SYNERGISTIC EMISSION OF RADIOFREQUENCY AND TARGETED PRESSURE ENERGY FOR POSTPARTUM LAXITY

REDUCTION OF ABDOMINAL SKIN LAXITY IN WOMEN POST-VAGINAL DELIVERY USING THE SYNERGISTIC EMISSION OF RADIOFREQUENCY AND TARGETED PRESSURE ENERGIES

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HIGHLIGHTS

- Investigated device can **significantly reduce** early signs of **postpartum laxity** in the abdominal area.
- Overall abdominal **skin laxity improved in 91%** of treated patients.
- The **umbilical circumference decreased** in over **95%** of the treated patients by **1.43 cm on average.**
- **90% of patients reported satisfaction** with the achieved treatment results at the 3-month follow-up.

Patient images before (left) and 3 months after 4th treatment (right).
The patient had severe laxity before treatments.

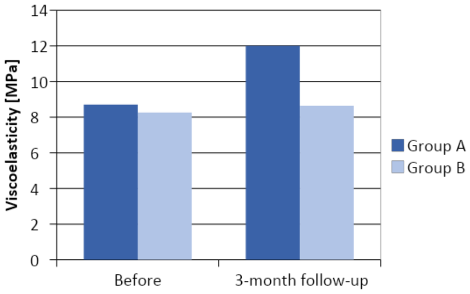
DESIGN AND METHODOLOGY

- 46 women with a history of vaginal delivery in the last 6-36 months were enrolled in the study.
- The subjects were divided into two groups: Group A received 4 abdominal treatments delivered once a week; Group B did not receive any treatment and served as a control group.
- Standardized photographs, circumferential measurements, and skin elasticity measurements were taken at baseline and 3 months post-treatment.
- 5-point Likert Scale questionnaire was used to assess patient satisfaction.

RESULTS

- In the treatment group, the average **skin viscoelasticity changes in individual patients totaled +37.6% or 3.29 Mpa** (retraction time -62.6ms/-22.5%; suction pressure + 1.21 Mpa /+13.9%) (all $p<0.0001$). In control group there was no statistically significant improvement.
- **Retraction time improved** in all patients while **suction pressure increased in 19 of them.**
- The assessment of digital photographs correlated with the viscoelasticity measurements as the **degree of skin laxity improved in 86 % of the patients in group A.**

Patient images before (left) and 3 months after 4th treatment (right).
“The patient had severe laxity before treatments”.



The average value of skin viscoelasticity before and three months after 4th treatment for both groups.

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Mini review

Synergy of Monopolar Radiofrequency Heating and Targeted Pressure Energy as an Innovative Approach to Cellulite Reduction

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Abstract

As much as 90% of women are experiencing altered skin topography due to cellulite. Nowadays, various treatment modalities are utilized for cellulite treatment, focusing on different approaches to address such a multifactorial condition. This article describes a unique technical solution combining two proven technologies in a standalone device to treat all major factors contributing to cellulite. The device utilizes a single applicator system that simultaneously delivers mechanical and thermal energy resulting in structural and functional changes in dermis and hypodermis.

Keywords: Cellulite; Radiofrequency; Targeted Pressure Energy

Abbreviations: AAD: American Academy of Dermatology; RF: Radio Frequency; TPE: Targeted Pressure Energy

Introduction

Gynoid lipodystrophy, commonly known as cellulite manifests as an alteration of the skin topography that occurs mainly in women on the pelvic region, lower limbs and abdomen. It is characterized by a padded or orange peel's appearance with dimpling and nodularity caused by herniation (protrusion) of subcutaneous fat within fibrous connective tissue [1]. Cellulite affects over 90% of women nearly in all stages of their lives, with the most noticeable onset in the age of 20-30 years. A variety of invasive and non-invasive treatment options are available to improve the appearance of cellulite. American Academy of Dermatology (AAD) recognizes various modalities that can effectively treat cellulite-e.g., thermal and mechanical energy, lasers and submission. Given the risks, downtime and inconvenience often related to minimally invasive or invasive approaches, non-invasive treatments are preferably sought by the patients.

Radiofrequency (RF) heating and mechanical energy are the gold standards in non-invasive cellulite treatment, since they can induce structural changes in the dermis and subcutaneous tissue to target multiple causes of cellulite effectively. There are currently various devices on the market that use either RF or mechanical energy to treat cellulite in a standalone regime or consecutively to enhance the results. Although it was evidenced that consecutive treatments lead to higher efficiency via the synergy of various physiological effects induced by the respective technologies [2-4], the simultaneous application may achieve even superior results due to the immediate synergy. Nevertheless, the technical requirements to combine such distinct technologies only allowed for their consecutive use so far. Recently, however, the latest advancements in technology solutions have emerged, and for the first-time simultaneous therapy with RF and mechanical energy has become available for cellulite.

Technical Solution Allowing Simultaneous Application

Emtone (BTL Industries Inc, Boston, MA) is the first and only device that simultaneously combines radiofrequency and mechanical targeted pressure energy (TPE) for the treatment of cellulite in the single therapy due to a unique technical solution developed and patented by BTL Industries Inc. Both energies are generated in the main device and effectively delivered to the desired area affected by cellulite using a handpiece applicator, equipped by easy to manipulate capacitive sense buttons and display which indicates the basic parameters of the therapy (Figure 1). The simultaneous application allows for the synergistic effect on fat protrusions and disruption of damaged collagen fibers followed by neocollagenesis and neoelastogenesis. This leads to thickening of the dermis, a better interlobular septage organization in the hypodermis, and improved skin appearance [4-6] (Figure 1).

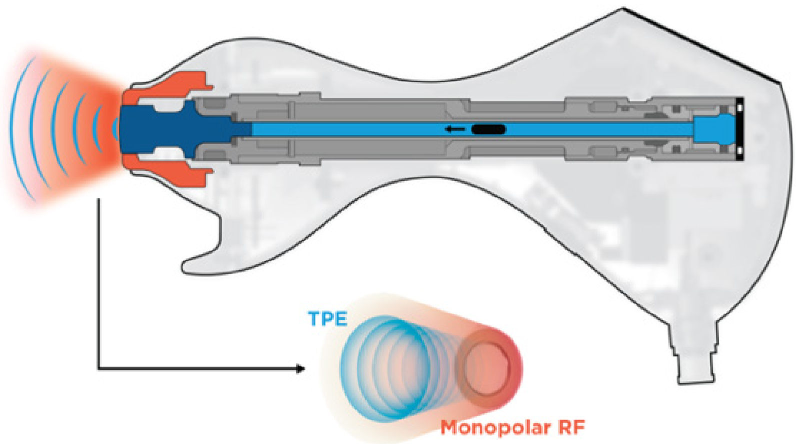

Figure 1: Emtone device simultaneously combines targeted pressure energy (TPE) and monopolar radiofrequency (RF) in a single handpiece.

Radiofrequency Component

Radio frequency refers to electromagnetic waves in the frequency range of roughly 20 kHz to 300 GHz. These are the frequencies with the ability to create heat through the oscillation of molecules while propagating within the tissue. Oscillating electrical currents force collisions between charged molecules and ions leading to friction and the formation of thermal energy. The heating effects of the RF technology can be used for a wide range of aesthetic applications such as for cellulite treatment [4,7-9]. Today, it is well known that RF heating of the skin leads to a thermally mediated reaction in the dermis associated with collagen remodeling followed by tissue tightening. Furthermore, the heat delivered beyond the dermis to the subcutaneous layer is presumed to be absorbed by adipocytes and interlobular septa to supposedly induce adipocyte shrinkage and better septa organization [4]. Subsequently, these processes result in the improvement of various tissue characteristics [2,4].

Emtone utilizes monopolar RF (with a frequency of 447 kHz) that is optimal for deeper penetration. The RF energy is emitted by a solid metal electrode, which is in direct contact with the patient's skin. The generated currents travel to the grounding pad ensuring a safe flow of the RF energy through the treated area (see Figure 2) and controlled energy delivery (Figure 2).

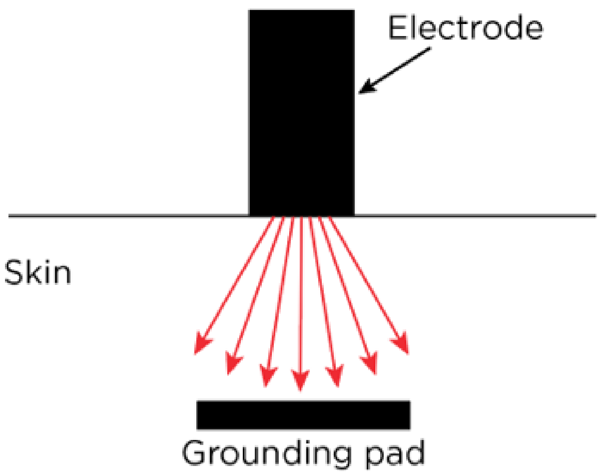

Figure 2: Energy flow during monopolar RF application, RF currents are schematically illustrated by the red lines.

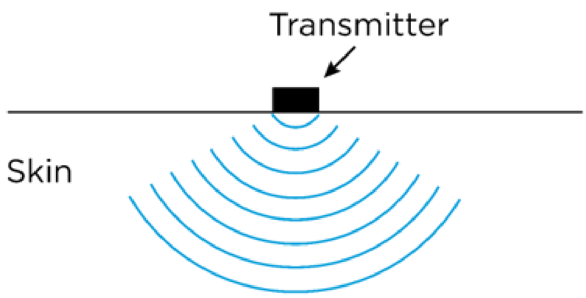

Figure 3: Blue lines illustrate transmission of the TPE energy into living tissue, propagation of the pressure waves.

Targeted Pressure Energy Component

Besides enhancing RF-induced changes, it is also observed that mechanical stimulation may improve local blood circulation and promote neovascularization [4]. Pressure waves should further increase cell proliferation of collagen and elastin fibers to improve skin elasticity and to revitalize the dermis. TPE also positively affects lymph transport, supposedly another key aspect associated with cellulite. TPE mechanical stimulation is based on the ballistic principle. The terminal apparatus of the TPE component is embedded in the handpiece and consists of a tube with a floating projectile accelerated towards an applicator tip by the pneumatic system. The compressor of the pneumatic system is placed in the main unit and in combination with mechanical parts it transforms TPE energy to the target tissue. A projectile is moved by the compressed air, while hitting a transmitter that conveys energy from the impact to the patient's body. This action is repeated in quick succession (frequency of 10 Hz) while resulting in the pressure waves of significant intensities (Figure 1 & 3).

Technical Challenges

The greatest challenge with developing such a device was combining two different technologies in a single applicator while maintaining high quality and safety standards. The applicator does not contain any visible fitting (screws, holes etc.). One of the most important sub-challenges was developing a system that can transmit RF energy through mechanically movable parts of the applicator while keeping the warranty of those components up to 1,000,000 shots. At the same time, with patients' comfort in mind, technical solutions possess impedance intelligence and real-time temperature monitoring for safe but highly effective treatment.

Conclusion

EMTONE is the only device of its kind that allows the use of a simultaneous combination of two proven technologies in cellulite treatment. This patented concept combining targeted pressure energy with radiofrequency heating allows leveraging both clinical and commercial synergies of combination from a single device applicator.

