated with the observers' assessment.

Example photos showing improved appearance of treated versus untreated thighs in two representative subjects are presented in Figures 2 - 3.

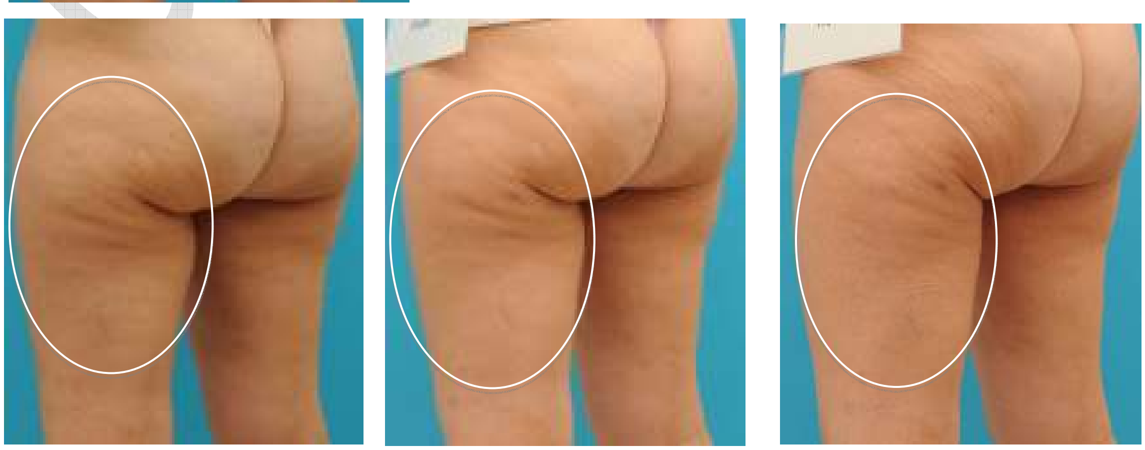

Figure 2: Back (up) and 45º view (bottom) photographs of one of the study subjects taken at week 1 (left), week 7 (middle) and week 10 (right). Treated area marked.

Figure 3: Side view photographs of one of the study subjects taken at week 1 (left), week 7 (middle) and week 10 (right). Treated area marked.

The results for the various end-point measurements are detailed as follows:

<u>Circumference</u>

Circumference evaluation was performed on both thighs using two methods. The conventional manual method was used on a weekly basis at the beginning of the patient's visit. Additionally, 3D captures taken at baseline and at weeks 7 (1 week follow-up) and 10 (4 weeks follow-up), were used to extract the thigh circumference at the exact same place where the manual measurements were performed. However, in many subjects this location was not fully available for the 3D captures as both thighs were in direct contact or left a cleft too small to allow a full capture of that region. For this reason the optical circumference evaluation could be performed at the same height as the manual for only 9/26 subjects. Additionally we used a novel mathematical algorithm embedded in the 3D software, to estimate the thigh circumference based on a 5cm section of the 3D model. We then proceeded to analyze the sets of data. The numerical results for all these techniques can be seen in tables 1a and 2a of the Annex.

Manual circumference measurements were analyzed for 23 subjects that finished all study visits. Circumference reduction at last follow-up visit comparing to baseline, was calculated in treated and untreated thighs. A statistically significant ($p<0,001$) higher reduction in treated versus untreated thigh was demonstrated with an average difference of 1.2 cm and a maximum difference of 4.5 cm.

In general we found that the optical circumference measurements were around 5% higher than the manual ones and, after running a Pearson Correlation Test, we found a Pearson Correlation Coefficient $r=0,91665$ with $p<0,001$ thus proving there is a very strong and statistically significant correlation between the manual and optical circumference measurements. The mathematical estimation technique falls somewhere in the middle being in average around 2,5% higher than the manual measurements. It shows high

Pearson Correlation Coefficients with both the manual measurements (r=0,94521 with p<0,001) ant the optical ones (r=0,96048 with p<0,001).

