

Predictability of the individual clinical outcome of extracorporeal shock wave therapy for cellulite

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Background: Extracorporeal shock wave therapy has been successfully introduced for the treatment of cellulite in recent years. However, it is still unknown whether the individual clinical outcome of cellulite treatment with extracorporeal shock wave therapy can be predicted by the patient's individual cellulite grade at baseline, individual patient age, body mass index (BMI), weight, and/or height.

Methods: Fourteen Caucasian females with cellulite were enrolled in a prospective, single-center, randomized, open-label Phase II study. The mean (\pm standard error of the mean) cellulite grade at baseline was 2.5 ± 0.09 and mean BMI was 22.8 ± 1.17 . All patients were treated with radial extracorporeal shock waves using the Swiss DolorClast® device (Electro Medical Systems, S.A., Nyon, Switzerland). Patients were treated unilaterally with 2 weekly treatments for 4 weeks on a randomly selected side (left or right), totaling eight treatments on the selected side. Treatment was performed at 3.5–4.0 bar, with 15,000 impulses per session applied at 15 Hz. Impulses were homogeneously distributed over the posterior thigh and buttock area (resulting in 7,500 impulses per area). Treatment success was evaluated after the last treatment and 4 weeks later by clinical examination, photographic documentation, contact thermography, and patient satisfaction questionnaires.

Results: The mean cellulite grade improved from 2.5 ± 0.09 at baseline to 1.57 ± 0.18 after the last treatment (ie, mean δ -1 was 0.93 cellulite grades) and 1.68 ± 0.16 at follow-up (ie, mean δ -2 was 0.82 cellulite grades). Compared with baseline, no patient's condition worsened, the treatment was well tolerated, and no unwanted side effects were observed. No statistically significant (ie, $P < 0.05$) correlation was found between individual values for δ -1 and δ -2 and cellulite grade at baseline, BMI, weight, height, or age.

Conclusion: Radial shock wave therapy is a safe and effective treatment option for cellulite. The individual clinical outcome cannot be predicted by the patient's individual cellulite grade at baseline, BMI, weight, height, or age.

Keywords: acoustic wave therapy, AWT, extracorporeal pulse activation therapy, EPAT, radial shock wave therapy, RSWT

Introduction

Gynoid lipodystrophy, better known as cellulite, is the most common lipodystrophic disease and is found in 85% of post-adolescent women.¹⁻⁴ Cellulite usually develops in particular anatomical areas, such as the thighs, buttocks, abdomen, and upper arms, and becomes visible through its classical “orange peel” appearance, characterized by an irregular, dimpled skin surface with thinning of the epidermis/dermis and the presence of nodular clusters of fat cells.¹⁻⁴ It represents not only a cosmetic concern

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for women, but often becomes a major psychological problem, impairing sporting activities, choice of clothing, and social interaction.

The pathophysiology of cellulite is related to various predisposing factors, such as biotype, heredity, ethnic background, body weight, age, hormonal changes, smoking, and genetic predisposition.^{1,2,4-6} Four main hypotheses regarding the etiopathogenesis of cellulite have emerged over recent decades: a different anatomical conformation of the subcutaneous tissue in women compared with men;^{7,8} changes in the biomechanical properties of epidermal and dermal tissues;⁸ excessive hydrophilia of the extracellular matrix increasing interstitial pressure and causing edema of the fatty tissue;⁹ and alterations in both microvascular and lymphatic circulation resulting in the often painful protrusion of subcutaneous adipose tissue into the lower reticular dermis, causing distinctive mattress-like surface irregularities.¹⁰ However, these hypotheses are mutually conflicting and do not consider recent advances in our understanding of the complex physiopathology of the adipose organ.¹⁰ For instance, one

cannot exclude that inflammation also contributes to the formation of cellulite.^{11,12}

Nevertheless, various treatments for cellulite have been developed over recent decades, focusing on skin tightening with radiofrequency or lasers, improving blood and lymphatic circulation using both physical treatments and pharmacotherapy, and treating deeper deformities with surgical subcision, laser treatments, ultrasound devices, or liposuction (summarized in Table 1). However, there is no single treatment of cellulite that is completely effective.^{13,14}

Extracorporeal shock wave therapy (ESWT) and radial shock wave therapy (RSWT) have been introduced as safe and effective treatment options for cellulite.¹⁵⁻²³ A shock wave is an acoustic pressure wave that is produced in any elastic medium, such as air, water, or even a solid substance.^{24,25} Shock waves differ from sound waves in that the wave front, where compression takes place, is a region of sudden change in stress and density.^{24,25} Both focused shock waves (ESWT) and radial shock waves (RSWT) are characterized by a high positive peak pressure (in mPa), a fast initial rise

Table 1 Various therapies for cellulite and their level of evidence based on published studies

Treatment	Related studies and their level of evidence*				
	IB	IIA	IIB	III	IV
ESWT/RSWT	Sattler et al ¹⁵ Knobloch et al ¹⁶ Russe-Wilflingseder et al ¹⁷	Braun et al ¹⁸ Angehrn et al ¹⁹ Christ et al ²⁰ Christ et al ²¹ Adatto et al ²²			Kuhn et al ²³
Radiofrequency	Mlosek et al ⁵⁰	Nootheti et al ⁵¹ Goldberg et al ⁵²	Sadick and Mulholland ⁵³ Sadick and Magro ⁵⁴		
Laser-assisted lipolysis	Prado et al ⁵⁵ Nagy and Vanek ⁵⁶				Katz et al ⁵⁷ Kim and Geronemus ⁵⁸
Topical herbs and retinol	Lis-Balchin ⁵⁹	Kligman et al ⁶⁰			
Topical phosphatidylcholine and LED	Saski et al ⁶¹				
ESWT + cryolipolysis		Ferraro et al ⁴⁴			
Focused ultrasound		Moreno-Moraga et al ⁶²			
Endermology		Collis et al ⁶³	Chang et al ⁶⁴ Smalls et al ⁶⁵ Mauriège et al ⁶⁶ Hexsel et al ⁶⁷ Rotunda et al ⁶⁸ Brandi et al ⁶⁹ Brandi et al ⁷⁰		
Weight loss					
Mesotherapy					
Carboxy therapy					
Liposuction				Coleman ⁷¹	
Lipolysis with topical phosphatidylcholine injections					Môle ⁷²
Cryolipolysis					Manstein et al ⁷³
Subcision					Hexsel and Mazzucco ⁷⁴