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SYNERGISTIC EFFECT OF SIMULTANEOUSLY DELIVERED RADIOFREQUENCY AND TARGET PRESSURE ENERGY FOR CELLULITE REDUCTION

CLINICAL EVALUATION OF SIMULTANEOUSLY APPLIED MONOPOLAR RADIOFREQUENCY AND TARGETED PRESSURE ENERGY AS A NEW METHOD FOR NON-INVASIVE TREATMENT OF CELLULITE IN POST PUBERTAL WOMEN

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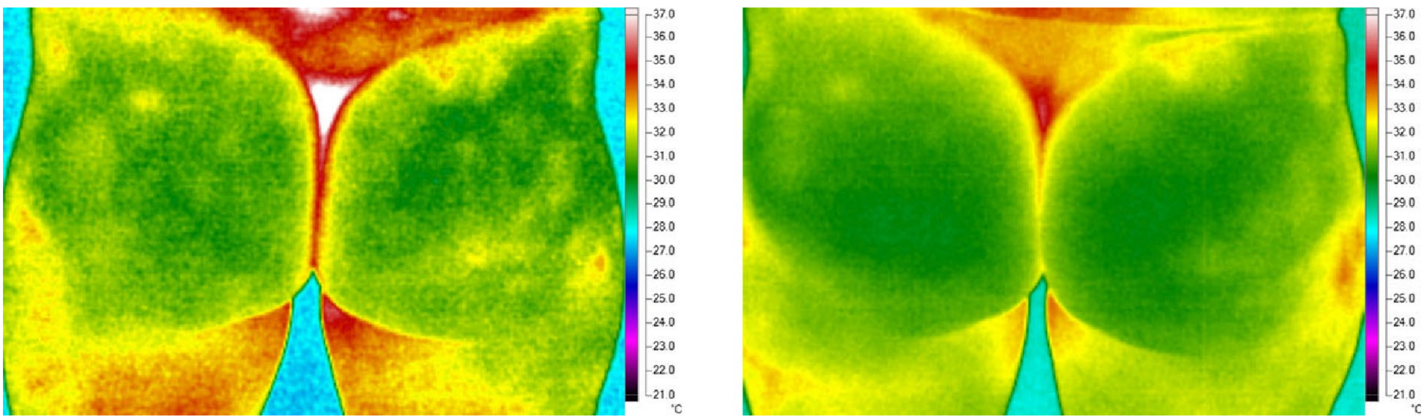
HIGHLIGHTS

- **Cellulite was reduced in 93% of cases** and 73% of patients showed good, very good, or excellent improvement.
- **97% of patients** reported they were **satisfied or very satisfied** with their treatment results.
- **Infrared thermography** showed improved thermal profile homogeneity 3 months post-treatment indicates **a more uniform blood supply** in the treated area.



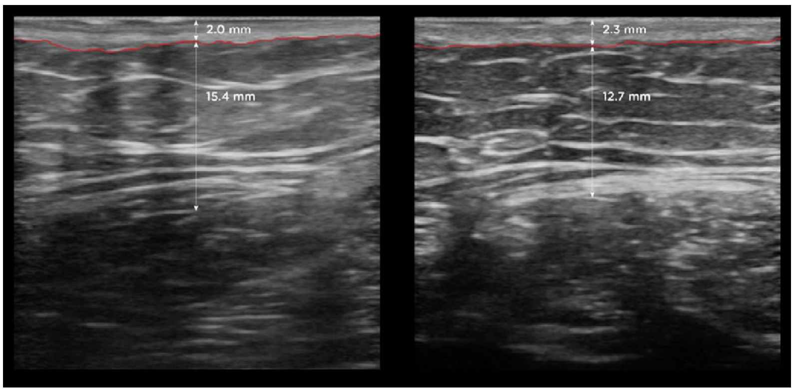
Thermography showing changes in the thermal profile before and 3 months post treatment

DESIGN AND METHODOLOGY

- 30 subjects received four 24-minute treatments of simultaneous RF and Targeted Pressure Energy on gluteofemoral region.
- Standardized photographs, circumferential measurements, ultrasound scans, and infrared images were taken at baseline and 3 months post-treatment.
- 5-point Likert Scale questionnaire was used to assess patient satisfaction.

RESULTS

- The study shows **54% improvement of cellulite** 3 months after all 4 treatments.
- Ultrasonography revealed **smoothening and thickening of the dermis** by 14% and reduced subcutaneous fat layer coupled with diminution of the fat protrusion effect.
- Hips **circumference decreased by 2.31 cm** on average.
- The density and the depth of cellulite dimples were reduced significantly.



Ultrasonography showing changes in dermal and subdermal tissues before (left) and 3 months post-treatment (right).

Example of patient photographs before (left) and 3 months post-treatment (right). The patient was graded as having “mild improvement”.

COMPARISON OF SIMULTANEOUS VS CONSECUTIVE APPLICATION OF RADIOFREQUENCY AND TARGETED PRESSURE ENERGY: HISTOLOGY STUDY

HISTOLOGICAL EXAMINATION OF SKIN TISSUE IN PORCINE ANIMAL MODEL AFTER SIMULTANEOUS APPLICATION OF MONOPOLAR RADIOFREQUENCY AND TARGETED PRESSURE ENERGY

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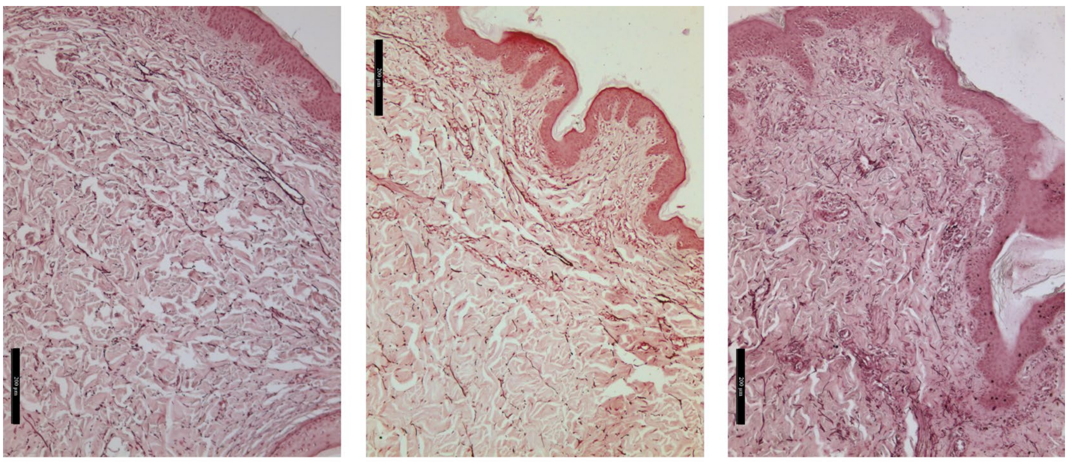
HIGHLIGHTS

- **Simultaneous application** of Monopolar Radiofrequency and Target Pressure Energy showed **profound improvement** in skin tissue when compared to consecutive treatments.
- Animals treated with simultaneous application showed **59% higher increase in collagen** and **64% higher increase in elastin** when compared to consecutive treatments.
- At 1-month follow-up simultaneous application showed **44% higher increase in thickness of the dermis** opposed to consecutive treatment.



Control **Consecutive** **Simultaneous**

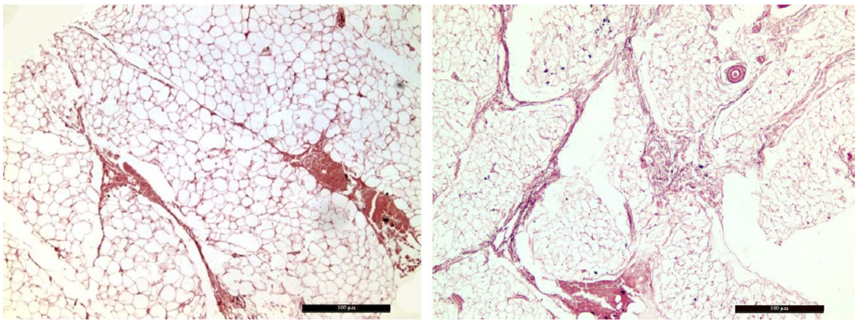
Histological comparison of collagen (pink bundles) and elastin (dark thick strains) densities 1 month after 4th treatment, detail of dermis; Orcein, bar 200 µm.

DESIGN AND METHODOLOGY

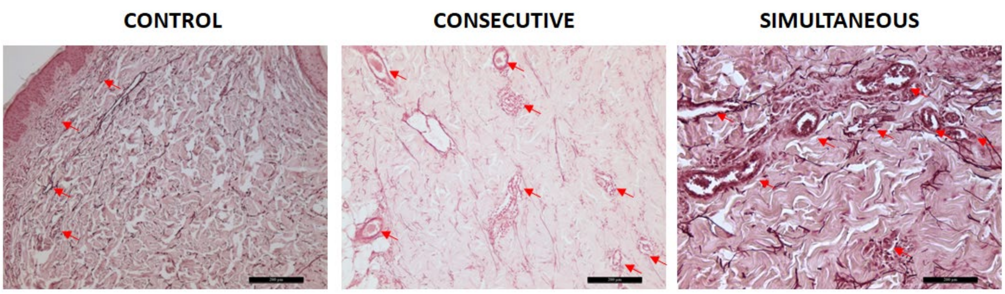
- Discover the difference between simultaneous and consecutive application of monopolar RF with Targeted Pressure Energy (TPE).
- All treated pigs received 4 weekly abdominal treatments.
- Animal histology, 5 pigs in total: 2 pigs treated by simultaneous emission of RF and TPE, 2 pigs by consecutive emission, and 1 untreated control pig.
- Skin biopsies were obtained at baseline, after 4th treatment, and at 1-month follow-up.

RESULTS

- This study shows that **simultaneous application** induces a **greater increase of collagen fibers, elastin fibers, and dermal thickness.**
- Combined **TPE and monopolar RF** caused an **increase** in the number of blood vessels in the dermis.
- Application of TPE and monopolar RF affected the **shape and size of adipocytes** (marker of lipolysis).
- The control animal did not show any significant changes.



Adipocytes and septa in hypodermis before (left) and 1-month after (right) simultaneous treatment, Orcein, bar 500 µm. Adipocytes are visibly smaller after RF/TPE treatment, while interlobular septa are better organized.



Samples taken at the 1-month follow-up, detail of dermis; Orcein, bar 200 µm; Blood vessels depicted by arrows.

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ORIGINAL CONTRIBUTION

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Reduction of abdominal skin laxity in women postvaginal delivery using the synergistic emission of radiofrequency and targeted pressure energies

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Summary

Objective: This study evaluates clinical efficacy of a novel device which uses combined emission of radiofrequency and targeted pressure energy, for reduction of abdominal skin laxity.

Methods: This was a multicentric, randomized, parallel group-controlled prospective study. Forty-six women 6-36 months after delivery with abdominal skin laxity were randomly assigned to Group A or Group B. Group A received four treatments with BTL UNISON device (BTL Industries Inc, Boston, MA, USA); and, Group B didn't receive any treatments. Skin viscoelasticity was measured using a skin analyzer at baseline and 3 months posttreatments. Standardized digital photographs were evaluated for the severity of skin laxity. Patient comfort and satisfaction were evaluated by standardized questionnaires.

Results: Subjects' weight remained stable. In 95% of treated patients the umbilical circumference decreased (average − 1.43 cm, $P < 0.0001$). The average of skin viscoelasticity changes in individual patients totaled + 37.6%/3.29 Mpa (retraction time − 62.6 ms/−22.5%; suction pressure + 1.21 Mpa/+13.9%) (all $P < 0.0001$). The overall elasticity improved in 90.9% of patients. The control group changes were insignificant. Based on independent photo assessment there was an improvement in the degree of skin laxity in 86% of treated patients. The average laxity score across all treated patients decreased from 1.79 (moderate laxity) at baseline to 1.1 (mild laxity) 3 months posttreatments. Ninety percent of treated patients expressed satisfaction with achieved results. Therapy didn't cause any pain.

Conclusions: We conclude the investigated device can significantly reduce signs of early postpartum laxity in abdominal area. As such, it is a promising alternative to surgical procedures.

KEYWORDS
postpartum, radiofrequency, skin elasticity, skin laxity, targeted pressure energy, viscoelasticity

1 | INTRODUCTION

Pregnancy as well as the actual child delivery result in complex changes to woman's body; loose abdominal skin appears as connective tissue fibers of collagen and elastin stretch.