Texture

Cellulite texture is composed of two main structures, dimples and nodules that contribute to its “orange peel appearance”. These two structures act at very different scales, as dimples can be several centimeters large and mainly affect the waviness of the skin, while nodules are 2-3mm structures affecting the roughness of the skin. Therefore, we analyzed the waviness and roughness of the skin separately on the outer thigh and inner thigh as the treatment protocol had established different parameters for each zone.

Dimples

The dimples analysis was performed from a 3D capture of a 50x60 mm area. The main parameter considered was the summed volume of all the dimples present on the sampled area. If the cellulite condition improves the dimples become shallower and their volume is reduced. Contrarily, if the cellulite condition worsens the dimples become deeper and their volume increases.

The data sets did not adjust to Normal Distribution, thus we proceeded to compare them with non parametric statistical tests (Wilcoxon test). The comparison results for Week 7 and Week 10 (follow –up visits) to Week1 (baseline) showed no statistically significant differences even though some difference was visually perceived and a trend could be observed in the data. Therefore we proceeded to an evaluation of those trends and patterns of changes through statistical simulation on a virtual larger population size (5 folds the original sample size) following the same trends.

On week 7 the measured values still did not reveal a significant change. On week 10, however, the difference between the treated and untreated leg was statistically significant with p<0,001 for the outer thigh region and p<0,05 for the inner thigh region. An example of the dimples evolution through weeks 1,7 and 10 for both legs can be observed on Figure 4.

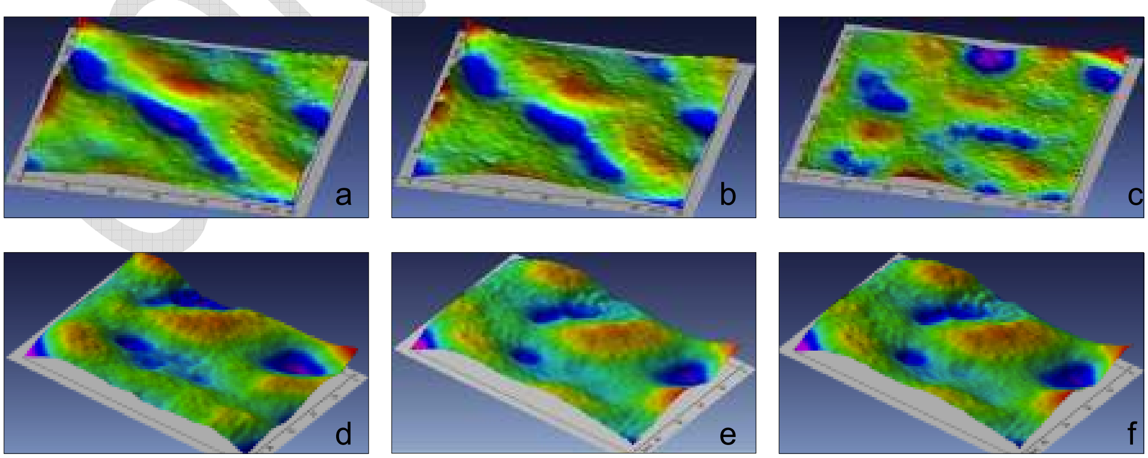

Figure 4: a, b and c: Dimples evolution on 3D captures in the treated thigh at weeks 1, 7 and 10 respectively. d,e and f: Dimples evolution on 3D captures in the untreated thigh on weeks 1,7 and 10.

Nodules

The nodules analysis was performed on a 50x60 mm area where roughness changes were studied for the assessment. Two parameters were considered: S_A and S_R. S_A is the Arithmetic Average Surface Roughness and is calculated by averaging the total amount of peaks and valleys of that surface. As nodules are the abundant source of peaks on the surface of cellulite skin, at a roughness level, a decrease of the S_A correlates directly to a decrease of the number and/or height of the nodules. The S_R is the Surface Ratio. It compares the skin surface of the captured area with a perfectly flat 50x60mm area. The closer the S_R value is to 1, the flatter is the surface and thus there are fewer nodules. The S_A parameter is often more useful for clinical assessment and therefore served as the criteria guiding our clinical evaluation; the S_R parameter is more sensitive to minute changes and is, for that same reason, more useful for the statistical analysis. An example of roughness changes and corresponding nodules condition for both thighs on weeks 1,7 and 10 is shown in Figure 5.

