



Review

Extracorporeal shock wave therapy (ESWT) for the treatment of cellulite – A current metaanalysis



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HIGHLIGHTS

- Both, focused & radial ESWT devices are effective in treating cellulite.
- Typically, one or two weekly sessions and 6–8 sessions overall were studied.
- Outcome parameters mainly focused on photographs, circumference measurements and ultrasound.
- Reporting quality showed substantial heterogeneity from 22 to 82 points with a mean of 57 points.

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ABSTRACT

Background: The aim of this metaanalysis was to investigate the effectiveness of extracorporeal shock wave therapy (ESWT) in cellulite.

Methods: Electronic databases (such as Ovid MEDLINE, Scopus and Ovid) as well as reference lists of the available studies were evaluated in June 2015 by two expert examiners. Assessment of each study's methodological quality was performed with the help of the published quality index tool by Downs and Black.

Results: This metanalysis included a total of eleven clinical trials on the effects of ESWT on cellulite with a total of 297 included females. Among the eleven clinical trials five randomized controlled trials on ESWT in cellulite with a total number of 123 females have been published so far. Both, focused as well as radial ESWT devices have been found effective in treating cellulite so far. Typically, one or two sessions per week and six to eight sessions overall were studied in the published clinical trials. Overall, outcome parameters mainly focused on digital standardized photographs, circumference measurements and specific ultrasound examinations. Reporting quality showed substantial heterogeneity from 22 to 82 points with a mean of 57 points.

Discussion: This metanalysis identified eleven published clinical studies on ESWT in cellulite with five randomized-controlled trials among them. There is growing evidence that both, radial as well as focused ESWT and the combination of both are able to improve the degree of cellulite. Typically, six to eight treatments once or twice a week have been studied. Long-term follow-up data beyond one year are lacking as well as details on potential combination therapies in cellulite such as with low level laser therapy (LLLT), cryolipolysis and others.

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1. Background

Cellulite is a widespread problem involving females' buttocks

and thighs based on the female specific anatomy. Given the higher number of fat cells stored in female fatty tissue in contrast to males, the gender specific dimorphism with subdermal septae orientated orthogonally towards the skin, and the ageng process of connective tissue lead to an imbalance between lipogenesis and lipolysis with subsequent large fat cells bulging the skin [1].

Recently, a case-control study in 15 lean women suffering from cellulite and age- and BMI-match controls identified significantly

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reduced Adiponectin expression using reverse transcription polymerase chain reaction (RT-PCR) among the cellulite-affected patients [2].

Non-randomized clinical data suggest that extracorporeal shock wave therapy (ESWT) is beneficial in terms of improved skin elasticity and revitalizing dermis in cellulite [3,4].

Beyond the aforementioned trials with small sample size and large confidence intervals, we do not have any high-level evidence to support the use of ESWT for non-invasive body contouring in cellulite. Therefore, we sought to evaluate the current published evidence on ESWT in cellulite based on a systematic metaanalysis. We seek to analyse the type of ESWT (radial and/or focussed ESWT), the device types, energy flux densities and pressures, frequencies, number of sessions, outcome parameters used and the length of the follow-up.

2. Methods

All studies included in this review were obtained after an electronic search. In June 2015 the database search was performed in Ovid Medline (www.pubmed.gov) and Scopus and Ovid in the English published studies using the following terms:

- 1. Cellulite and either
 - 2. Extracorporeal shock wave therapy
 - 3. ESWT
 - 4. Shock wave
 - 5. Acoustic wave
 - 6. Treatment
 - 7. Therapy

A hand search followed the electronic assessment. Abstracts were reviewed and analysed accordingly. Study design, inclusion and exclusion criteria, shockwave treatment modalities (device type, energy flux densities, number and timing of treatments) as well as the outcome measures determined were of distinct interest.

2.1. Methodological quality assessment

The quality index tool published by Sara Downs and Black [5] was applied to determine the study quality of the included studies. It is an appropriate tool for both, randomized and non-randomized trials with a high Test-retest and inter-rater reliability. This assessment was done by two independent analysts and the mean value was determined.

3. Results

The electronic assessment using the following combinations retrieved the following results:

- “Cellulite” and “Extracorporeal shock wave therapy” = 4 results.
 - “Cellulite” and “ESWT” = 2 results.
 - “Cellulite” and “shock wave” = 7 results.
 - “Cellulite” and “acoustic wave” = 11 results.
 - “Cellulite” and “treatment” = 220 results.
 - “Cellulite” and “therapy” = 185 results.
- This resulted in a total of 429 electronic results.

After removal of duplicate and redundant publications, a total number of 17 studies were suitable for initial review. 11 studies were extracted for further detailed review and among them, 11 studies were considered appropriate for inclusion in this meta-analysis. A PRISMA flow chart is illustrating this (Fig. 1).