The demand for noninvasive esthetic procedures for skin tightening increases. Technologies such as Radiofrequency (RF),[1–6] High-intensity Focused Ultrasound (HIFU),[7,8] Laser,[9] Infrared IR),[10] and pressure energy devices[5] are used to improve the esthetic appearance and self-confidence of patients.

Primary effects of RF heating is the subsequential production of new fibrillar components of connective tissue (collagen and elastin fibers) or their contraction and remodeling which was previously demonstrated in histological examinations.[1,2] In case of RF treatment, thickening of dermal layer can be also observed.[1] These thermal effect-based treatments are used across almost all body areas today.[11–14] Combinations of different modalities are commonly used such as RF with pressure waves.[5] IR energy and/or Vacuum.[2]

Since RF treatment has been used safely both as standalone and in combination with other modalities to treat skin laxity, we sought to determine the clinical efficacy of a novel device which combines emission of RF and targeted pressure energy simultaneously, to treat the abdomen of postdelivery women affected by skin laxity.

2 | METHODS

This was a multicenter, randomized, parallel group-controlled prospective study. Forty-six postdelivery women aged between 21 and 42 years were randomly assigned to Group A or Group B. The primary inclusion criteria included visible abdominal skin laxity, history of a vaginal delivery 6-36 months prior to the time of enrolment, postbreastfeeding, gynecologic examination without complications. Exclusion criteria included any metal implants, pregnancy (current or planned), and/or any other esthetic intervention in abdominal area after the last vaginal delivery. Informed consent was obtained from each patient. Subjects were instructed to maintain their lifestyle and avoid application of any products with risks of changing the appearance of skin.

Subjects in Group A received 4 weekly treatments on the abdomen using the BTL UNISON device (BTL Industries Inc), with each treatment encompassing approximately 12-15 minutes of application. The tissue was heated to surface temperatures of 40-45°C which was verified using the built-in IR thermometer. Initial power setting was set at 60%, but was subject to minor changes later to the treatment depending on individual patient's heat tolerance. After each treatment a Visual Analogue Scale (VAS) form was used to determine patient's comfort level. Subjects in Group B didn't receive any treatment and served as a control group.

Standardized photographs were obtained at the baseline and at 3-month follow-up. Randomized images were evaluated by three clinical specialists for the degree of skin laxity (0-3 scale; 0 = no laxity, 1 = mild, 2 = moderate, 3 = severe). In both Groups, skin elasticity was measured 5 cm below umbilicus (DermaLab skin analyzer, Cortex Technology, Hadsund, Denmark) and waist circumference was measured using a spring-loaded tape. For statistical analysis of obtained results the paired t-test was used at significance level $\alpha = 5\%$. At the follow-up, patients in Group A completed a 5-point Likert scale subjective satisfaction questionnaire. Subject's weight was monitored throughout the study.

3 | RESULTS

Of the 46 patients enrolled, 43 completed the full study protocol (22 in Group A, 21 in Group B). Subjects' weight remained stable (±2 kg of pretreatment weight in all patients except for 3). The average change was found insignificant. See Table 1 for detailed Group A patient data) and Table 2 (for the control group averages).

In over 95% of patients from Group A (n = 21) the umbilical circumference decreased, with a mean loss of 1.43 ± 1.08 cm ($P < 0.0001$). The largest reduction was seen in patient ID14 who lost 4 cm; one subject increased in circumference by 1 cm. In the control group, the change was minor and statistically insignificant (−0.3 ± 1.7 cm; $P > 0.05$).

FIGURE 1 Patient images before (left) and 3 months after 4th treatment (right). The patient had severe skin laxity before treatments

FIGURE 2 Patient images before (left) and 3 months after 4th treatment (right). The patient had severe skin laxity before treatments

TABLE 1 Patient data

		BMI (kg/m)		Waist size (cm)		Skin elasticity (VE/E [Mpa]/Ret[ms])			Average laxity score		
	Age	Before	3 M	Before	3 M	Before	3 M	Change	Before	3 M	Change
ID1	38	26.3	26.3	96.4	95.0	8.4/8.0/276	10.9/9.1/198	2.5/1.1/−78	1.3	1.0	0.3
ID2	28	31.5	30.1	101.7	99.3	11.3/9.1/215	10.9/8.7/203	−0.5/−0.4/−12	1.0	1.3	−0.3
ID3	24	28.7	28.3	100.7	99.8	11.2/10.5/246	14.7/10.7/175	3.5/0.2/−71	1.3	1.0	0.3
ID4	21	21.7	21.7	75.8	75.0	9.6/8.3/209	16.4/9.8/147	6.8/1.5/−62	3.0	1.0	2.0
ID5	41	22.7	22.7	99.8	98.8	9.3/9.7/282	12.9/10.2/203	3.6/0.5/−79	2.3	1.3	1.0
ID6	24	31.2	30.5	115.9	114.0	8.6/6.4/209	7.5/6.0/197	−1.1/−0.4/−12	1.7	1.3	0.3
ID7	39	27.9	27.3	101.7	100.7	7.5/8.8/373	10.7/10.5/273	3.1/1.7/−100	2.0	2.0	0.0
ID8	25	25.2	25.2	104.5	103.0	10.8/8.5/201	17.4/10.4/140	6.7/1.9/−61	2.7	0.3	2.3
ID9	28	22.1	22.1	97.9	97.0	6.1/6.9/278	7.4/7.5/241	1.3/0.6/−37	0.7	0.3	0.3
ID10	42	35.8	35.3	105.5	103.9	11.2/11.3/263	12.4/10.7/209	1.1/−0.5/−54	3.0	2.0	1.0
ID11	38	21.4	21.2	79.0	75.0	7.8/9.2/304	11.0/11.1/220	3.2/1.9/−84	1.7	1.3	0.3
ID12	29	22.3	21.8	89.0	87.5	8.0/7.8/257	13.2/9.5/184	5.2/1.7/−73	2.0	0.3	1.7
ID13	40	27.7	28.0	92.5	92.0	8.9/8.7/267	13.4/10.5/191	4.5/1.8/−76	1.7	1.0	0.7
ID14	35	24.7	25.4	93.0	89.0	7.1/8.6/325	11.1/10.4/225	4.0/1.8/−100	2.0	1.7	0.3
ID15	37	22.7	22.5	82.5	80.5	5.0/7.5/345	7.6/9.1/266	2.7/1.6/−79	0.7	0.3	0.3
ID16	40	19.5	19.4	80.5	79.5	5.5/7.0/342	8.1/8.6/249	2.7/1.6/−93	1.7	1.0	0.7
ID17	30	21.0	20.6	79.0	80.0	11.1/9.7/231	17.6/11.6/164	6.5/1.9/−67	1.7	1.3	0.3
ID18	36	22.1	21.9	83.0	82.5	12.1/10.5/221	20.2/12.5/156	8.1/2.0/−65	2.7	2.0	0.7
ID19	39	26.1	26.0	90.0	88.4	4.7/9.1/485	5.5/9.1/429	0.9/0.0/−56	0.7	0.3	0.3
ID20	33	26.4	26.5	86.0	84.3	10.3/11.5/312	12.2/13.8/275	1.9/2.3/−36	1.0	1.0	0.0
ID21	25	24.8	24.8	97.6	96.8	7.4/7.6/266	8.7/9.3/239	1.4/1.7/−27	2.0	1.0	1.0
ID22	26	25.4	25.5	98.0	96.5	9.8/10.6/284	14.0/12.7/228	4.2/2.1/−56	2.7	2.3	0.3
AVG	32.6	25.3	25.1	93.2	91.7	8.7/8.9/281	12.0/10.1/219	3.3/1.2/−63	1.8	1.1	0.7

In Group A, the average of skin elasticity changes in individual patients totaled + 37.6% or 3.29 Mpa (retraction time – 62.6 ms/−22.5%; suction pressure + 1.21 Mpa/+13.9%) (all $P < .0001$). The overall viscoelasticity improved in 90.9% (n = 20) of patients; elasticity in 2 patients decreased by 4% and 12%, respectively. The retraction time improved in all patients while the suction pressure increased in 19 of them, remained unchanged in one subject, and decreased in two subjects. The overall deviation in skin analyzer calibration averaged 4.9% and 6.8% for baseline and follow-up measurements, respectively. In the control group, the overall elasticity improved in 11 patients (52%) and deteriorated in 10 patients (48%), with the total change averaging + 4.3% (+0.18 Mpa;−1.95 ms) (calibration deviation 6.0% and 6.1%).

Based on assessment of patients' photographs in Group A, there was an improvement in the degree of skin laxity in 19 (86%) of patients, in two patients (9%) the laxity score remained unchanged, in one patient (5%) the score slightly increased (1.0-1.3). The average laxity score across all patients decreased from 1.91 (moderate laxity) at baseline to 1.1 (mild laxity) 3 months posttreatments. See Figures 1 and 2 for examples of patient photographs.

At the follow-up 90% of treated patients expressed satisfaction with achieved results; the average score totaled 4.32 points on a 1-5 scale. Remaining 10% of patients reported they were neutral (n = 1; 5%) or slightly dissatisfied (n = 1; 5%) with results of the treatments. Therapy didn't cause any pain to the subjects (average VAS score of 1.7 corresponds to very mild to none discomfort).

4 | CONCLUSION

This study presents an initial evaluation of a device which simultaneously emits monopolar RF and targeted pressure energy, when used for abdominal skin tightening.

The data suggest that the application of RF heating and the mechanical component induce changes in the connective and subcutaneous tissues at 3 months posttreatments. This is further supported by results of the control group which didn't show any

TABLE 2 Control group results (n = 21)

	Before	3 M	Change	*T*-Test
Weight (kg)	69.0 ± 11.4	68.6 ± 11.5	−0.3 ± 1.0	$P > 0.05$
BMI (kg/m)	24.2 ± 4.3	24.1 ± 4.3	−0.1 ± 0.4	$P > 0.05$
Wasit size (cm)	89.8 ± 9.1	89.5 ± 9.9	−0.3 ± 1.7	$P > 0.05$
Skin elasticity VE/E (Mpa)/Ret (ms)	8.3/8.5/292	8.6/8.7/290	0.4/0.2/−2	$P > 0.05$

significant changes, and in which the results of measurements followed a rather random pattern. In the treated group, both the pressure necessary to pull up the skin and the time needed for the skin to retract to the original position changed; this indicates an overall increase in skin elasticity. Besides other, dermal laxity is generally associated with deterioration in both quality and quantity of elastin and collagen fibers. As such, it's very likely that the change in elasticity is directly driven by stimulation of neocollagenesis and neoelastinogenesis induced by the two applied energies. The loss of circumference was not a primary intended effect, and can potentially be caused either by heat-induced lipolytic reaction or by connective tissue tightening (or by a combination of both).

The clinical improvement observed in patient photographs strongly correlated with the baseline severity of their indication. Patients whose laxity was graded as "severe" at baseline (n = 5) improved on average by 1.33 (from 2.80 to 1.47) whereas patients with "mild" laxity (n = 7) only improved on average by 0.19 (from 0.95 to 0.76). These initial data suggest that patients with severe deterioration of elasticity can most benefit from the treatments. Another conclusion is that before and after photographs are not suitable evaluation methodology for patients with only "mild" laxity; despite their average score improved insignificantly, their abdominal elasticity measured through the suction pressure and retraction time improved in 86% of cases, with the average change of 22% (+0.78 Mpa, −52 ms). No adverse events were reported.

All the results were statistically independent of baseline age, height, and BMI. Weight loss seemed to be negatively influencing skin laxity, as the only three patients with weight loss $\geq$ 2 kg also showed a decrease in total measured elasticity. Larger cohort study is necessary to confirm or disprove such interpretation. Due to absence of a standardized validated scale for measuring abdominal skin laxity, the results can't be thoroughly compared to previous studies published on other RF-based devices; yet we seem to have observed a higher percentage of patients with visible improvements compared to what authors observed in studies on facial stamping devices.[15,16]

Despite certain limitations and space for further research, we conclude the investigated device can significantly reduce signs of early postpartum laxity in abdominal area. As such, it is a promising alternative to surgical procedures in the rapidly growing demand.