Notes: *Level IB: evidence from at least one randomized controlled trial. Level IIA: evidence from at least one controlled study without randomization. Level IIB: evidence from at least one other type of experimental study. Level III: evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies. Level IV: evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.⁷⁵

Abbreviations: ESWT, extracorporeal shock wave therapy; RSWT, radial shock wave therapy; LED, light-emitting diode.

in pressure (approximately a few microseconds or less), a diffraction-induced tensile wave following the positive pressure amplitude that can generate cavitation, and a short life cycle of approximately 10–20 μ seconds (Figure 1).^{24–29} Extracorporeal shock wave lithotripsy is widely used for stone management in urology.³⁰ ESWT and RSWT are byproducts of lithotripter technology. Since the late 1980s, they have been introduced into treatment for various diseases of the musculoskeletal system, such as plantar fasciopathy, Achilles tendinopathy, medial tibial stress syndrome, greater trochanteric pain syndrome, lateral and medial epicondylitis, and calcifying tendonitis of the shoulder.^{27–29,31,32} Shock waves have both a direct and indirect effect on treated tissues. The direct effect is the result of the energy of the shock wave being transferred to the targeted tissues. The indirect effect is the result of the creation of cavitation bubbles in the treated tissue.^{24,25,29} It has been hypothesized that both the direct and indirect effects produce a biological response in the treated tissues.^{24,25,29}

ESWT devices share two technical key characteristics of extracorporeal shock wave lithotripsy devices used for stone management, namely the electrohydraulic, electromagnetic, or piezoelectric generation of pressure waves and the generation of focused or so-called defocused pressure waves.^{29,33} Radial shock waves are generated ballistically, ie, by

accelerating a bullet that strikes an applicator, transforming the kinetic energy of the bullet into a radially expanding pressure wave (Figure 1).^{29,32,33} In this regard, it is of note that, in several studies on ESWT/RSWT for cellulite, the therapy was termed acoustic wave therapy (AWT)^{15,17,20,22} or extracorporeal pulse activation therapy (EPAT).^{21,22} The terms AWT and EPAT are proprietary names of the manufacturer of the corresponding devices (Storz Medical, Tägerwil, Switzerland; see also Russe-Wilfingseder et al¹⁷). AWT is registered as "... non-medical electric and electronic apparatus and instruments for the generation and application of shock waves or pressure waves in the fields of cosmetics and beauty care",³⁴ and EPAT as "... electronic apparatus and parts of the apparatus for generating and applying pressure or shock waves for use in the fields of cosmetics and beauty care".³⁵ The similarity between AWT, EPAT, and RSWT has been addressed in several papers in the literature.^{21,36,37}

Unaddressed in the studies on ESWT/RSWT for cellulite carried out to date^{15–23} is whether the individual clinical outcome of the therapy can be predicted by the patient's cellulite grade at baseline, age, body mass index (BMI), weight, height, and/or age. This was addressed in the present study using RSWT. We hypothesized that the individual clinical outcome of RSWT for cellulite can be predicted by the patient's cellulite grade at baseline and the patient's BMI.

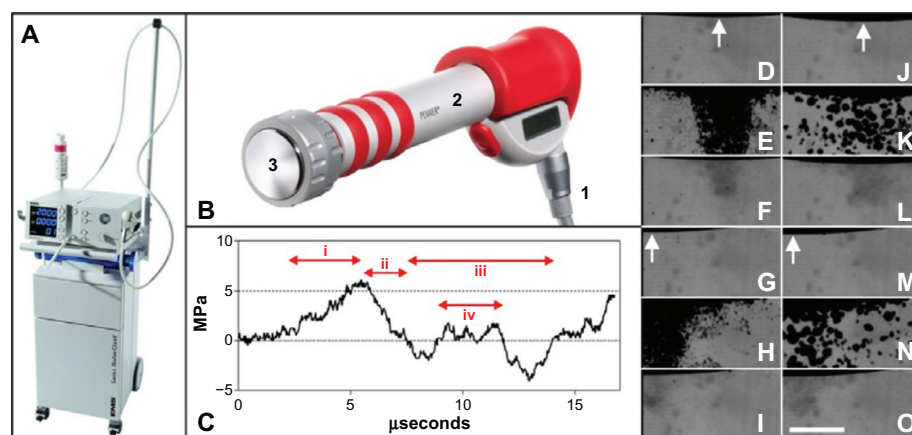


Figure 1 Principles of radial shock wave technology.

Notes: (A) DolorClast® device (Electro Medical Systems SA, Nyon, Switzerland) used in the present study. (B) Power+ hand piece of the Swiss DolorClast device with the 36 mm applicator used in the present study. Compressed air (1) is used to fire a projectile within a guiding tube (2) that strikes a 36 mm diameter metal applicator (3) placed on the skin. The projectile generates stress waves in the applicator that transmit pressure waves noninvasively into tissue. (C) Pressure wave generated with the Swiss DolorClast device, measured at a distance of 1 mm from the applicator (Power+ hand piece, 36 mm applicator, device operated at 4 bar air pressure and 15 Hz impulse frequency as used in the present study). After a delay of approximately 2 μ seconds, the pressure wave shows an increase in (positive) pressure (i), followed by a decrease in pressure (ii) with reaching zero at approximately 8 μ seconds, a subsequent period of negative pressure (iii) interrupted by a period of positive pressure (iv). (D–O) Cavitation bubbles (black dots) in degassed water generated during the phase of negative pressure of radial shock waves generated with the Power+ hand piece and the 36 mm applicator of the Swiss DolorClast device operated at 4 bar air pressure at 15 Hz (D–I) as used in the present study or at 1 Hz (J–O) either at the center of the applicator (D, E, F, J, K and L) or the edge of the applicator (G, H, I, M, N and O). Note that the arrows point to the center of the applicator. Maximum cavitation is shown in (E, H, K and N). The images shown in (D, G, J and M) were taken approximately 1.5 mseconds before the cavitation maximum, and images shown in (F, I, L and O) were taken approximately 1.5 mseconds after the cavitation maximum. Cavitation lasted for approximately one mseconds. The pictures were taken with a high-speed CCD camera (Photron Ultima APX; Photron, Tokyo, Japan) with a framing rate of 300,000 frames per second and an exposure time of 1/2,700,000 seconds. The scale bar in (O) represents 10 mm. Note that the cavitation field (and thus the pressure field below the applicator) is broader when generating radial shock waves at 15 Hz (D–I) than at 1 Hz (J–O). This phenomenon is observed for many radial shock wave devices (Császár et al, submitted for publication).