3.1. Trial characteristics

Among the eleven clinical studies included in this metaanalysis, we found 5 randomized-controlled trials, 5 cohort studies and one case report. The findings of the five randomized trials are highlighted in a historical order (Fig. 2) and with detailed study characteristics in Table 1.

3.1.1. Randomized-controlled trials (level 1b evidence)

3.1.1.1. Adatto et al., 2010 [6]. Adatto and coworkers performed a randomized trial with 1:1 allocation and an intra-individual control with 25 females. Six radial ESWT sessions were performed with a Storz D-Actor 200 with 2.6–3.6 bar at 15 Hz and 3.000 impulses on a 10 × 15 cm rectangle on a single leg six times twice a week. Follow-up was at 12 weeks. Changes in the skin structure were evaluated using the DermaTOP System (Eotech, Paris, France). Skin elasticity measurements were performed using the Dermalab Device (Cortex Technology, Hadsund, Denmark). The difference between treated and untreated legs was statistically significant with regard to depressions, elevations, roughness and elasticity after the first follow-up visit.

3.1.1.2. Knobloch K et al., 2013 [7]. Knobloch and coworkers performed a single-center, double-blinded, randomized-controlled trial with a 1:1 allocation. The primary outcome parameter was the photo-numeric Cellulite Severity Scale (CSS) proposed by Doris Hexsel determined by two blinded, independent assessors based on standardized photographs. The intervention group received six sessions of focused ESWT (Storz Duolith, 2.000 impulses, 0.35 mJ/mm², every week) at both gluteal and thigh regions plus specific gluteal strength exercise training with 3 × 15 repetitions per day. The control group (group B) received six sessions of SHAM-ESWT (0.01 mJ/mm², 2.000 impulses) plus specific gluteal strength exercise training. Knobloch found the cellulite severity scale CSS in the intervention group was 10.9 ± 3.8 before focused ESWT and 8.3 ± 4.1 after 12 weeks (P = 0.001, 2.53 improvement, 95% confidence interval (CI) 1.43–3.62). The CSS in the placebo group was 10.0 ± 3.8 before intervention and 10.1 ± 3.8 after 12 weeks (P = 0.876, 95% CI 1.1–0.97). The change of the CSS in group A versus group B was significantly different (P = 0.001, –24.3 effect size, 95% CI –36.5 to –12.1).

3.1.1.3. Russe-Wilflingseder et al., 2013 [8]. Russe-Wilflingseder and coworkers performed a placebo controlled double-blinded, prospectively randomized clinical trial with 17 patients with a 2:1 allocation (11 verum, 5 placebo) for evaluation of cellulite treatment. The patients were treated once a week for 7 weeks, a total of 8 treatments with the radial ESWT Storz D-ACTOR[®] 200. Data were collected at baseline, before 8th treatment, at 1 month (follow-up 1) and at 3 months (follow-up 2) after the last treatment with a patients' questionnaire, weight control, measurement of circumference and standardized photography. Treatment progress was further documented using a specially designed 3D imaging system (SkinSCAN(3D), 3D-Shape GmbH) providing an objective measure of cellulite (primary efficacy criteria). Patient's questionnaire in the verum group revealed an improvement in number and depth of dimples, skin firmness and texture, in shape and in reduction of circumference. The overall result (of skin waviness, Sq and Sz, surface and volume of depressions and elevations, Vvv and Vmp) at two follow-up visits indicates a more than medium sized superiority (MW = 0.6706) and is statistically significant (pWeil-Lachin = 0.0106).

3.1.1.4. Schlaudraff et al., 2014 [9]. Schlaudraff and coworkers included 14 females with cellulite in a prospective, single-center,