DISCLOSURES

The authors have no commercial interest in BTL and received no compensation for this study. Klaus Fritz, Carmen Salavastru, and Magdalina Gyurova have no relevant conflicts to declare.

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ORIGINAL CONTRIBUTION

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Clinical evaluation of simultaneously applied monopolar radiofrequency and targeted pressure energy as a new method for noninvasive treatment of cellulite in postpubertal women

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Summary

Introduction: This study investigates noninvasive cellulite treatments based on simultaneous application of monopolar radiofrequency (RF) and targeted pressure energy to evaluate efficacy and safety and to see whether simultaneous application has any benefits in noninvasive cellulite treatments.

Methods: Thirty women with cellulite (fibrous/adipose/aqueous types) received 4 gluteofemoral treatments (~24 minutes; ~1000 cm^2) using a simultaneous application of RF and targeted pressure energy. Clinical improvement was assessed using a pentile grading scale and satisfaction questionnaires. Hip/thigh circumference was measured. Ultrasonography and thermography observed changes in dermal/subcutaneous tissue composition and in gluteofemoral thermal profile. Evaluation at 3 months posttreatment was compared against the baseline.

Results: The clinical improvement averaged 2.17 ± 0.95 (54% improvement). Cellulite was reduced in 93% of cases, while 73% of patients showed good/very good/excellent improvement, with most significant improvement seen in patients with moderately severe cellulite. Hips and thigh circumference decreased on average by 2.31 cm and 2.13 cm, respectively ($P < .001$). Patient satisfaction was very high, averaging 4.47 ± 0.57 points (1-5 scale). Ultrasonography revealed smoothing and thickening (+0.28 ± 0.15 mm) of the dermis and an average reduction of 1.96 ± 1.60 mm in fat thickness ($P < .05$). Subjects with significant cellulite reduction had a more homogenous thermal profile at follow-up as a result of therapy-induced diminution of topographic skin defects. No adverse events were recorded.

Conclusion: The application is effective and safe for treating cellulite. The level of clinical improvement after 4 sessions is comparable to results reported after 6-20 sessions in studies on stand-alone RF/laser/targeted pressure energy devices. The technology is promising and deserves further attention and research.

KEYWORDS
cellulite, noninvasive, radiofrequency, targeted pressure energy

1 | INTRODUCTION

Gynoid lipodystrophy is a skin condition affecting predominantly postpubertal women (prevalence is around 85%-98%).[1-4] It causes topographic changes to the skins surface as a result of alternations in dermal and subcutaneous tissues, leading to “orange peel” like skin.[3,5,6] These gender-specific cutaneous alterations are caused by connective tissue fibrosis where the perpendicular orientation of the fibrous septa in women and its shortening allow fat cells to protrude into the dermis and cause dimpling,[1,5] which further increases with decreased skin elasticity[7] and thickness, as well as with impaired microcirculation and blood flow.[3,6]

A consecutive application of different treatment modalities is a frequent approach to improve clinical efficacy when treating cellulite noninvasively, such as the application of diathermy immediately followed by a targeted pressure energy.[8] Noninvasive radiofrequency (RF) devices are effective for induction of neocollagenesis and neoelastogenesis through heating of the dermis and subcutaneous tissue.[7,9] RF has also been reported to increase local blood flow[10] and to affect subcutaneous adipocytes, inducing their apoptosis.[11] All this leads to overall tightening and reshaping of the treated area.[12] The application of intense mechanical waves of short duration (μs) and intensities of around 10 MPA improves blood and lymphatic microcirculations,[13,14] causes neovascularization, promotes lipolysis, and increases collagen fiber density, as well as improves skin elasticity[1,12] and activates fat-splitting enzymes.[14,15] Previous literature confirms the efficacy of RF and targeted pressure energy[3,12,16] for cellulite reduction, yet the efficacy of their simultaneous application has not been described yet. This study evaluates this treatment approach and aims to investigate any incremental benefits to practitioners or to the concept of noninvasive cellulite treatments in general when the two energies are applied simultaneously.

2 | METHODS

We treated 30 women (avg. 34 years, BMI 25.9 kg/m^2) who exhibited gluteofemoral cellulite using a system which combines the emission of monopolar RF and targeted pressure energy in a single applicator (BTL UNISON, BTL Industries, Boston, MA). Subjects received 4 weekly treatments (~24 minutes each, ~1000 cm^2 on gluteofemoral region). Conductive cream was applied to the skin, and the applicator was moved across the treated region. Skin temperatures of 40-45°C were reached within 90 seconds of the treatment. The mechanical component stimulated the tissue, inducing sensations similar to an intensive massage.

Standardized photographs taken at the baseline and 3 months posttreatments were given to masked clinical specialists to grade the level of clinical improvement on a 0- to 4-point pentile arbitrary scale. Circumferential hip and thigh measurements were taken. Subjects’ weight was monitored. Subjective satisfaction was assessed by a 5-point Likert scale questionnaire. Diagnostic ultrasound scans and skin surface thermal photographs were taken on five randomly selected patients as a secondary evaluation. The ultrasonography (Mindray M7 UZV 4D, 10 MHz linear transducer) of spots strongly affected by cellulite was used to examine the dermis/subcutaneous tissue composition before and 3 months after treatments. The infrared thermography was used to examine the gluteofemoral temperature profile before and 3 months after treatments. The data were statistically evaluated using a paired two-tailed Student’s *t* test and a one-tailed Wilcoxon signed-rank test (α set at 5% for both).

3 | RESULTS

Cellulite was significantly improved with the combined RF and targeted pressure energy protocol. The clinical improvement score averaged 2.17 ± 0.95, corresponding to moderate or 54% ± 24% improvement 3 months posttreatment. In 93% (n = 28) of cases, a visible reduction in cellulite was noted, while 73% (n = 22) of patients showed “good” or above average improvement (Table 1). Most significant improvement was seen in patients with moderately severe cellulite. The density and depth of dimples were reduced significantly in patients who were graded as “excellent improvement.” In the follow-up, the circumference decreased compared to the baseline on average by 2.31 cm on the hips and by 2.13 cm on each thigh ($P < .001$).

The average weight has not changed significantly (−0.43 kg). All patients had strong postprocedure erythema which resolved within 60 minutes; no adverse events were reported.

Subjective satisfaction averaged 4.47 ± 0.57 points, while 97% (n = 29) reported they were satisfied or very satisfied with treatment results. Ultrasonography revealed smoothing and thickening of the dermis (avg. +0.28 mm or 14%) and a reduced subcutaneous fat layer (avg. −1.96 mm or −9%) coupled with diminution of the fat protrusion effect. Both changes were statistically significant ($P < .05$) (Table 2). Infrared thermography showed improved thermal profile homogeneity 3 months posttreatments in 2 patients who were graded as having “very good improvement” on the clinical improvement scale. The baseline images showed more irregularities corresponding to topographic skin defects which were reduced with the improved skin texture after treatments. The remaining 3 patients did not show any significant changes (See Figures 1-3).

4 | DISCUSSION

This study shows significant improvement of cellulite after 4 simultaneous RF and targeted pressure energy treatments.

TABLE 1 Evaluation of clinical improvement

Scale	Patients (#)	Patients (%)
0%-20% (no improvement)	2	6.7
21-40% (mild improvement)	6	20.0
41%-60% (good improvement)	11	36.7
61%-80% (very good improvement)	7	23.3
81%-100% (excellent improvement)	4	13.3

TABLE 2 Circumferential measurements and ultrasonography results

Measurement	Baseline	Follow-up	Difference	*P*-value
Hip circumference (cm; n = 30)	105.3 ± 8.4	103.0 ± 8.6	−2.3 ± 1.6	<.001
Thigh circumference (cm; n = 30)	63.9 ± 6.9	61.8 ± 6.9	−2.1 ± 1.7	<.001
Thickness of dermis (mm; n = 5)	2.0 ± 0.2	2.3 ± 0.2	0.3 ± 0.1	<.05
Thickness of subcutaneous tissue (mm; n = 5)	21.5 ± 3.7	19.5 ± 4.7	−2.0 ± 1.6	<.05

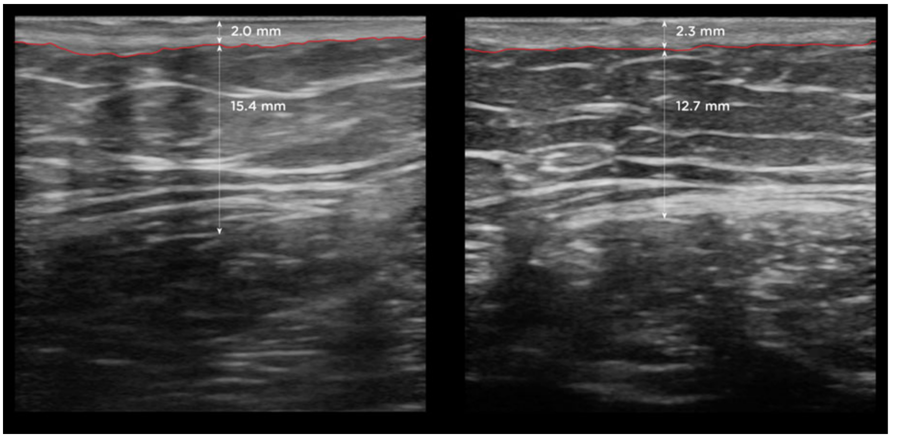

FIGURE 1 Ultrasonography showing changes in dermal and subdermal tissues before (left) and 3 months posttreatment (right)

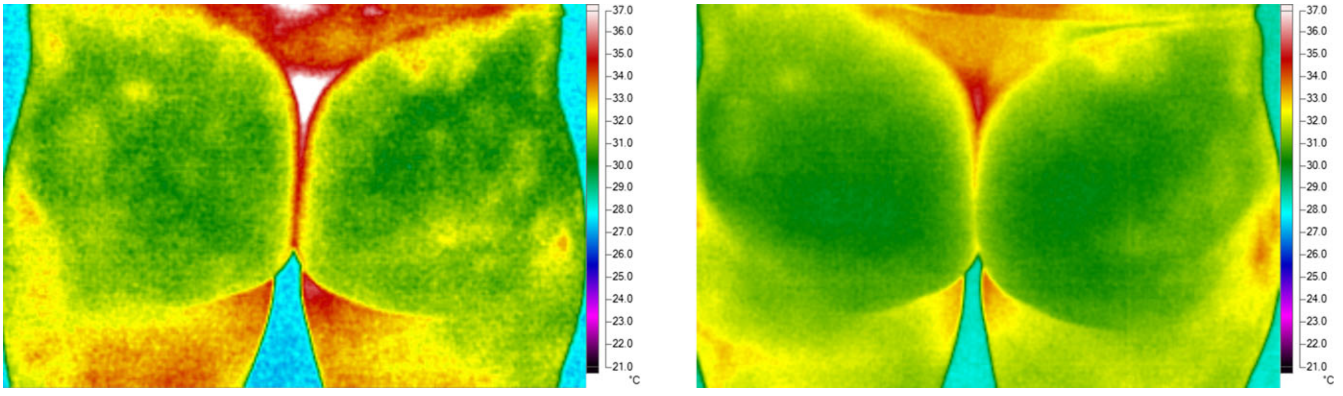

FIGURE 2 Thermography showing changes in the thermal profile before and 3 months posttreatment

FIGURE 3 Example of patient photographs before (left) and 3 months posttreatment (right). The patient was graded as having "mild improvement"

Standard deviation of observed circumferential changes can be explained by diverse anthropometric values of the subjects (BMI range 20-36 kg/m^2). Levels of subjective patient satisfaction exceeded the results from masked clinical evaluation which suggests patients could recognize changes difficult to identify by the naked eye, such as increased skin elasticity, texture, and a sense of improved blood perfusion. A reduction in the causes of cellulite was further evidenced by ultrasonography. Comparison of thermal images suggests that skin temperature profile inhomogeneity is a function of cellulite severity, but further research is necessary to validate such hypothesis.