Materials and methods

Study design

Fourteen Caucasian females with cellulite were enrolled in a prospective, single-center, randomized, open-label Phase II study. The mean (\pm standard error of the mean) patient age was 42.4 ± 2.81 (23–57) years. Mean BMI was 22.8 ± 1.17 (18.7–32.9). The inclusion and exclusion criteria are summarized in Table 2. Informed consent was obtained from each patient before treatment. The study was approved by the ethics committee of Canton Geneva (Geneva, Switzerland) under registration number GE 08-40 and by the Swiss Agency for Therapeutic Products (Swissmedic, Bern, Switzerland) under registration number 2009-MD-0005. The study is registered with ClinicalTrials.gov (NCT01974115).³⁸

Determination of cellulite grade

The mean cellulite grade of the patients at baseline was 2.5 ± 0.09 (range 2–3). Cellulite grades were determined by clinical inspection of the patients' skin (documented by digital photography) and by contact thermography.

Photographs of the patients were taken before the treatment cycle and at each follow-up using a D80 digital camera system (Nikon, Tokyo, Japan), PocketWizard transceivers (LPA Design, Burlington, VT, USA), and StudioMax III lighting equipment (Photogenic Professional Lighting, Bartlett, IL, USA), with standardized lighting settings and distance to the patient at each photographic session. Patients were asked to fully contract the buttock muscles each time

Table 2 Inclusion and exclusion criteria applied in the present study

Inclusion criteria

Healthy women <60 years of age, with cellulite grade 2–3
Unchanged hormonal treatment for <6 months
Commitment to the study and ability to follow the medical directions during the study
Signed informed consent form

Exclusion criteria

Previous surgery in the treated area (especially liposuction)
Medical and/or cosmetic treatment of cellulite ongoing or within the last 3 months
Infection and/or tumor disease within the treatment area
Anticoagulation therapy and/or hemorrhagic disorders
Pregnancy
Significant weight fluctuations (caused by disease or diet)
Modified hormonal treatment
Drugs (eg, corticosteroids, nonsteroidal anti-inflammatories)
Vascular abnormalities
Previous treatment with ESWT/RSWT

Abbreviations: ESWT, extracorporeal shock wave therapy; RSWT, radial shock wave therapy.

a photograph was taken. This aimed to fully show and standardize the appearance of the cellulite and thus to avoid any “softening effects” due to varying muscle tone that might change the visibility of the cellulite.

Contact thermography was performed using the Cell-Meter® System Professional Cellulite Thermodetector (IPS Srl, Milan, Italy) that was applied directly on the skin of the treated areas. The temperature is displayed in a color code, with brown-orange-yellow indicating cold areas (29.5°C – 30.5°C) and bluish shades indicating warm areas (32°C – 33.5°C). Cellulite grades, determined by clinical inspection of the skin, correlated well with the contact thermography data.

Treatment

All patients were treated with radial extracorporeal shock waves using the Swiss DolorClast device (Electro Medical Systems, SA, Nyon, Switzerland) and the Swiss DolorClast Power+ hand piece with the 36 mm applicator (Figure 1). Patients were positioned on a treatment table as indicated in Figure 2 and the areas of the posterior thigh and the anatomical buttock area were treated. The medial and lateral lines of the thigh served as borders of the treatment area which extended superiorly until the buttock crease and inferiorly 5 cm above the popliteal crease.

Patients were treated unilaterally with 2 weekly treatments for 4 weeks on a randomly selected side (left or right), totaling eight treatments on the selected side. After application of coupling gel, treatment was performed at 3.5–4.0 bar, with 15,000 impulses per session, and applied at 15 Hz. Impulses were applied homogeneously over the posterior thigh and buttock area.

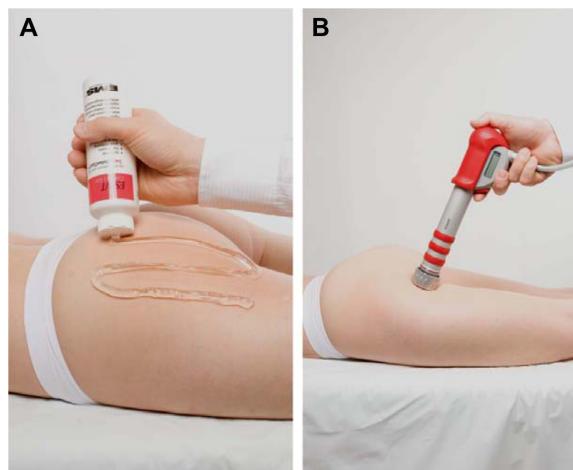


Figure 2 Radial shock wave therapy for cellulite.

Notes: (A) Application of coupling gel. (B) Treatment with the Power+ hand piece of the Swiss DolorClast® device (Electro Medical Systems, Nyon, Switzerland).

Evaluation of clinical outcome

The condition of each patient's skin was evaluated before treatment, after the last treatment, and at a follow-up visit 4 weeks after the last treatment. At both the last treatment and at follow-up, patients completed a detailed questionnaire with scores for treatment comfort, pain intensity, and satisfaction, while also indicating undesired effects, such as bruising.

Statistical analysis

The mean and standard error of the mean were calculated for all investigated variables. Dependence of the clinical outcome of RSWT (calculated as the individual difference in cellulite grades either between baseline and after the last treatment [$\delta-1$] or between baseline and follow-up [$\delta-2$]) on the patients' initial cellulite grade at baseline, BMI, weight, height, age, pain during the treatment, feeling of comfort during treatment, and satisfaction at the end of treatment (or at the end of the follow-up period) was tested using Spearman's nonparametric rank correlation. Because $\delta-1$ and $\delta-2$ were each tested against eight variables, an effect was considered statistically significant if its associated *P*-value was smaller than $0.05/8=0.00625$ considering the Bonferroni correction for multiple hypothesis testing.³⁹ Spearman's nonparametric rank correlation was also used for testing the relationship between $\delta-1$ and $\delta-2$. In this case, the effect was considered to be statistically significant if the associated *P*-value was smaller than 0.05. Calculations were performed using

GraphPad Prism version 5.0 for Windows (GraphPad software, San Diego, CA, USA).