PRISMA 2009 Flow Diagram

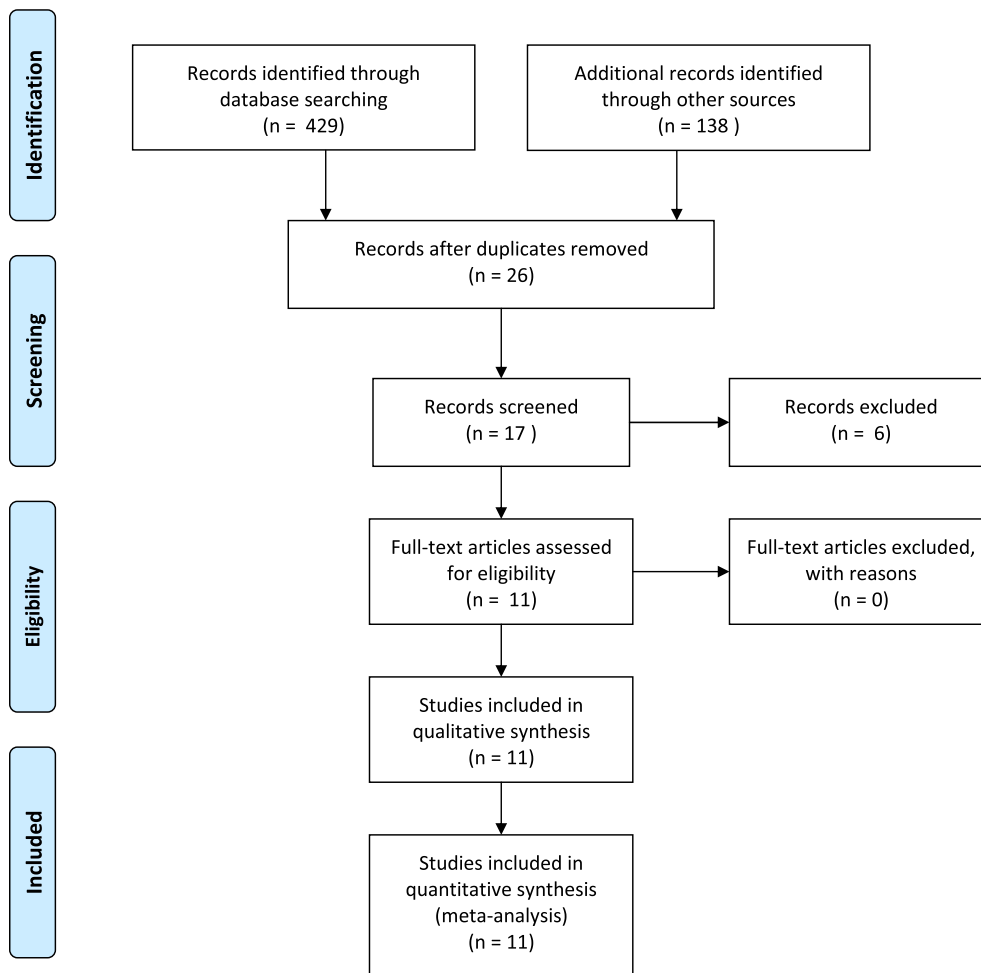


Fig. 1. PRISMA chart on the included and excluded ESWT studies in this metaanalysis.

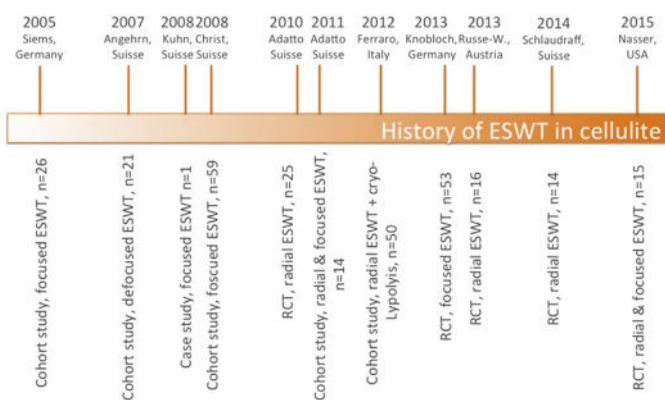


Fig. 2. Timeline of the published evidence on radial and/or focused extracorporeal shock wave therapy (ESWT).

randomized, open-label Phase II study using a radial ESWT device. All patients were treated with radial extracorporeal shock waves using the Swiss DolorClast[®] device (Electro Medical Systems, S.A., Nyon, Switzerland) with an intra-individual control. Patients were treated unilaterally only with 2 weekly treatments for 4 weeks on a randomly selected side (left or right), totalling 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 7500 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. The mean cellulite grade at baseline was 2.5 ± 0.09 and mean BMI was 22.8 ± 1.17 . The mean cellulite grade improved from 2.5 ± 0.09 at baseline to 1.57 ± 0.18 after the last treatment (ie, mean $\delta-1$ was 0.93 cellulite grades) and 1.68 ± 0.16 at follow-up (ie, mean $\delta-2$ 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 $\delta-1$ and $\delta-2$ and cellulite grade at baseline, BMI, weight, height, or age.

3.1.1.5. Nassar et al., 2015 [10]. Nassar and coworkers performed a randomized controlled trial with a 1:1 allocation with an intra-individual control (single leg treatment only) using a combined radial and focused ESWT approach. Focused ESWT was performed with a Storz SC1 device with 0.56–1.24 mJ/mm² energy flux densities and 1,500 impulses per leg. This was followed by radial ESWT on the same leg with 2.6–5 bar, 16 Hz and 3,000 impulses in eight

Table 1
All included clinical studies on the effects of extracorporeal shock wave therapy (ESWT) on cellulite with details on study design, number of participants, type, device and treatment parameters, number of treatments, follow-up and main results of the trials.