Goldberg et al[17] and Wanitphakdeedecha et al[18] applied six RF-based treatments and showed moderate reduction in cellulite, with 10% of nonresponding and 8% of dissatisfied patients, respectively. Other studies on noninvasive RF or laser treatments included 6-20 treatment sessions (Harth et al,[19] Lach et al,[20] Mlosek[21] et al, Manuskiatti[22] et al, Wanitphakdeedecha et al[23]). Targeted pressure energy studies for cellulite reduction included 6 sessions (Knobloch et al,[16] Christ et al[15]), 8 sessions (Schlaudraff et al[24] Steinert et al[25] Nassar et al[26]), or 12 sessions (Hexsel et al[27]). Suction-based evidence then speaks about a minimum of 15 treatments (Kutlubay et al[28] Gülec[29]). All studies report mild-to-moderate improvements.

The results presented herein show significant reduction in cellulite 3 months after 4 treatments. This suggests that the simultaneous emission of two energies effectively treats cellulite in shorter treatment times compared to stand-alone or consecutive application of RF, laser, or targeted pressure energy. We hypothesize the energies applied together may induce different (enhanced) physiological reactions in the treated tissue compared to their stand-alone application; this, however, needs to be verified by further research.

DISCLOSURES

The authors have no commercial interest in BTL and received no compensation for this study. Klaus Fritz, Carmen Salavastru, and Magdalina Gyurova have no relevant conflict to declare.

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ORIGINAL CONTRIBUTION

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Histological examination of skin tissue in the porcine animal model after simultaneous and consecutive application of monopolar radiofrequency and targeted pressure energy

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Abstract

Background: The cosmetic appearance of skin is substantially influenced by the organization of connective fibers and underlying subcutaneous tissue. It has been previously documented that radiofrequency and pressure energies alone are able to improve skin appearance; however, detailed histological evaluation should be done to determine their synergistic effect.

Aims: This histological study investigates the difference between simultaneous and consecutive application of monopolar radiofrequency with targeted pressure energy on porcine skin.

Methods: In a total of four weekly abdominal treatments, simultaneous emission of the energies was applied to two pigs (12 minutes per session); additionally, two pigs were treated consecutively (12 + 12 minutes per session). The 5th pig served as a control subject. Biopsies were obtained at baseline, after the 4th treatment, and at 1-month follow-up. Primary outcomes were to document changes of dermal and hypodermal tissues.

Results: In the treated subjects, the amount of collagen and elastin fibers increased significantly ($P < .001$). At follow-up, simultaneous application showed a significantly higher increase in collagen and elastin fibers (by 59% and 64%, respectively), when compared to consecutive. Thickness of the dermis increased more in the pigs treated simultaneously (+848.8 µm/50.17%; $P < .001$). Treated tissue also showed the upper part of dermis to be rich in blood vessels and better organized interlobular septa in hypodermis. No significant change was observed in the control subject.

Conclusion: Simultaneous application produces significantly more profound changes, when compared to consecutive treatment. Further research is needed but our findings represent a new potential treatment of various skin conditions like cellulite or laxity.

KEYWORDS
collagen, dermis, elastin, radiofrequency, targeted pressure energy

1 | INTRODUCTION

Public health awareness coupled with body image perception is increasingly changing how people look at both objective and subjective cosmetic problems such as scars, cellulite, breast size, or rhytides. Following patients' demand, more than 4.8 million cosmetic procedures were performed in the United States in 2018 according to the American Society for Aesthetic Plastic Surgery.[1]

Cellulite is a common cosmetic concern that is present in at least 80% of postpubertal women.[2] It seems that the dimpled or orange-peel appearance of the skin's surface usually observed on thighs, abdomen, and/or buttocks is due to structural changes of the skin, accumulation of subdermal fat, and decreased lymphatic drainage in the area, as a result of insufficient vascularization and metabolism.[3] The cosmetic appearance of the skin is also substantially influenced by the quality of connective tissue. Collagen and elastin fibers are especially responsible for the elasticity and firmness of the skin as they contribute to healthy and smooth skin texture.[4] Moreover, the connective tissue in subcutaneous fat forms fibrous bands which envelop clusters of adipocytes and thus maintain the integrity of the fat tissue.[5,6] It has been evidenced that the severity of cellulite corresponds with the relative high ratio of adipose vs connective tissue volume, while a strong network of connective tissue in the fat layer may prevent adipocytes from protruding into the overlying dermis.[7]

Treatments of cellulite aim to reduce skin laxity, improve the blood/lymphatic circulation and the metabolic rate, diminish the subdermal fat, and increase the density of connective tissue.[2,3,8-11] In general, these changes are induced either by heating or mechanical stimulation of dermis and the underlying fat layer. Various noninvasive technologies such as ultrasound, laser, pressure waves, and radiofrequency (RF) are used to improve the appearance of the skin by inducing effects such as fat lipolysis/reduction, neocollagenesis, neoelastinogenesis, and neoangiogenesis.[2,3,8,9,12-19]

Despite different mechanisms of action, RF-induced heating of dermal and subdermal tissues and pressure energy have similar effects. It was recently reported that monopolar radiofrequency simultaneously applied with targeted pressure energy (TPE) is a viable new method for noninvasive treatment of cellulite and skin laxity in postpubertal women.[10,20] While the RF field heats the dermal and subdermal tissues to primarily achieve remodeling of loose connective fibers and fat reduction, the TPE applies pressure to the treated area and, besides the connective tissue remodeling, it increases local metabolism and lymphatic drainage.

In this study, porcine animal model of the human skin[21] was used to investigate the hypothesized superior effect of these two energies applied simultaneously in comparison with a consecutive therapy. We sought to document positive changes in dermal and subdermal tissues with increasing numbers of collagen and elastin fibers, as well as signs of angiogenesis and reduction of adipocytes size by means of lipolysis. Documenting fat cells lysis is beyond the scope of this study since pure weight loss rarely if ever diminishes cellulite.[2]

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

All experiments in this study were performed in concordance with relevant laws and regulations on the protection of animals used for scientific purposes. An ethical committee approval was received prior to commencement of this study. A porcine model was chosen for this experiment because the pigskin is remarkably similar to the human skin.[21] This study design was therefore considered suitable to provide safety and efficacy evidence which can be applicable for use on humans.

2.2 | Subjects and experimental groups

For ethical reasons, the minimum possible number of animals (N = 5) was used. The sample size of the study was chosen to align as close as possible to the 3 Rs principle of animal experimentation.

The pigs were approximately 140 days old (average weight of 70 kg). The animals were kept in normal environmental conditions under an 11 hours day/13 hours night light cycle and were given access to food and water ad libitum.

One animal served as a control. Two animals were consecutively treated; first with monopolar RF and then with TPE. The other two animals were treated simultaneously with RF and TPE energies.

FIGURE 1 Investigated device. EMTONE combines radiofrequency and targeted pressure energy in one single applicator

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2.3 | Experimental device

The device used in this study (EMTONE, BTL Industries Inc; see Figure 1) consists of two units with combined output in one single applicator. The first unit generates radiofrequency field, which provides heating to the dermal and subdermal layers. The second unit provides targeted pressure energy with frequency of 10 Hz and pressure strength of 1.5-4 bar propagating into the dermal and subdermal layers.

2.4 | Treatment protocol

Prior to treatment, the animals were first anesthetized with ketamine (10 mg/kg, intramuscular) and then kept under general anesthesia by dosage up to 20 mg/kg, iv The animals were treated on the abdominal area (*Regio abdominis lateralis*; approximately 25 square inches) in four sessions during a 4-week period (one procedure per week). Conductive cream was applied prior to the procedure.

With respect to the temperature increase caused by the RF component, the skin temperature was monitored and maintained in the range of 40-45°C with the help of the built-in IR thermometer in the device's applicator and a Fluke Ti200 thermal camera (Fluke Corp.).

2.4.1 | Consecutive treatment (CT) group

In each of the four sessions, first, a monopolar RF was applied for 12 minutes by means of the EMTONE device. The power was set to 75%-85% of the device output (max. 150 W). Immediately after the RF therapy, TPE was applied to the same abdominal area for another 12 minutes. The power of the TPE was set to 4 units on the device pressure scale (1.5-4 bar). One consecutive session thus comprised 24 minutes of net application time.

2.4.2 | Simultaneous treatment (ST) group

The parameters of the simultaneous use of RF and TPE were identical to those used in the consecutive treatment group, only delivered at the same time. The procedure lasted 12 minutes.

2.5 | Biopsy acquisition

Biopsies were taken under general anesthesia before the first treatment, after the 4th treatment, and 1-month after the last treatment (follow-up). At each stage of the experiment, samples were taken from each of the five pigs (total of 15 tissue biopsies) with a Kruuse Biopsy Punch 8 mm (KRUUSE). The biopsies were obtained perpendicularly to the skin surface, so the tissue samples contained epidermis, dermis, and hypodermis. The wounds were treated with chlorhexidine and tetracycline afterward.

The samples for histology examination were fixed in a 10% aqueous solution of neutral buffered formalin (Merck KGaA) at room temperature for 48 hours. After the fixation, the pieces were washed in running water, dehydrated in increasing concentrations of ethanol, cleared by incubation in xylene, and embedded in paraffin. The serial sections (3-5 µm thick) were performed with a microtome (Leica RM2235).

2.6 | Histology

Ten slices were prepared from each biopsy specimen. Five of them were stained for collagen and five for elastin. Quantitative analysis of collagen and elastin was performed with the ImageJ software[22] by semi-automatic segmentation in HSB (Hue-Saturation-Brightness) color system. The collagen and elastin fibers were selected and their densities were expressed as a portion of area (range from 0 to 100), which they encompassed in the studied images of approximate size 0.4 mm^2, covering reticular and papillary dermis. In addition, on each slice the dermis thickness, collagen bundles thickness or elastin fiber thickness and the cross-sectional area of adipocytes were measured. The presence of blood vessels in studied samples was qualitatively examined and commented by experienced histologist.

For collagen examination, de-waxed and hydrated paraffin sections were stained with Weigert's hematoxylin, washed in acidified water, dehydrated in ethanol, cleared in xylene, and mounted in Entellan® (Merck KGaA).

Elastin fibers were visualized with Orcein. De-paraffin and hydrated slides were stained for 30 minutes in 1% Orcein solution, passed twice in 70% ethanol, stained in Harris Hematoxylin for 1 minute, dipped in acid alcohol, dehydrated in ethanol, cleared in xylene, and mounted in Entellan® (Merck KGaA).

Microscopic observations and estimations of adipose tissue were performed with a Leica DM1000 LED microscope, equipped with the Leica Application Suite Core Software. The software automatically determines the area of adipocyte cells per slice and expresses the mean area of cells.

2.7 | Statistical analysis

The results are expressed as the mean ± standard deviation (SD). All data points were analyzed with the JASP software (version 0.9.2.0; University of Amsterdam) using a two-way analysis of variance (ANOVA), followed by Tukey's post hoc multiple comparison tests to reveal the significant difference in means of the studied groups (simultaneous/consecutive/control). Multiple paired t tests were performed to assess any significant differences between data taken after the final treatments and at the 1-month follow-up. The level of significance was set at $\alpha = 0.05$, and it was adjusted using Bonferroni correction in the case of multiple comparisons.

3 | RESULTS

During the treatments, no side effects were registered apart from mild transient erythemas caused by the heating and the physical interaction between the applicator and the skin. The erythema subsided in approximately 1 hour after the treatment. During the histology examinations, no lasting or permanent injuries to the dermal or the subdermal tissues were observed.