Results

The mean cellulite grade improved from 2.5 ± 0.09 (range 2–3) at baseline to 1.57 ± 0.18 (range 0.25–2.75) at the end of the treatment (ie, the mean $\delta-1$ was 0.93 cellulite grades). At the end of the follow-up period, the mean cellulite grade was 1.68 ± 0.16 , ranging between 0.5 and 2.75 (ie, the mean $\delta-2$ was 0.82 cellulite grades). The individual $\delta-1$ varied between 0 grades (ie, no improvement) and 1.75 grades, and the individual $\delta-2$ between 0 grades and 1.5 grades (Figure 3). Accordingly, compared with baseline, no patient's skin condition worsened during treatment and follow-up. The treatment was well tolerated and no unwanted side effects were observed (note that discomfort during treatment and reddening of the skin up to 24 hours after each treatment session are usual side effects of RSWT and were therefore not considered unwanted side effects).

No statistically significant (ie, $P < 0.05/8$) correlation was found between $\delta-1$ or $\delta-2$ and cellulite grade at baseline, BMI, weight, height, age, pain during treatment, feeling of comfort during treatment, or satisfaction at the end of treatment (or at the end of the follow-up period, Figures 4 and 5).

For eleven of the 14 patients, the condition of the skin further improved or remained constant during the interval between the last treatment and follow-up (Figure 6).

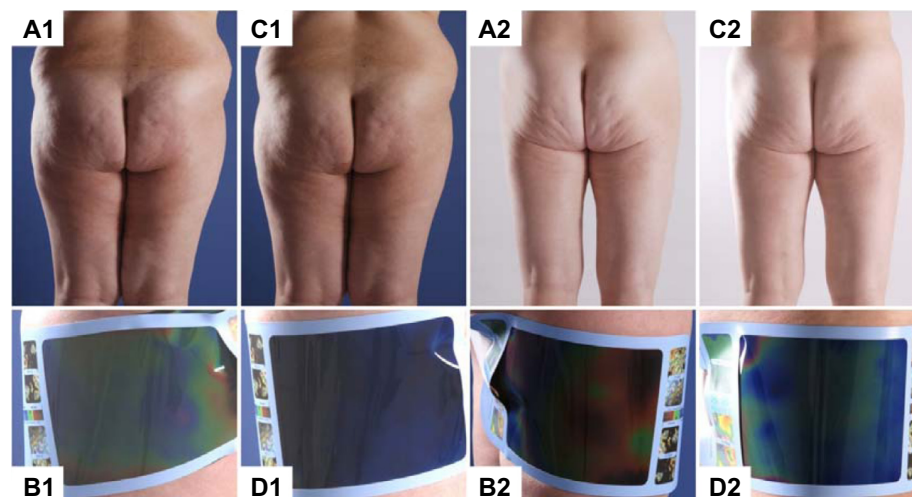


Figure 3 Treatment of two patients (1, 2) with cellulite using radial extracorporeal shock wave therapy.

Notes: (A1 and A2) Clinical picture at baseline. (B1 and B2) Contact thermography at baseline. (C1 and C2) Clinical picture 4 weeks after the last treatment (follow-up). (D1 and D2) Contact thermography at follow-up. (A1–D1) A 29-year-old female (body mass index 32.9, weight 84.3 kg, height 160 cm). Radial extracorporeal shock wave therapy performed on the left side improved the cellulite from grade 3 at baseline to grade 1–2 at follow-up (ie, $\delta-2$ was 1.5). Despite this objectively substantial treatment success, the patient's satisfaction was only 5 on a scale ranging from 0 (maximum dissatisfaction) to 10 (maximum satisfaction). (A2–D2) A 51-year-old female (body mass index 20.8; weight 53.3 kg; height 160 cm). Radial extracorporeal shock wave therapy performed on the right side improved the cellulite from grade 2–3 at baseline to grade 1–1.5 at follow-up (ie, $\delta-2$ was 1.25). This patient was very satisfied with the treatment (9 on a scale ranging from 0 to 10). Patient consent was obtained to publish the above images.

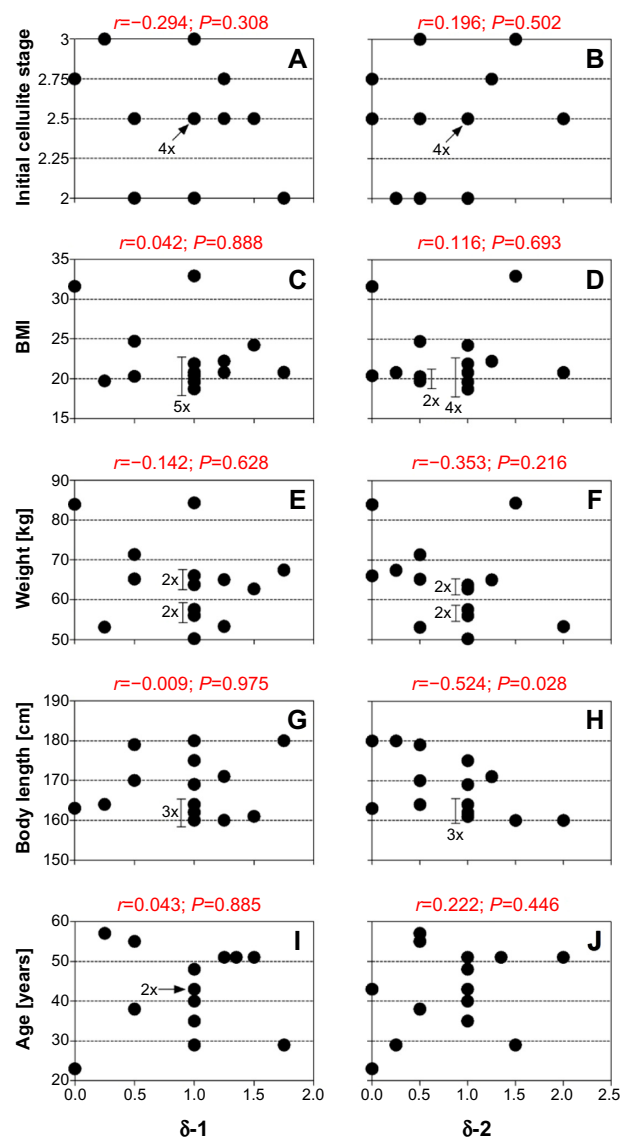


Figure 4 Clinical outcome of radial extracorporeal shock wave therapy for cellulite as a function of the patients' initial cellulite grade at baseline (A and B), BMI (C and D), weight (E and F), height (G and H) and age (I and J) (calculated as individual difference in cellulite grades either between baseline and after the last treatment [δ -1] or between baseline and at follow-up [δ -2], respectively; the higher δ -1 and δ -2, the better the treatment success).