As for the dimples, no data set adjusted to a Normal distribution and when comparing treated and untreated thigh at weeks 1 to week 7 and 10, no statistically significant difference was found even if visually some improvement could be perceived. Thus, again we performed a simulation analysis with a population 5 times larger, the S_R parameter of the anterolateral region showed statistically significant differences ($p<0,05$) between the treated and untreated thigh when performing the Wilcoxon Test. No other parameter showed differences for week 7 on the simulation. On week 10, however, both S_A and S_R showed statistically significant differences on the anterolateral region ($p<0,01$ for both parameters) and the posterior thigh region ($p<0,05$ for both parameters). Their significance is reinforced by the fact that these results were achieved also when simulating a population only 3 times larger than the original.

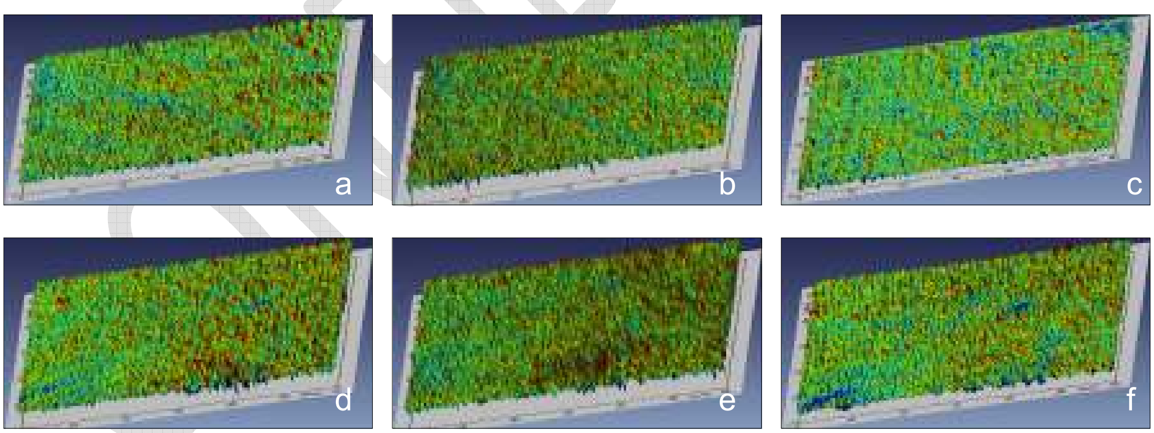

Figure 5: a b and c: Nodules evolution on 3D captures in the treated thigh at weeks 1, 7 and 10 respectively. d, e and f: Nodules evolution on 3D captures in the untreated thigh on weeks 1,7 and 10.

Firmness

The firmness measuring technique consisted of a 4g air jet blown perpendicularly over the skin. The skin deformation caused by the air jet was captured in 3D and the characteristics of the cavity were evaluated. Two parameters were chosen as the most representative, the Mean Depth (MD) and the Volume of Deformation (VD). The Mean Depth (MD) represents the average depth of deformation caused by the air jet. As changes of firmness will result in a more or less collapsed skin, the MD is extremely useful for the clinical assessment, especially when changes of firmness are not necessarily homogenous in the three dimensions of space. Thus, on the follow-up measurements, the skin deformation can take different shapes (Figure 6). However the MD describes changes in only one dimension and can be sometimes a slightly insensitive parameter when performing statistical analysis. Therefore we also considered the Volume of Deformation (VD) as a second complementary parameter. VD alone can't give a full firmness assessment as width and length reduction can produce a VD decrease even if the depth of the deformation increases. But at the same time, as its variations represent changes in the three dimension space, it can be a very sensitive parameter, particularly useful for statistical analysis.