Table 1 lists the average collagen/elastin amounts, dermis thickness, collagen bundles thickness, elastin fiber thickness, and the cross-sectional area of the adipocytes measured in this study in the treated pigs. Results of the control group showed a stability of measured parameters in time (changes in studied quantities were shown to be negligible and therefore statistically insignificant).

3.1 | RF/TPE induces neocollagenesis and neoelastinogenesis

It should be noted that both consecutive and simultaneous treatments (hereafter, CT and ST, respectively) resulted in increased collagen and elastin fiber amount (Table 1, Figure 2 and also Figure 6). While both CT and ST showed a significant increase in the two proteins after the fourth treatment, as well as at 1-month follow-up ($P < .001$), the RF/TPE applied simultaneously showed a significantly higher increase. In conclusion, there was observed by 59% and 64% greater improvement of collagen and elastin fibers in ST subjects, respectively, compared with CT 1 month post-treatment ($P < .001$). These differences strongly suggest a synergistic effect between RF and TPE when used simultaneously.

Overall, 1 month after the last treatment the area encompassed by collagen fibers in measured slices increased by 10.34 (CT) and by 16.47 (ST) when compared to baseline. The increase in collagen fiber area registered immediately after the fourth treatment was 9.80 (CT) and 13.84 (ST), respectively. At follow-up, collagen fibers were covering on average up to 79% (ST) of studied area. Interestingly, the difference in the amount of collagen between the fourth treatment and the 1-month follow-up (hereafter, AF and FU, respectively) was statistically significant only in the simultaneously treated animals (Bonferroni $\alpha = 0.004$, $P < .001$), indicating the synergistic effects of RF and TPE.

The area encompassed by elastin fibers increased on average by 4.12 and 5.27 (CT, AF, and FU, respectively; $P < .001$), and 6.84 and 8.63 (ST, AF, and FU, respectively; $P < .001$). At the follow-up, elastin fibers were covering on average up to 15% (ST) of studied area. None of the differences observed between 4th treatment and 1-month follow-up were statistically significant ($P \geq .10$).

Figure 3 shows changes in the collagen bundles thickness and the elastin fiber thickness (see also Table 1). Again, greater and significant improvement was measured in the ST group in comparison with the CT. Especially, the increased thickness of elastin fibers was mild to modest in case of CT, showing no change after the treatments and only 23.46% change at the follow-up (yet significant against control at $P < .001$). The enlargement of collagen fibers at the FU examination compared with the AF results was statistically significant only in ST subjects ($P < .001$).

3.2 | RF/TPE increases dermal thickness

Both consecutive and simultaneous treatments resulted in an increased dermal thickness with the latter showing greater effect (Table 1 and Figure 4). Compared with the baseline, dermal thickness in the CT group showed a 26.56% and 38.06% increase (AF and FU, respectively; $P < .001$). Simultaneous treatments showed an even greater increase compared with the CT group (AF = 41.51% and FU = 50.17%; $P < .001$).

The dermal thickness showed a higher increase in ST pigs compared with the animals treated consecutively (by 70% AF and by 44% FU, $P < .001$), suggesting once again that a greater synergistic effect is possible when RF and TPE are used simultaneously.

3.3 | RF/TPE affects hypodermal tissue

The average area of fat cells decreased in both CT and ST groups with the difference between the two groups being negligible (Figure 5; AF $P = .98$ and FU $P = .91$). Compared with the control, in both treated groups the area of adipocytes decreased significantly by approximately 25% (see Table 1). one-month follow-up samples from both CT and ST animals showed that the fat cells had not grown in size compared to when measured immediately after the 4th treatment. This observation may indicate that metabolism in the treated sites was still accelerated, as the signs of enhanced vascularization were seen at 1-month follow-up (Figure 6 and Figure 1). As expected, the occurrence of blood vessels was increased in both CT and ST groups compared with the control.

Apart from the recognized increase in collagen and elastin thickness observed in the dermis, the histological examination revealed that collagenous and elastic fibers constituting the hypoderm septa were also influenced by the RF/TPE energies. At the 1-month follow-up, the interlobular septa were visibly better organized in the pigs treated simultaneously, as shown on Figure 5.

4 | DISCUSSION

This study shows that the simultaneous application of monopolar RF and targeted pressure energy positively influences both the dermal and subdermal tissues. Importantly, the simultaneous use of the two energies exhibits clearly measurable synergistic effect compared with consecutive treatment. This was primarily demonstrated by more profound elevation in the connective tissue amounts. Specifically, both collagen and elastin fibers showed enhanced thickness that resulted in a denser and more compact papillary and reticular dermis. In comparison with consecutive treatment, there was

TABLE 1 Collagen and elastin fiber amount and thickness, dermis thickness, and adipocytes' area. Data expressed as the mean ± standard deviation (SD). The differences against baseline are given as well in percent where appropriate. *P*-values generated by ANOVA are presented in separate columns

Tx Group/Units	Baseline (±SD)	AF (±SD)	FU (±SD)	Baseline vs AF	Baseline vs FU	*P*-value (vs Baseline)
Area of collagen fibers [-][a]						
CT	64.00 (2.41)	73.80 (1.50)	74.34 (3.23)	9.80	10.34	$P < .001$
ST	62.60 (2.12)	76.45 (1.26)	79.08 (0.94)	13.84	16.47	$P < .001$
P-value (ST vs CT)		$P < .01$	$P < .001$			
Area of elastin fibers [-][a]						
CT	6.50 (2.44)	10.62 (1.50)	11.77 (2.01)	4.12	5.27	$P < .001$
ST	6.15 (0.96)	12.98 (1.82)	14.78 (2.68)	6.84	8.63	$P < .001$
P-value (ST vs CT)		$P < .01$	$P < .001$			
Collagen fiber thickness [μm]						
CT	15.44 (4.45)	25.60 (4.90)	27.13 (5.38)	10.16 (65.77%)	11.69 (75.69%)	$P < .001$
ST	15.59 (5.22)	28.30 (6.00)	33.35 (8.80)	12.71 (81.54%)	17.76 (113.96%)	$P < .001$
P-value (ST vs CT)		$P < .01$	$P < .001$			
Elastin fiber thickness [μm]						
CT	1.15 (0.23)	1.13 (0.46)	1.41 (0.40)	−0.01 (−0.94%)	0.27 (23.46%)	$P > .05$; $P < .001$
ST	1.15 (0.40)	1.46 (0.34)	1.89 (0.42)	0.30 (26.33%)	0.74 (64.05%)	$P < .001$
P-value (ST vs CT)		$P < .001$	$P < .001$			
Dermis thickness [μm]						
CT	1553.84 (74.21)	1966.56 (166.95)	2145.28 (145.45)	412.73 (26.56%)	591.45 (38.06%)	$P < .001$
ST	1691.90 (110.14)	2394.26 (93.13)	2540.72 (117.16)	702.36 (41.51%)	848.82 (50.17%)	$P < .001$
P-value (ST vs CT)		$P < .001$	$P < .001$			
Adipocytes' area [μm^2]						
CT	2109.03 (533.24)	1643.16 (578.42)	1664.57 (446.52)	−465.88 (22.09%)	−444.47 (21.07%)	$P < .05$; $P < .01$
ST	2175.49 (632.85)	1667.84 (630.21)	1591.95 (547.04)	−507.64 (23.33%)	−583.54 (26.82%)	$P < .05$; $P < .001$
P-value (ST vs CT)		$P > .05$	$P > .05$			

Abbreviations: AF, after 4th treatment; CT, consecutive treatment; FU, 1-mo follow-up; ST, simultaneous treatment; Tx, Treatment.
[a]Area of collagen and elastin fibers in examined slices of approximate size 0.4 mm^2; range 0-100.

a more profound collagen fiber increase of 59% and also a more profound elastin fiber increase of 64% in pigs treated simultaneously. This increment of connective tissue led to a substantially thicker dermis at the 1-month follow-up while we observed on average an additional 591.45 μm (CT) and 848.82 μm (ST) of dermal tissue. The interlobular septa in adipose tissue also showed to be better organized at 1-month follow-up in pigs treated simultaneously (Figure 5).

As a marker of lipolysis, we measured the area of adipocytes. Any decrease in the fat cell size is an indicator of intracellular lipid content's reduction.[23] Our observations indicate that both CT and ST were similarly effective regarding the subdermal lipolysis, although the maximal relative (26.82%) and absolute (583.54 μm^2) levels of improvement were achieved in ST pigs. Trelles et al have found that RF-based treatment of cellulite produced a decrease in the lipid content and changes in their membranes. The authors believe that this would lead to cell ruptures and their death, as well as, extrusion of the lipid content out of cells.[3] Our findings corroborate these results, as we observed a reduction in adipocytes' size due to decreased content of intracellular lipid reservoirs after four treatment sessions. The fat cells shrinkage is believed to be due to accelerated cellular metabolism and hence the release of free fatty acids by the radiofrequency field,[15] and partially due to increased vascularization (discussed below) induced by both RF/TPE energies.[12,13,19,24]

Besides lipolysis, RF and targeted pressure energy are also known to induce neocollagenesis and neoangiogenesis. Meyer and co-authors reported that the application of RF leads to the increased dermal thickness and type I collagen in rats. More importantly, the study also showed an increase in the expression of fibroblast growth factor 2 (FGF2), an important signaling protein involved in angiogenesis, and consecutively in the microvessel density.[13]

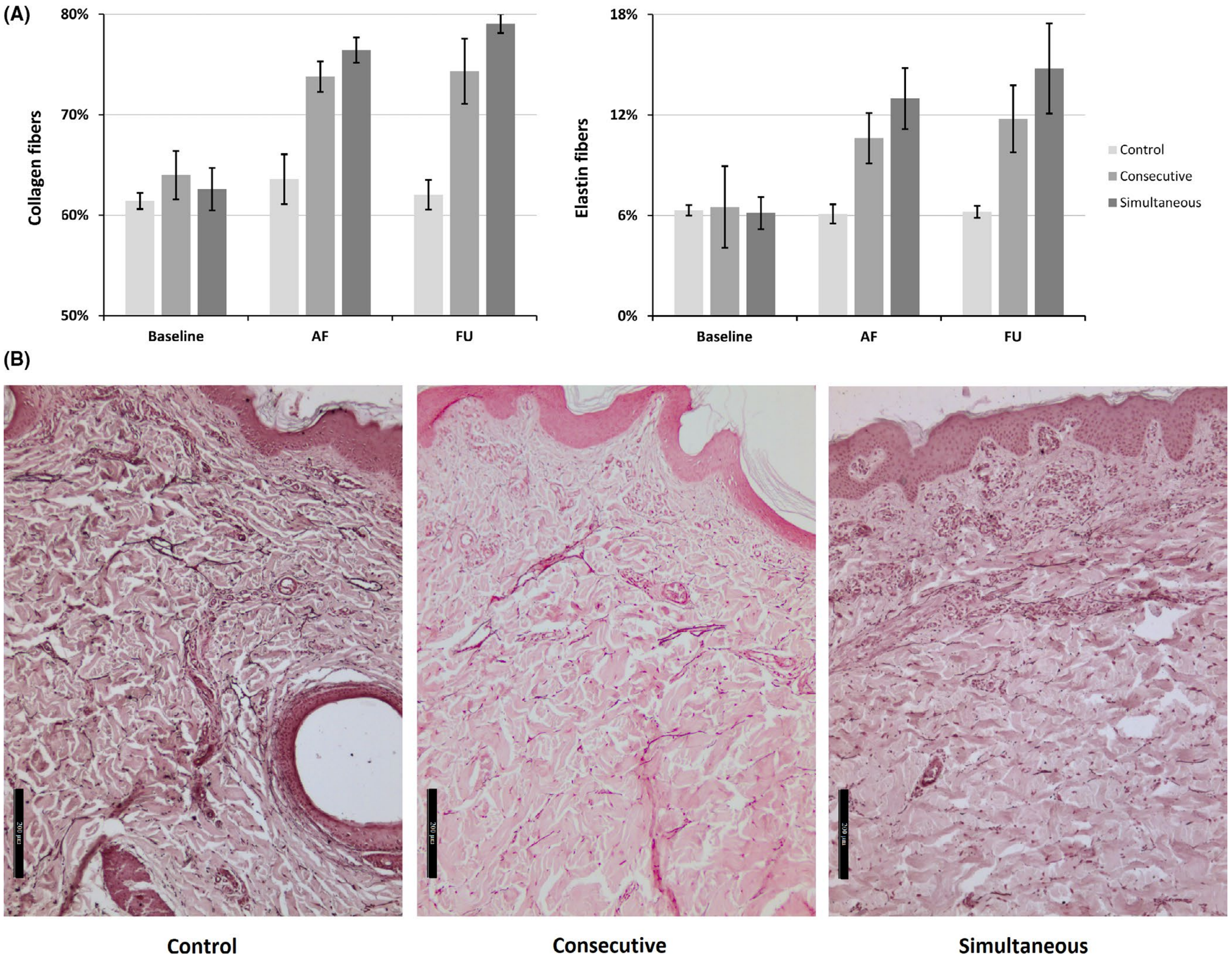

FIGURE 2 Increase of collagen and elastin amount—area encompassed on examined slices (A, mean ± SD). B, shows illustrative histological comparison of control/consecutive/simultaneous samples at 1-mo follow-up. The collagen and elastin fibers are denser and thicker in the consecutive/simultaneous samples. Samples of treated tissue are also showing greater vascularization, especially in the upper part of reticular dermis. Detail of the dermis, bar 200 μm