Notes: Each dot represents an individual patient; overlapping data are indicated. The Spearman's nonparametric rank correlation coefficients (r) and the corresponding P -values are provided in red on top of each panel.

Abbreviation: BMI, body mass index.

However, there was no statistically significant correlation between δ -1 and δ -2 ($P=0.105$).

Discussion

The results of the present study are generally in line with earlier reports of successful treatment of cellulite with RSWT in the literature.^{15,17,20–22} RSWT can improve the clinical picture by one cellulite grade on average. However, to the authors' knowledge, the present study is the first to demonstrate that the individual clinical outcome of RSWT for cellulite cannot be predicted by the patient's individual cellulite grade at

baseline, BMI, weight, height, or age. We hypothesize that the same applies to ESWT for cellulite.

In our clinical experience, the patient's perception of their individual cellulite grade and consequently their satisfaction with the result of treatment for cellulite varies widely from one patient to another and is truly subjective. Normally, patients with low cellulite grades are more demanding and therefore more difficult to manage in their expectations, even if there is an objectively confirmed clinical improvement. This was confirmed in our analysis because patient satisfaction, the most important end point of any treatment for cellulite, did not correlate with δ -1 or δ -2. There were patients with δ -1=1 (ie, improvement by one cellulite grade) who were very satisfied, whereas other patients with δ -1=1 were not satisfied at all (Figure 5E). For the clinical setting, this observation underlines the role of the therapist, who must correctly evaluate the suitability of the candidate for a cellulite treatment and must manage the patient's expectations accordingly. For studies evaluating existing or new cellulite treatments, this observation underscores the crucial importance of applying objective analytical methods, such as contact thermography and standardized photographic documentation (in full muscular contraction), because satisfaction scores may suffer from variations in their consistency. Note that individual patient satisfaction scores were either not reported or not correlated with individual objective outcome measures in the studies of ESWT/RSWT for cellulite published to date.^{15–23} Standardized yet easy clinical analysis of the severity of cellulite should include easy, effective, and reproducible measurement tools. In our opinion, clinical evaluation serves for classification of the cellulite grade, double contrast photography as applied in the present study provides a visual contour analysis, and contact thermography measures the superficial blood perfusion of the skin. Recoil and elasticity measurements, as applied in some studies of ESWT/RSWT for cellulite,^{15,20,21} are helpful in small treatment areas but may considerably vary over the length of a thigh depending on changing quality and thickness of the skin in the respective parts.

In recent years, ESWT/RSWT has become the best studied therapy option for cellulite (Table 1). This is most likely due to the fact that ESWT/RSWT is noninvasive, does not require administration of drugs, and can be easily accomplished within a few minutes per treatment session. It is justified to consider ESWT (ie, focused shock waves) and RSWT (ie, radial shock waves) as very similar therapeutic options for cellulite. This is due to the fact that the energy signatures of ESWT and RSWT share fundamental physical characteristics, such as high peak pressure, a fast initial rise in pressure, a low tensile amplitude

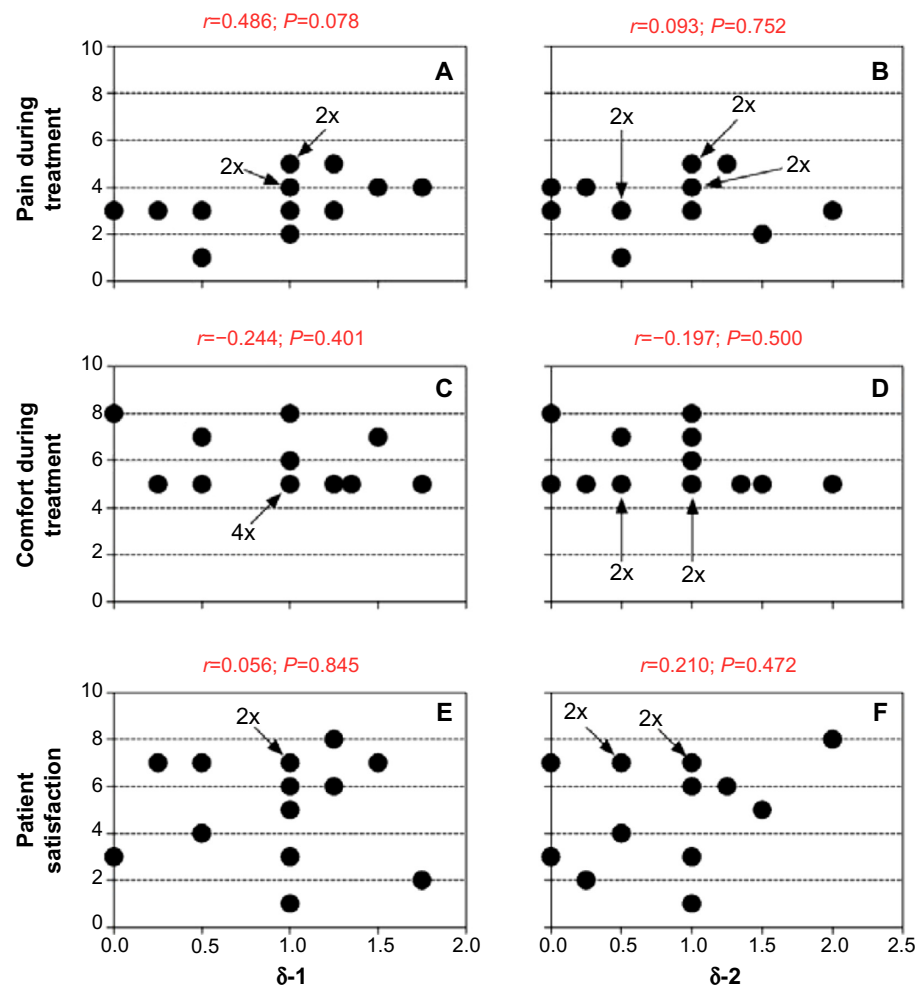


Figure 5 Clinical outcome of radial extracorporeal shock wave therapy for cellulite as a function of the patients' pain during the treatment (**A** and **B**), the patients' feeling of comfort during treatment (**C** and **D**), and the patients' satisfaction with treatment (**E** and **F**) (calculated as individual difference in cellulite grades either between baseline and after the last treatment [$\delta-1$] or between baseline and at follow-up [$\delta-2$], respectively; the higher $\delta-1$ and $\delta-2$, the better the treatment success).