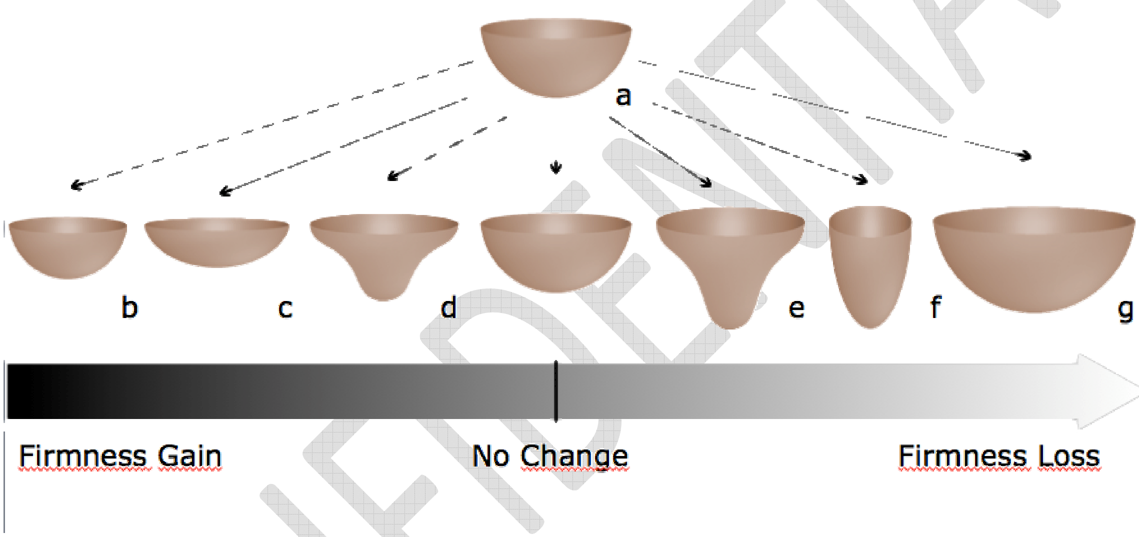

Figure 6: a. Ideal skin deformations at week 1. b. Ideal follow-up deformation where all the firmness parameters improved. c &d. Skin deformation with partial firmness improvement. e & f. Skin deformation with partial firmness loss. g. Ideal skin deformation caused by a complete firmness loss.

Only the data set from weeks 1 and 10 adjusted to a Normal distribution. Parametric tests (paired Student t test) were applied to those weeks while non parametric test were used for the others. No statistical difference was found for the MD and VD of either region for the week 7 to week 1 comparisons. When simulating a population 3 times larger, a statistically significant difference ($p<0,05$) was found for the MD of both zones when comparing the treated and the untreated thigh. For the week 10- week 1 comparison, only the VD of the posterior thigh region showed a statistically significant difference ($p<0,05$) even though the VD of the anterolateral region was close to it with $p=0,053$. When performing a simulation with a population twice as big, the rest of parameters showed a significant difference with $p<0,05$ for both MD and $p<0,01$ for the VD of the anterolateral region.

An example illustrating images of the 3D captures for firmness assessment are demonstrated in Figure 7 below.