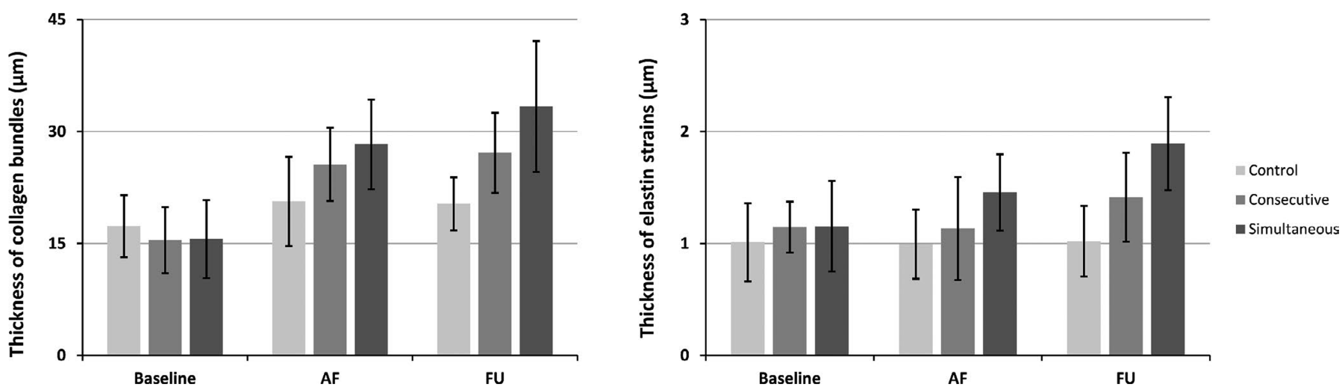

FIGURE 3 Collagen bundles and the elastin fiber strain thickness in μm (mean ± SD)

Fibroblasts, the cells maintaining the skin's structural integrity, are very similar to osteoblasts, the bone-forming cells. It is well documented that the osteoblasts are responding to mechanic stimuli which upregulate numerous genes.[25] Targeted pressure energy administered externally to the tissue is a form of mechanical stimulation which leads to both osteogenesis and

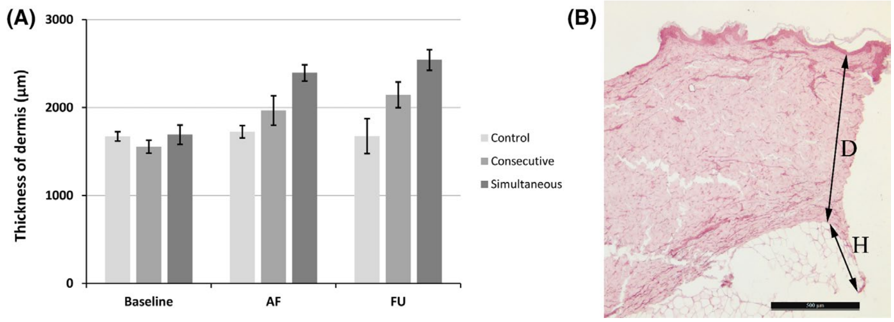

FIGURE 4 Dermis thickness in µm (A, mean ± SD). B shows illustrative assessment of dermis thickness (D). Subcutaneous tissue (H) is seen below the reticular dermis; bar 500 µm

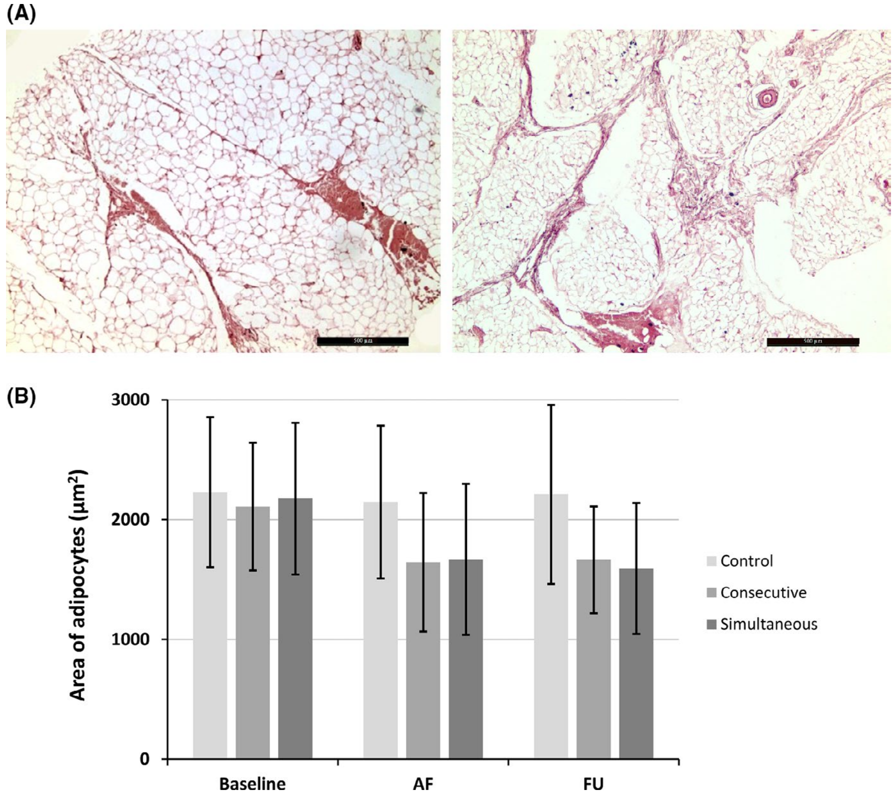

FIGURE 5 A, Visualize adipocytes and interlobular septa in hypodermis before and 1 mo after simultaneous treatment; bar 500 µm. Adipocytes are visibly smaller after RF/TPE treatment, while septa are visibly thicker and better organized. 5b shows results of measurement of adipocytes' area in µm^2 (mean ± SD)

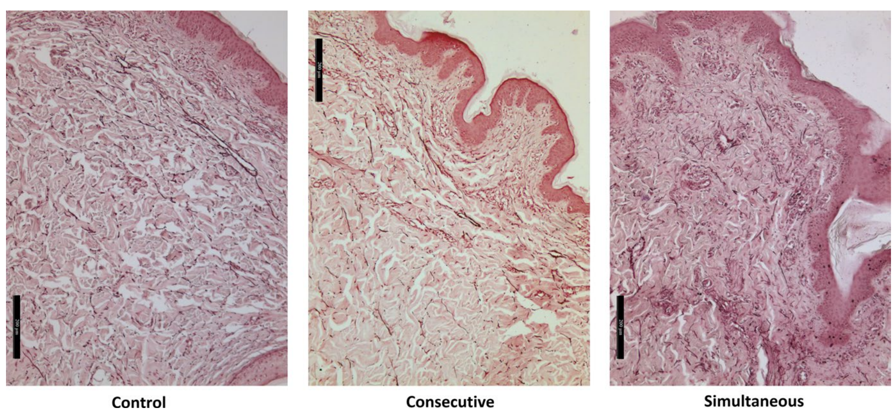

FIGURE 6 Illustration of increased vascularization. Samples were taken at 1-mo follow-up. Consecutive/simultaneous samples are showing greater vascularization, denser organization, and thickness of connective fibers in comparison with the control. Detail of the dermis; bar 200 µm

angiogenesis, stimulating both the osteoblasts and the fibroblasts, respectively.[12,19,24,26] De Lima Morais et al further observed that pressure energy leads to an overexpression of FGF2 and its receptor, fibroblast growth factor receptor 1 (FGFR1), leading to angiogenesis. Moreover, they also reported that mechanical stimulation led to increased collagen synthesis and dermal thickness[12] also observed in our study, particularly in synergy with the RF energy. It has been documented that the application of mechanical stress affects thermal stability of collagen molecules, resulting in a more efficient thermal stimulation and consequent remodeling,[27,28] which may explain the more pronounced results of simultaneous application documented in our study.

Angiogenesis and an increased metabolic rate are important factors contributing to the treatment of cellulite, due to the fact that the condition is at least in part caused by insufficient lymphatic drainage.[2,3] The combined application of RF and TPE, which produced an increased vascularization in this animal study, may be therefore a suitable combination for noninvasive treatment of cellulite.[10] Despite the fact that microvessel density was not measured in our study, the evaluation of histological samples (see Figure 6) revealed that RF/TPE combination used simultaneously might be a more powerful tool for the induction of angiogenesis than any consecutive or single application treatment.

Elastinogenesis and collagenesis induced by the RF/TPE application may possibly further improve the visual appearance of the skin. A thicker dermis with decreased laxity (due to increased elastin content[10]) would be more resistant to bulging caused by the underlying fat cells. In addition, the reduction in adipocytes' size may decrease the bulging effect as well. Moreover, the better-organized septa in adipose tissue should also favorably support the outcomes of therapy as the strengthened network of fibrous bands maintains the integrity of the subcutaneous layer and prevents the fat lobules from protruding into the dermis.[5,6]

This histological study might benefit from longer follow-up observational period. However, the length of the follow-up (1 month after the last treatment) is comparable to other existing histological studies examining the effect of RF treatment on human skin.[9,14,15,29-31] These experiments report collagen (and elastin) increase in the skin after RF irradiation with follow-ups ranging from 1 week to 3 months, showing great diversity among the experimental designs. On the other hand, one of the strengths of our study is the quantitative objective evaluation of the composition of dermal/subdermal tissue and verification of the observed changes by the examination of control subject.

5 | CONCLUSION

This porcine model study indicates that the simultaneous application of RF and targeted pressure energy may be a suitable treatment for various skin conditions such as cellulite and skin laxity. The combined application of these energies showed enhanced synergistic effects in several instances. Compared with the consecutive application of the modalities, the simultaneous use of these two fields exhibits a more beneficial effect on animal dermal and subdermal tissues, with regard to connective fiber density and dermal thickness. Additionally, a decrease in lipid content was achieved, reducing the size of adipocytes. Further research is needed to confirm the enhanced vascularization observed in the dermal tissue.

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CONFLICT OF INTEREST

Brian M. Kinney MD is a medical advisor to BTL. Dian Kanakov MD and Penka Yonkova PhD have no conflicts to declare.