Notes: Each dot represents an individual patient; overlapping data are indicated. Pain was assessed using a visual analog scale ranging from 0 (no pain) to 10 (maximum pain). The feeling of comfort was assessed using a scale ranging from 0 (maximum dissatisfaction) to 10 (maximum satisfaction), and patients' satisfaction using a scale ranging from 0 (maximum dissatisfaction) to 10 (maximum satisfaction). The Spearman's nonparametric rank correlation coefficients (r) and the corresponding P -values are provided in red on top of each panel.

that can generate cavitation, and a short life cycle. Some authors have offered the following physical definition of “real” shock waves:^{26,27} a high positive peak pressure, sometimes more than 100 mPa, but more often approximately 50–80 mPa; a fast initial rise in pressure during a period of less than 10 nanoseconds; a low tensile amplitude (up to 10 mPa); a short life cycle of approximately 10 μ seconds; and a broad frequency spectrum, typically in the range of 16–20 MHz. It is well known that radial shock waves do not fulfill the characteristics set out by this physical definition of real shock waves (see also Figure 1).^{29,40} Some ESWT devices generate pressure waves that fulfill the characteristics set out by this physical definition of real shock waves, whereas others do not.^{29,40,41} Among those ESWT devices that do not produce real shock waves is the electromagnetic Duolith® device (Storz Medical)⁴¹ that has recently been introduced

into ESWT for cellulite.¹⁶ Another device that was used in several studies for treating cellulite is the D-Actor® 200 (Storz Medical).^{15,17,22} The pressure waves generated by this device are termed “low-energy radial shockwaves” in the literature.⁴² In contrast, Russe-Wilflingseder et al¹⁷ described the D-Actor 200 device as a “vibrating massage system”. Regardless of these different descriptions in the literature, the D-Actor 200 device is making use of the same construction principle as the Swiss DolorClast and accelerates a projectile by means of compressed air. For this reason, the D-Actor 200 device generates pressure waves that are very similar to the pressure waves generated by the Swiss DolorClast device, including the possibility of generating cavitation (Császár et al, submitted for publication).

Because the studies on ESWT/RSWT for cellulite considerably vary with respect to the level of evidence, shock

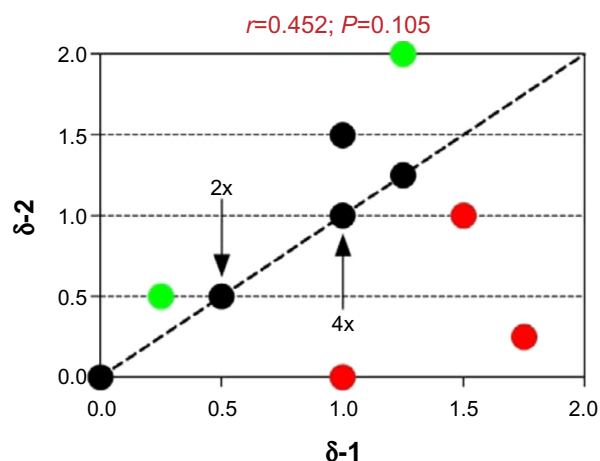


Figure 6 Relationship between the individual difference in cellulite grades between baseline and after the last treatment ($\delta-1$) and between baseline and at follow-up ($\delta-2$) after radial extracorporeal shock wave therapy for cellulite (the higher $\delta-1$ and $\delta-2$, the better the treatment success).

Notes: Each dot represents an individual patient; overlapping data are indicated. Red, black, and green dots/asterisks indicate patients whose cellulite grade worsened, remained unchanged, or improved, respectively, during the follow-up period compared with the situation after the last treatment. The Spearman's nonparametric rank correlation coefficient (r) and the corresponding P -value are provided in red on top of the panel.

wave device used, and treatment protocol, they are discussed separately, as follows.

In an early pilot study, Braun et al¹⁸ treated 20 patients with “severe cellulite measured with a pinch test”¹⁸ using the electromagnetic DermaSelect® shock wave device (Storz Medical). The average age of the patients was 37.25 (range 19–56) years and their mean BMI was 29.18 (range 20–41.6). Each patient received six treatment sessions with 2,400 impulses per session on the left leg (the time interval between treatments, size of the treatment area, and energy flux density of the shock waves were not provided). According to the authors' subjective impressions of the treated leg and photographic analyses, a significant improvement in skin surface was shown for more than 70 percent of the patients. However, treatment success was not expressed according to changes in cellulite grades.

Angehrn et al¹⁹ treated 21 female patients with cellulite (grade 1, $n=5$; grade 2, $n=6$; grade 3, $n=10$) using defocused shock waves generated with the electrohydraulic ActiVitor-Derma® device (SwiTech Medical, Kreuzlingen, Germany). Treatment consisted of 12 sessions at intervals of 3–4 days, treatment of the skin of the lateral left and right thigh with 4,000 impulses per thigh per treatment session, homogeneously distributed over an area of 160 cm² per side with an energy flux density of 0.018 mJ/mm². BMI was 20–24 in ten patients, 25–29 in nine patients, 30–34 in one patient, and 35–40 in one patient. End points were subjective opinion of improvement and collagenometry measurements

performed with the high-resolution ultrasound system, Collagenoson® (Minhorst, Meudt, Germany). At the end of the treatment period, two patients showed clear worsening of collagenometry results compared with baseline, five patients showed some worsening, two patients showed no change, eight patients showed improvement, and four patients showed clear improvement compared with baseline. There was no correlation between the outcome of collagenometry and individual cellulite grade. Seventeen of the 21 patients (81%) subjectively assessed their outcome as improved. Seven patients evaluated the treatment as not suitable (pain during treatment), six patients assessed it as suitable (no pain during treatment), and eight patients were indifferent. The authors concluded that their results provided evidence that low-energy defocused ESWT caused remodeling of the collagen within the dermis of the tested region.