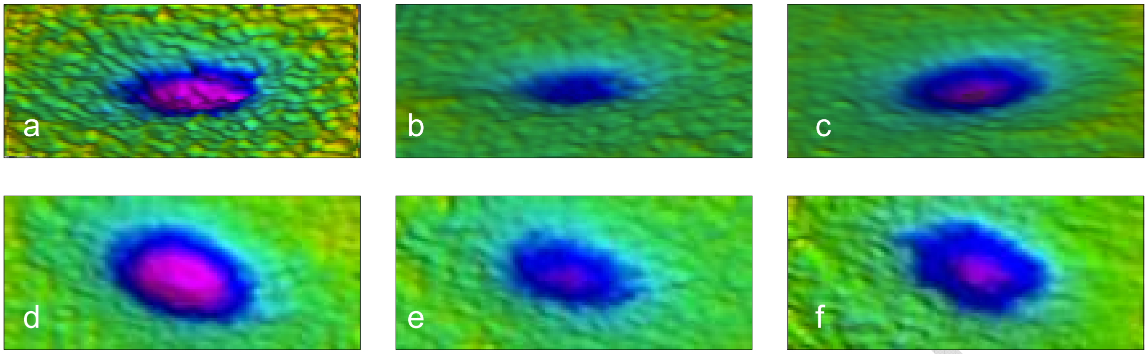

Figure 7: a, b and c: Firmness evolution on 3D captures in the treated thigh at weeks 1, 7 and 10 respectively. d, e and f: Firmness evolution on 3D captures in the untreated thigh on weeks 1,7 and 10.

<u>Thigh Volume</u>

As previously mentioned in the circumference section, a 3D capture of both thighs was performed. Ideally the volume comparison would be carried out on a 10cm high portion of each thigh. This portion should include the point where the manual circumference was measured (Figure 8). However, this point was not always accessible and the portion had to be taken at another point. In these cases, even if the area used for volume 3D capture did not include the manual measurement, the portion of thigh evaluated was large enough to be representative of the whole thigh evolution.

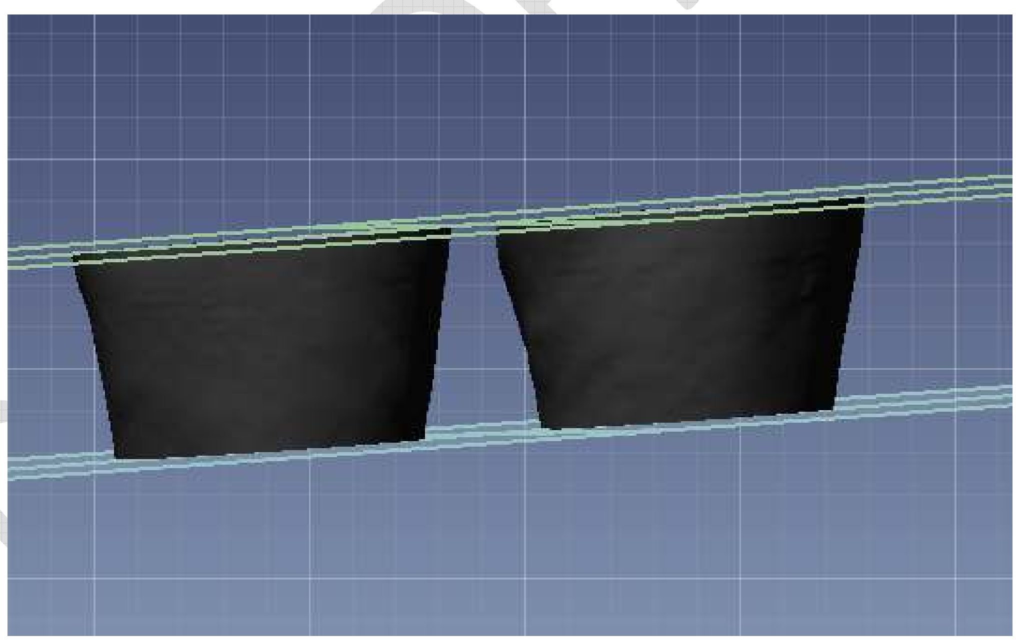

Figure 8: Selection of the thighs portions for Volume evaluation.

Additionally, the thigh volume affected by the treatment corresponds mainly to the skin volume of the thigh affected by an RF treatment with a 2cm penetration depth. Therefore, thigh volume change was established by assessment of skin volume changes of the first 2 centimeters of the thigh section. The differences can be seen in the thigh sections illustrated in Figure 9. This method doesn't change the results, only their scale, and this new volume proportion was marked as V'.