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EMTONE™: SYNERGY OF **SIMULTANEOUS DELIVERY OF RF AND TARGETED PRESSURE ENERGY** FOR CELLULITE REDUCTION

SAFETY AND EFFICACY OF NOVEL TECHNOLOGY FOR CELLULITE TREATMENT BASED ON SIMULTANEOUS APPLICATION OF MONOPOLAR RADIOFREQUENCY AND TARGETED PRESSURE ENERGY

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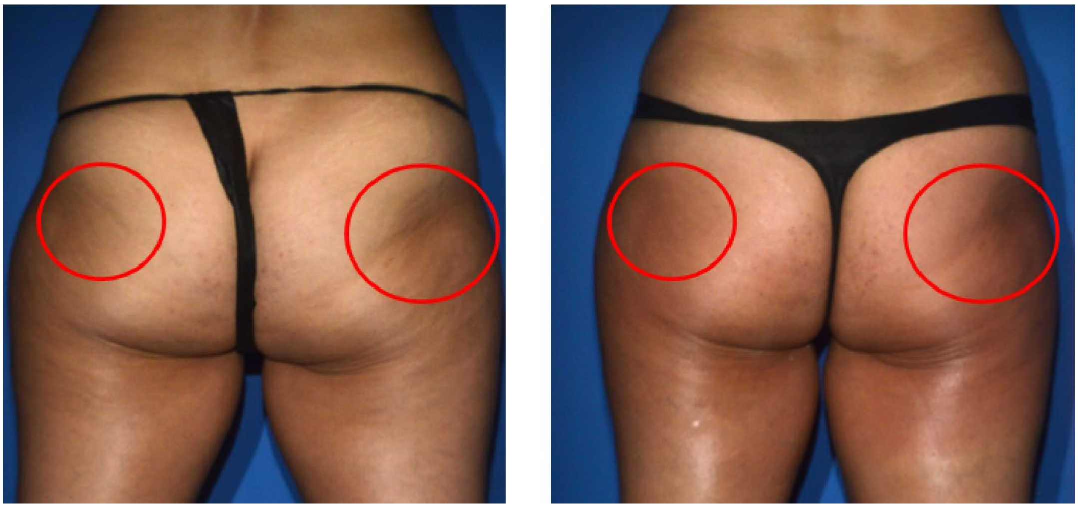
HIGHLIGHTS

- **30 subjects** with **cellulite** (grade 2 to 3) were enrolled. All subjects underwent **four treatments** (two sessions per week) **in desired area**.
- **87%** of the subjects reported **improvement** in the appearance **of the treatment area**.
- **Total of 86%** of the photographs were rated as **significant improvement in the treated area**.
- **90%** of the patients would undergo the EMTONE treatment again.



Example of patient photographs before (left) and after 4th treatment.

DESIGN AND METHODOLOGY

- Each treatment lasted **15 to 24 minutes depending on** the size of **treated area**.
- **Weight** and **photographs** were recorded at the baseline and immediately after the last treatment. Patient satisfaction and treatment comfort were assessed using questionnaires.
- **Three blinded evaluators** evaluated all photographs and rated the **improvement according to the GAIS** (Global Aesthetic Improvement Scale).

Example of patient photographs before (left) and after 4th treatment.

RESULTS

- Digital photographs demonstrated **significant improvement in cellulite** and **skin quality**.
- **80%** were satisfied with the treatment results.
- Subjects found the treatments **comfortable** and were **highly satisfied** with the treatment results.

BASELINE

1 MONTH FU

Example of patient photographs before (left) and after 4th treatment.

EMTONE® TECHNOLOGY FOR CELLULITE REDUCTION: MECHANISM OF ACTION

There are many invasive and non-invasive approaches to the treatment of cellulite. These include lymphatic drainage, manual or mechanical massage, acoustic wave therapy, and application of laser or radiofrequency (RF) based treatments. These approaches are either used on a standalone principle or in combination with each other in order to enhance the results. The purpose of combined therapies is to achieve higher efficiency via the synergy of various physiological effects induced by the respective technologies. EMTONE combines monopolar RF and Targeted Pressure Energy. As such, it introduces a unique non-invasive solution combining two proven approaches to the treatment of cellulite. Due to the simultaneous effects, the therapy time is reduced and the results are significantly improved.

PATHOPHYSIOLOGY OF CELLULITE

Cellulite is considered to be a common topographical alternation of the human skin, which mostly occurs in the dermis and hypodermis. 80 – 90% of post-pubertal women are affected by some form of cellulite. The main causes of this skin condition are heredity, unhealthy lifestyle and hormonal changes.

Prevalence of cellulite in women is much higher than in men. Compared to men, women have a larger number of fat cells (adipocytes) in the subcutaneous tissue (hypodermis), which also has a greater propensity to deposit fat. Due to this predisposition, excessive calorie intake in women will cause an increase in adipocyte enlargement.

The fat cells are located in chambers (lobules) which are separated by vertical and horizontal connective tissue septae. Due to the increasing number (hyperplasia) and size (hypertrophy) of the adipocytes, the fat chambers become distended and are pushed up against the skin surface. Moreover, the collagen in female skin has different arrangements - fibers of connective tissue are oriented perpendicular to the skin surface, while male collagen bonds form approximately 45° angles. Shortening of these septae due to fibrosis and loss of their elasticity provokes retraction and causes depressions that are characteristic for cellulite.

Previously described anatomical alternations lead to a dimpled and uneven surface of the skin, generally known as the orange peel, mattress or cottage cheese skin appearance. As a consequence the capillary system is constrained by the enlarged adipose tissue, resulting in a reduction of blood and lymph flow, and an increased storage of waste products[1,2].

EFFECT OF EMTONE ON TARGET TISSUE

Collagen

Collagen, as the main component of connective tissue, is also an important structural part of the dermis and hypodermis. The hypodermis connective septae influenced by cellulite are characterized by rigid structure of fibrotic collagen fibrils.
The simultaneous emission of monopolar RF and Targeted Pressure Energy represented by thermal and mechanical energies activates the function of metalloproteinases (MMP's) in the extracellular matrix. MMP's are responsible for the degradation of the collagen protein structure[5,6]. The mechanical stress concurrently results in dissociation of fibrils, a reduction in their structural density thereby increasing conformational freedom and reducing their thermal stability. Due to this phenomenon the temperature required for collagen denaturation is decreased[3,4]. Thermal stimulation thus leads to a disruption of the intramolecular hydrogen bonds and a partial shrinkage of collagen triple helix can be observed at lower temperatures. As a direct consequence, the collagen remodeling and the neocollagenesis are initiated sooner. Micro-inflammatory stimulation of fibroblasts caused by heat accumulation results in their proliferation. This causes a significant increase in production of procollagen mRNA[7]. The heating

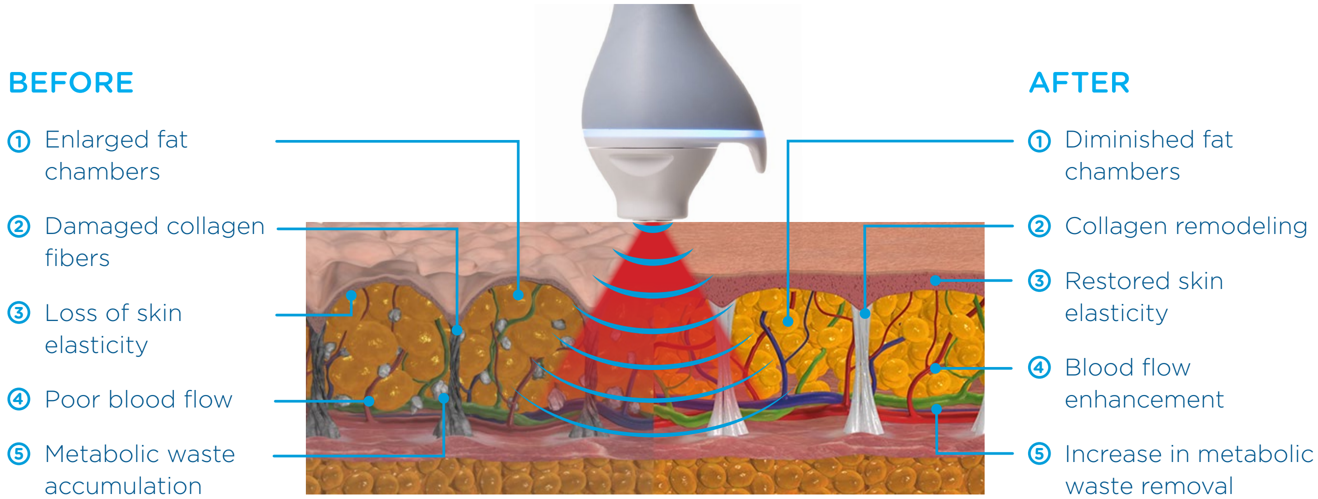


Figure 1: Illustration of skin structure changes after EMTONE treatment.

of collagen to the critical temperature of 42°C stimulates the production of HSP47 protein. This protein is involved in the formation of collagen at the endoplasmic reticulum, and ensures proper conformation of the collagen tertiary structure. This is necessary for collagen's correct function[8]. Exposure to the mechanical energy accelerates proliferative activity of fibroblasts and creates a suitable environment for the synthesis of new collagen and elastin by reducing oxidative stress in the tissue[9,10].
The simultaneous effect of mechanical and thermal energy results in the disruption of old damaged collagen fibers followed by the synthesis of new healthy ones. The fibroblasts concurrently produce new elastin fibers. These facts lead to a thickening of the dermis, relaxation of connective septae in the hypodermis and an increase in elasticity.

Adipocytes

Applied monopolar RF waves penetrate into the deeper layers of the skin, where the heat is absorbed by different cells. Different kinds of tissue absorb different amounts of heat depending on their electrical resistance (impedance). The electrical impedance is determined by tissue water content (water is a very good electrical conductor). Fat tissue has a much lower water content (10 – 20 %) and therefore a higher impedance (3000 – 5000 Ω/cm2) compared to other tissues such as muscle (water content 70 – 75 % and electrical impedance 100 – 220 Ω/cm2). Due to the impedance of the tissue, the electrical current is converted to thermal energy according to the formula (1), where I = current, Z = tissue impedance, and T = time of application. This relation shows that tissue with a higher electrical impedance is heated more intensively than tissue characterized by a lower impedance[12].

$$\text{Energy (Joules)} = I^2 \times Z \times t \tag{1}$$

As a result of tissue exposure to heat and mechanical stimulation, the properties of the cell membranes are changed. A higher permeability of the cell membrane, in particular, allows fluids to move rapidly through the membrane and an acceleration of the cell metabolism can be observed[11]. A combination of both energies stimulates the blood circulation and contributes to the formation of new blood vessels (angiogenesis). These alternations lead to the activation of enzymes responsible for the breakdown of fat (lipids) stored in adipocytes. As a direct consequence, the size of fat chambers is significantly reduced[12].

Blood and lymph circulation

Mechanical massage using circular motions towards the lymphatic nodes results in a lymphatic drainage effect, which helps increase the removal of water and metabolic waste from the affected tissue. Proper function of the lymphatic system thus decreases the overall toxic load of the cell.
Sufficient blood supply is one of the main prerequisite for the physiological function of the healthy tissue and the proper healing of impaired tissue including neocollagenesis, neoelastinogenesis and physiological function of the adipocyte metabolism. As mentioned above, blood circulation is promoted by angiogenesis and mechanical stimulation provided by Targeted Pressure Energy and vasodilatation caused by radiofrequency thermal effect. Thermal induced metabolism acceleration and reduction in chamber size concurrently relax the constricted blood vessels.

All the mentioned effects (increase of neocollagen fibers, adipocyte metabolism acceleration, increased waste product removal and blood circulation) produce a thicker and more flexible dermis and cause a reduction of fat chamber size, relaxation of connective septae and an overall improvement in skin condition.

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