Christ et al^{20,21} treated a total of 59 female patients with cellulite grade 2 or 3 with planar or radial shock waves generated with the electromagnetic Cellactor® SC1 device (Storz Medical). Group 1 ($n=15$, mean age 44.6 years, mean BMI 24.4) was treated with planar shock waves generated with the C-Actor hand piece of the Cellactor SC1 device (six treatment sessions at intervals of 3–4 days, treatment of lateral and medial thigh areas as well as the buttocks, total of 3,200 impulses per treatment session with an energy flux density of 0.25 mJ/mm² homogeneously distributed over a total area of 20×30 cm). Group 2 ($n=44$, mean age 45.5 years, mean BMI 25.3) was treated identically but with eight treatment sessions. End points were the elasticity of the skin measured with the DermaLab® device (Cortex Technology, Hadsund, Denmark) and the structure of the connective tissue in the dermis evaluated with the DermaScan® ultrasound device (Cortex Technology) before and after treatment. The mean skin elasticity in group 1 patients was improved by 46% after treatment and by 78% at 3-month follow-up compared with baseline. In group 2, the mean improvement in skin elasticity was 72% after treatment, 95% at 3-month follow-up, and 105% at 6 months after baseline. The structure of the connective tissue also improved between baseline and the 6-month follow-up. Statistical analysis was not performed to evaluate the impact of BMI on the results in this study.

Kuhn et al²³ presented a case report concerning a 50-year-old woman with grade 3 cellulite on her left thigh treated with the ActiVitor-Derma device (four therapy sessions, 800 impulses per session, energy flux density 0.115 mJ/mm²). Based on high frequency, high resolution ultrasound measurements, contact thermography, and histopathologic

biopsies, the authors reported “some improvement in the epidermis and the extracellular matrix of the dermis”.²³

Sattler et al¹⁵ compared three treatments for cellulite. Group 1 (eleven patients, mean age 40 years, mean BMI 27) was treated with radial shock waves generated with the ballistic D-Actor 200 device (a mean of 6.2 treatment sessions, an average of 1,909 impulses per treatment session; device operated at 2.4–3.0 bar and a frequency of 15 Hz). Group 2 (eleven patients, of whom nine were included in the analysis, mean age 34 years, mean BMI 23) was treated with planar shock waves generated with the C-Actor hand piece of the electromagnetic Cellactor SC1 (a mean of 6.1 treatment sessions, 1,000 impulses per treatment session with an energy flux density of 0.35 mJ/mm²). Group 3 (eight patients, of whom seven were included in the analysis, mean age 40 years, mean BMI 23) was treated with a combined radial and planar shock wave protocol (a mean of 6.4 treatment sessions; 2,350 radial pulses on average followed by an average of 1,925 planar impulses per treatment session; radial impulses generated by operating the control unit at 2.6–3.0 bar; planar impulses with an energy flux density of 0.35 mJ/mm²). Treatment was focused either on the buttock and dorsal thigh area or on the ventral thigh area, depending on the individual clinical picture. End points were visual impression of the skin (analyzed on photographs), patient satisfaction, and skin elasticity (measured with the DermaLab device) 3 months after the last treatment session compared with baseline. Patients in group 1 had the best result. Analysis of the photographs showed an optimum treatment result for five (46%) patients, a satisfactory treatment result for three (27%) patients, and a not significant treatment result for three (27%) patients (specific criteria for optimum, satisfactory, and not significant were not specified). For patients in groups 2 and 3, the corresponding data were: an optimum treatment result in 1/9 (11%) and 2/7 (29%), respectively; a satisfactory result in 5/9 (56%) and 4/7 (57%), respectively; and a not significant result in 3/9 (33%) and 1/7 (14%), respectively. A statistical analysis was not performed. It is of note that the authors did not recognize any change in skin elasticity as a result of shock wave treatment (mean data for group 1, 11.6 mPa at baseline, 10.0 mPa after treatment, and 10.1 mPa at 3-month follow-up; mean data for group 2, 12.1 mPa at baseline, 10.8 mPa after treatment, and 12.1 mPa at 3-month follow-up; mean data for group 3, 10.3 mPa at baseline, 10.4 after treatment, and 10.9 at 3-month follow-up). The authors discussed the limitations of their study,¹⁵ ie, small numbers of patients, and differences in mean age and mean BMI between the groups, but concluded that treatment for

cellulite with radial shock waves might be the best choice (as also performed in the present study).

Adatto et al²² treated 25 women of mean age 42.6 (range 27–63) years with a mean BMI of 24 (range 17–31) on one leg each with the ballistic D-Actor 200 device (a mean of six treatment sessions within 4 weeks with an average of 3,000 impulses per treatment session; device operated at 2.6–3.6 bar and with a frequency of 15 Hz). The authors compared, for each patient, the treated leg with the untreated leg 1 week and 12 weeks after the last treatment. The evaluation was performed with measurements of skin elasticity using the DermaLab device. Furthermore, three-dimensional images of the skin structure were recorded using the DermaTOP® system (Eotech, Paris, France). Adatto et al²² found that skin elasticity, roughness elevation, and skin depression improved in a statistically significant manner on the treated legs compared with the untreated legs. They concluded that the D-Actor 200 device can be used effectively to treat cellulite without any side effects.

In a double-blind, randomized controlled trial, Knobloch et al¹⁶ randomly assigned 53 women to either focused shock waves using the electromagnetic Duolith device (n=25; mean age 41.4 years, mean BMI 24.2±3.2 kg/m²; six sessions of ESWT every 1–2 weeks, with 2,000 impulses at 4 Hz, and an energy flux density of 0.35 mJ/mm²) or sham treatment (n=28; mean age 45.0 years, mean BMI 25.3±4.5 kg/m²; six treatment sessions every 1–2 weeks, with 2,000 impulses and an energy flux density of 0.01 mJ/mm²). In addition to ESWT or sham-ESWT, all patients underwent specific gluteal strength exercise training. Among other measurements, the primary end point was score on the photonumeric Cellulite Severity Scale (CSS) determined by two blinded, independent assessors. ESWT reduced the mean CSS from 10.9±3.8 at baseline to 8.3±4.1 at 12 weeks after the last treatment, whereas sham-ESWT did not (CSS at baseline 10.0±3.8; CSS 12 weeks after the last treatment 10.1±3.8). The difference between the two groups was statistically significant ($P=0.001$). The authors concluded that the combination of ESWT and gluteal strength training was superior to gluteal strength training and sham-ESWT in moderate to severe cellulite in terms of CSS in a 3-month perspective. It remains unknown why females with documented cellulite grade 0 according to Nürnberger and Müller,⁷ ie, no cellulite, were eligible for and enrolled in this study. Furthermore, the authors described that they performed an intention-to-treat analysis because seven sham-treated women were lost to follow-up. However, they did not describe which of the various available methods for handling missing data in clinical trials they applied.⁴³