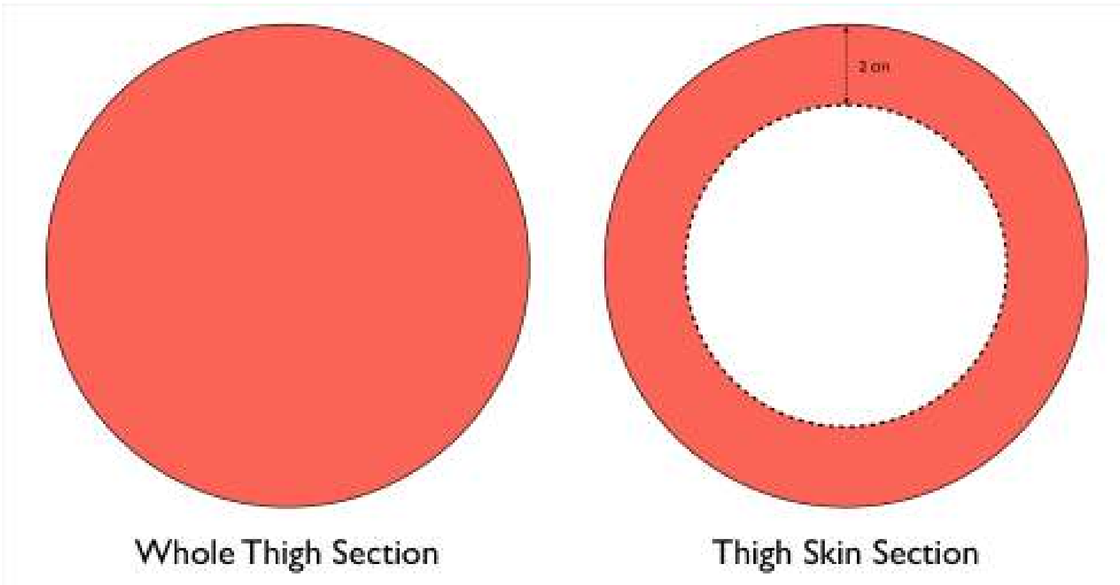

Figure 9: Section of the thighs portions for Volume evaluation

Results demonstrated a trend of slightly better improvement of volume (V') in treated thigh versus untreated when comparing week 7 to baseline.

Simulation of a population 5 times larger found a statistically significant difference ($p<0,05$) between the treated and untreated thigh at week 7

<u>Ultrasound measurements of Skin Structure</u>

<u>Dermis Thickness and Density</u>

An Ultrasound Device was used along the thighs of each patient with a 22MHz probe realizing between 50 and 80 scans. Measurements of Dermis Thickness (DT) and Dermis Density (DD) can be performed on every scan. DT is a metric distance given in µm and DD depends on the tissue's echogenic level. Tissues with a considerable amount of ordered structures, as collagen, are highly echogenic and present a high DD. An increased DD on the dermis is closely related, although not exclusively, to collagen increase. Therefore the DD is a semi-quantitative parameter (as it indicates increase or decrease of the dermis constitutive elements) and semi-qualitative parameter (as echogenicity changes also depend on the dermis composition). The DT and DD for every thigh and week were the result of averaging 10 DT and DD measurements regularly spaced along the thigh. Only the outer thigh region was measured in this case.

Results demonstrated a trend of improvement in DD and DT values measured on weeks 7 and 10.

Figure 10 illustrates the results obtained and the apparent differences between legs.

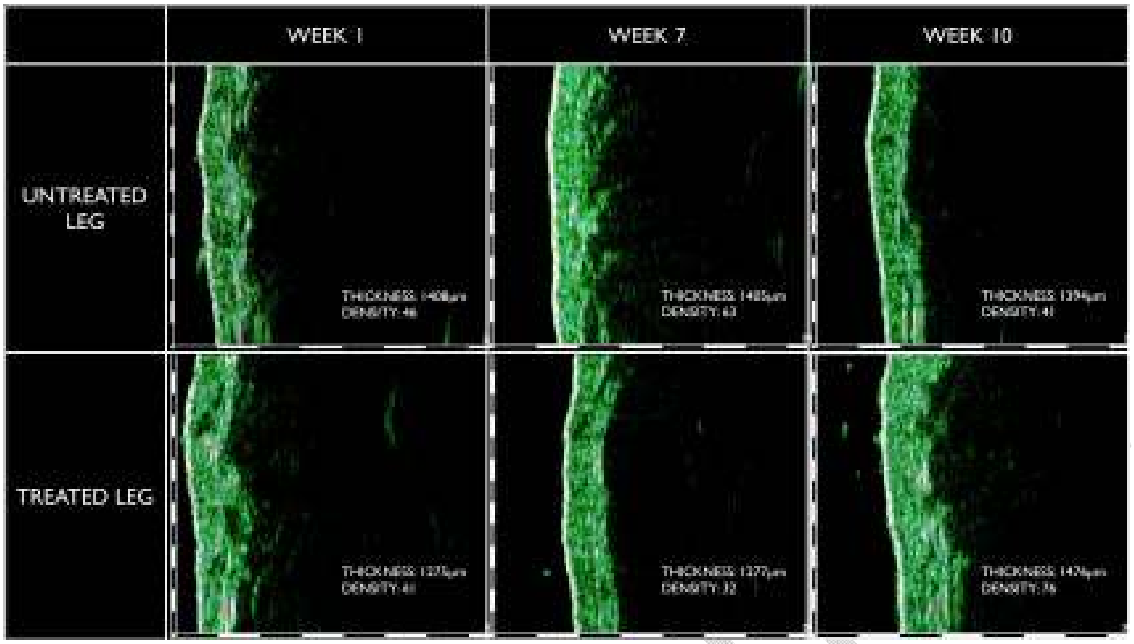

Figure 10: Ultrasound scans for the untreated and treated thighs of one patient for weeks 1, 7 and 10 with their respective DT and DD.

All the Ultrasound data sets adjusted to a Normal distribution. Simulation of a population twice as large following the same trends, showed a statistically significant difference ($p<0,05$) for the DD when comparing the results of week 10 to the week 1.

<u>Dermis homogeneity</u>

The Standard Deviation associated with every DT and every DD used for our evaluation was obtained. As the Standard Deviation is indicative of the sample dispersion, the Standard Deviation found within every thigh is representative of the homogeneity of its dermis. Thus heterogeneous skin, with a highly variable dermis thickness and/or density should have higher Standard Deviations. Hence we compared the Standard Deviation of the Dermis Thickness (SDT) and the Standard Deviation of the Dermis Density (SDD) to see if they could provide more information about the treatment effects on the skin. The numerical results can be found in table 1a of the annex.

From a visual point of view, greater skin homogeneity (thus lower SDT and SDD) translates into a flatter dermis-hypodermis junction as there would be less and/or smaller fat tissue protrusions into de dermal tissue. According to the numerical results, the SDTs of the treated thigh present a much softer increase than the untreated thigh, suggesting that the treatment may be acting as a buffering agent thus being consistent with the other tests results. The SDDs follow a similar trend on week 7, most probably for the same reasons. On week 10, though, the SDD of the treated thigh rose very close to the untreated thigh levels. In this case the loss of homogeneity is probably related to the neocollagenesis processes that are starting to take place. All these observations are visible on the ultrasonograms present in Figure 10.

Discussion

This current study demonstrated the safety and efficacy of the Maximus device for cellulite improvement and circumference reduction. Considering one of the goals of this study, to introduce optical tests as an objective measurement method to assess clinical trials, the consistency of the results as well as the clinical evaluation, give us confidence in these high sophisticated tools.

Several possible bias sources can affect the results interpretation. The first may be the diversity of our subject population. The wide age range and diversity in cellulite condition among subjects is reflected in the high values of Standard Deviations of the study results demonstrating that a logically wide range of results was also found. Milder cellulite degree patients will have less room for improvements and older patients may have a reduced neocollagenesis capacity, etc. Despite this, positive and consistent results were found, underscoring the treatment efficacy even in restrictive conditions.