Russe-Wilflingseder et al¹⁷ randomly assigned 16 women with cellulite (mean age 42.7±7.4 years, mean BMI 22.5±1.85 kg/m²) to either radial shock waves using the D-Actor 200 device (n=11; eight treatments once a week; 1,000 impulses at 2–3 bar air pressure applied using a DI15 deep impact transmitter (Storz Medical, Tägerwilten, Switzerland); 2,500 impulses at 3–5 bar applied by the D-Actor transmitter D20-S; frequency of shock waves not provided) or sham treatment (n=5; treatment protocol identical to the RSWT protocol but using a placebo hand piece that did not emit shock waves). Clinical outcome was assessed by a patient satisfaction questionnaire, weight control, measurements of thigh circumference, visual appearance of the skin in standardized photographs, and an analysis of images taken with a specially designed three-dimensional imaging system. Patients were investigated at baseline, before the last treatment, and at 1 and 3 months after the last treatment. By combining the results of four efficacy criteria at the two follow-up visits, the authors found a statistically significant improvement in the skin of women treated with radial shock waves but not for those treated with placebo. The authors concluded that radial shock wave treatment is safe and efficient for patients with cellulite. This is in line with the results of the present study.

Finally, a study by Ferraro et al⁴⁴ warrants mention. The authors treated 37 women and 13 men with the Proshock Ice® device (Promoitalia, Milan, Italy) in five different areas: abdomen (five women, nine men), ankles (three women, one man), arms (five women, three men), buttocks (six women), and thighs (18 women). The authors described the Proshock Ice device as a combination of a controlled cooling system (“freezing probe”) and a shock wave generator (“shock probe”) with “pressure variable from 50 to 500 bar, and with impulses that have a duration of 8 mseconds”.⁴⁴ Unfortunately, it remains unclear what this actually means, given that radial shock wave devices are usually operated with an air pressure of 1–5 bar, have a maximum pressure of 100 bar (10 mPa), and a duration of approximately 20 μseconds.^{29,40} Ferraro et al⁴⁴ applied tissue-specific (fat edematous cellulite, fibrous cellulite) treatments (freezing probe, shock probe) for 20–60 minutes every 15 days for 8 weeks (an average of 3.73 treatment sessions per patient). In addition to evaluations of each patient’s individual subjective impression of the effect and objective clinical data such as skin-fold thickness and hepatic markers, the authors investigated skin biopsies of treated and untreated tissue to detect apoptosis, laminin, and collagen. The results showed statistically significant reductions in circumference of the treated body regions (abdomen, on average 6.86 cm; ankles, on average 2.25 cm; arms, on average

2.75 cm; buttocks, on average 5 cm; thighs, on average 5.78 cm) with no change in body weight. Microscopic investigation of the skin biopsies showed signs of dying fat cells (adipocytes) and an inflammatory process in the treated tissue. Ferraro et al⁴⁴ discussed their method as a “noninvasive alternative to conventional liposuction for patients who require only small or moderate removal of adipose tissue and cellulite or who are not suitable candidates for surgical approaches to body contouring”.⁴⁴

Conclusion

Several studies have demonstrated that cellulite can be treated effectively and safely with ESWT and RSWT. The main conclusion of the present study is that the individual clinical outcome of treatment with shock waves for cellulite cannot be predicted by the patient’s cellulite grade at baseline, age, BMI, weight, or height.

Several questions regarding ESWT/RSWT for cellulite remain open and should be addressed in future studies. For instance, the striking difference between the results reported by Christ et al^{20,21} and those reported by Sattler et al¹⁵, regarding treatment-related changes in skin elasticity, require an independent reanalysis. The higher efficacy of RSWT relative to ESWT in treating cellulite¹⁵ should also be investigated. Presumably, the most important task will be to unravel the molecular and cellular mechanisms of shock waves in skin and fat tissue. In this regard, it is of note that several potential mechanisms have been proposed in the literature, comprising improved microcirculation, apoptosis of fat tissue, and improved lymph circulation (Table 3). Many of these mechanisms may be secondary to the activation of C nerve fibers in the skin by shock waves

Table 3 Various potential molecular and cellular mechanisms of action of shock waves on skin/fat tissue that have been proposed in the literature

Proposed mechanisms	Reference
Stimulation of blood and lymph circulation	Braun et al ¹⁸
Increased membrane permeability	Braun et al ¹⁸
Stimulation of the exchange of blood lipids	Braun et al ¹⁸
Stimulation of metabolism	Angehrn et al ¹⁹
Reduced oxidative stress	Christ et al ²¹
Increased antioxidants (including ascorbic acid)	Siems et al ⁷⁶
Induction of neocollagenogenesis and neoelastinogenesis	Kuhn et al ²³
Increased angiogenesis	Ferraro et al ⁴⁴
Expression of vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen	Angehrn et al ¹⁹
Apoptosis of fat cells triggered by inflammation	Ferraro et al ⁴⁴
Activation of C nerve fibers in the skin and release of substance P	Present study

and the release of substance P.^{45,46} Substance P is one of the body's neurotransmitters for pain and heat,⁴⁷ and is responsible for causing slight discomfort during and after shock wave treatment.²⁹ Capsaicin is a neurotoxin that can deplete sensory nerves of their content of substance P.⁴⁸ A recent study showed an age-related decrease in thrombomodulin-positive cells and vascularity in the skin, and demonstrated that topical application of capsaicin to the skin may boost factor XIIIa-positive dendrocytes, thrombomodulin-positive cells, and the blood vessel network of the skin.⁴⁹

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Author contributions

K-US, MCK, NBMC and CS provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in either drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

K-US has served as a paid consultant for and received benefits from Electro Medical Systems (Nyon, Switzerland), the manufacturer and distributor of the Swiss DolorClast radial shock wave device. MCK and NBMC report no conflicts of interest. CS serves as a paid consultant for and receives benefits from Electro Medical Systems.

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