The specific area and structure of the thigh should also be considered for two main reasons. First, the inner and outer thigh areas express histological tissue differences at a skin level, and go through different mechanical stress during the daily routine. Second and maybe the major reason, is that the treatment protocol established different treatment times and RF intensities for each zone, therefore, differences are to be expected between them. Additionally, simulation interpretations can be useful but, if taken without the due precautions, might be misleading. Our aim, when performing them, was to increase the sensitivity of the statistical test in order to reveal differences in the results that are statistically not discernable with a relatively small sample size. We self-imposed a size limit of five times the size of our real sample, as we didn't want to sacrifice scope in the search of sensitivity. The differences found are only applicable to the study's sample, as a real population sample with the size of the simulated ones may or may not have shown exactly the same trends that we observed.

The results presented in the previous section consistently point to three main conclusions:

- The treatment results observed on week 7 are mainly related to the skin´s heat-induced retraction.
- The treatment results observed on week 10 are the result of long term heat-induced neocollagenesis and tissue remodeling.
- The treatment also plays a role as a "buffer" against the expected evolution trend of the cellulite condition

The optical circumference results support the manual measurements as an objective follow-up tool, given the high correlation observed. The 5% of average difference between these two measuring techniques may have two main causes. The manual measurement may tend to underestimate circumferences as there will always be an inclination to slightly tighten the measuring band. There may be evidence of this on the circumference decrease observed on the untreated legs, (which was statistically not significant). This underestimation, however, is not a problem as it is a consistent error that does not interfere with the results. The 3D technique, on the other hand, may tend to slightly overestimate the measurements as small unavoidable balancing movements of the patients during the 3D capture may interfere. Thus, the actual thigh circumferences are probably in between the manual and optical values. The manual measurement remains as the standard method with minor result deviations and ease of use. The optical methods can offer a more sophisticated objective non-contact technique which is not as cumbersome and slow as the whole range 3D capture.

Circumference results were the first to indicate that treatment results are more of a long-term skin remodeling process and are not only related to skin retraction, as the thigh circumference had a better improvement on week 10 than on week 7.

The texture measurements are consistent with this finding. Both dimples and nodules showed a significant improvement, through simulations, for week 10 results. The need for an increased sensitivity on a statistical level is partially related to the scale of the measured structures. Dimples and nodules are the consequence of the fatty tissue protrusions into the dermis. Their reduction is linked to increased circulation, dermis reinforcement and fatty tissue reduction. On week 10 the dermis reinforcement seems to be the main cause, as circulatory improvement would've already been effective on week 7. Dermis reinforcement is mostly related to new collagen synthesis adding mechanical strength to the dermal layers creating a "roof effect" of fatty tissue containment.

Both the firmness and ultrasound results reinforce that theory as some firmness and Dermis Density gains are exclusively observed on week 10. Dermis Density indicates that a remodeling and enrichment process has started in the dermis. The skin homogeneity results, however, indicate that week 10 may be a very incipient stage of this process. Its results show that both thighs are becoming increasingly heterogeneous. However, the heterogeneity in treated thigh skin thickness is significantly less than the one seen on the untreated thigh. Probably this reflects the treatment effects "buffering" the cellulite progression without being able to totally compensate it.

Measurements of week 10, however, were probably too soon and a longer follow up duration might have been better. Neocollagenesis normally takes at least one month to begin since its induction and takes another three to six months for collagen and other cellular matrix components build up. Therefore, the subtle and compensatory effects observed on week 10 are part of this initial process and possibly, on the following weeks, would have been manifested on a stronger level.

Conclusions

Considering one of the goals of this study to introduce optical tests as objective measurement to assess clinical trials, the consistency of the results as well as the clinical evaluation, give us confidence in these highly sophisticate tools, however, study sample size for measurements of cellulite changes should probably be larger with less variability in subjects ages and cellulite condition. Circumference measurement results of both manual and optical methods demonstrated that the Maximus system (TriLipo technology) is a safe and effective treatment for improvement of cellulite appearance and for circumference reduction.

Observations of subjects' photos by objective viewers demonstrated visual improvement in cellulite condition of treated thigh versus untreated demonstrating the clinical efficacy of the Maximus.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content of the paper.

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