Author	Year	Study design	Level of evidence	Number of patients	Type of ESWT	Device type	Energy flux densities	Pressure	Number of sessions	Follow-up	Outcome measures
Siems et al.	2005	Cohort study	3	26 (intra-individual control, one treated leg)	Focused ESWT	DermaSelect, Storz Medical	0.16 mJ/mm ² , 1000 impulses	–	3–6 sessions	2 weeks	<ul style="list-style-type: none"> Mitigation of oxidative stress
Angehrn	2007	Cohort study	3	21	Low-energy defocused ESWT	ActiVitor-Derma	0.018 mJ/mm ² , 40.000 shots	–	12 (twice a week)	8 weeks	<ul style="list-style-type: none"> Improvement of high resolution ultrasound with collagen remodelling
Kuhn	2008	Case study	4	1 (intra-individual control, one treated leg)	Focused ESWT	ActiVitor-Derma electrohydraulic device, SwiTechMedical	0.115 mJ/mm ² , 4 Hz, 800 impulses on 2 × 2 cm ² sample	–	4	unclear	<ul style="list-style-type: none"> Epidermal improvement, neocollagenogenesis
Christ	2008	Cohort study	3	59	Planar ESWT	Storz CellActor SC1	0.25 mJ/mm ² , 3200 impulses per session	–	6 (n = 15) or 8 (n = 44) sessions (twice a week)	3 & 6 months	<ul style="list-style-type: none"> Skin elasticity improvement 105% at 6 months f/u
Adatto	2010	RCT, 1:1 allocation	1b	25 (intra-individual control, one treated leg)	Radial ESWT	Storz D-Actor 200	–	2.6–3.6 bar, 15 Hz, 3000 impulses on 10 × 15 cm rectangle	6 twice a week	12 weeks	<ul style="list-style-type: none"> Improvement on skin roughness, number of depressions and elevations
Adatto	2011	Cohort study	3	14	Radial and focused ESWT	Storz CellActor SC1	0.45–1.24mH/mm ² , 1500 impulses	3–4 bar, 3000 impulses	8 (twice a week)	12 weeks	<ul style="list-style-type: none"> Reduction of subcutaneous fat layer
Ferraro	2012	Cohort study	3	50	Radial ESWT + cryo-lipolysis	Proshockice (Promoltalia)	–	50–500 bar, 1–6 Hz combined with a freezing probe for cryolipolysis	4 sessions every 15 days	12 months	<ul style="list-style-type: none"> Mean fat thickness reduction by 3 cm Circumference reduction by 4.5 cm
Knobloch	2013	RCT, 1:1 allocation, 1b gluteal strength training ± focused ESWT	1b	53	Focused ESWT	Storz Duolith	0.35 mJ/mm ² 2000 impulses	–	6 (once a week)	12 weeks	<ul style="list-style-type: none"> Improvement of Cellulite Severity scale CSS from 10.9 to 8.3 by 24% (double-blinded standardized photographic evaluation)
Russe-Wilflingseder	2013	RCT, 2:1 allocation	1b	16 (11 verum, 5 placebo)	Radial ESWT	Storz D-Actor 200	–	2–3 bar, 3.500 impulses	8 (once a week)	12 weeks	<ul style="list-style-type: none"> Subjective patient improvement Photoscore improvement
Schlaudraff	2014	RCT, 1:1 allocation	1b	14 (intra-individual control, one treated leg)	Radial ESWT	EMS Swiss DolorClast	–	3.5–4 bar, 15.000 impulses, 15 Hz	8 (twice a week)	4 weeks	<ul style="list-style-type: none"> Improvement of cellulite grade by 0.93 grades
Nassar	2015	RCT, 1:1 allocation	1b	15 (crossleg study, 1 leg being treated, one served as intraindividual control)	Focused and radial ESWT	Storz SC1	0.56–1.24 mJ/mm ² 1500 impulses, per leg	2.6–5 bar, 16 Hz, 3.000 impulses	8 (twice a week)	12 weeks	<ul style="list-style-type: none"> Crossleg study Reduction of subcutaneous fat layer from 1.4 ± 0.4 cm to 1.0 ± 0.3 cm at 3 months follow-up 1.7 cm circumference reduction

sessions twice a week. Follow-up was done 12 weeks after. Reduction in both thigh circumference and subcutaneous fat layer thickness, measured through ultrasound, was observed.

3.1.2. Cohort studies (level of evidence 3)

3.1.2.1. Siems et al., 2005 [11]. Siems and coworkers were the first who we retrieved to report on the effects of focused ESWT on cellulite. They performed a thorough cohort study with 26 females with lipedema and/or cellulite with a mean age of 45 years. Patients were treated with a Storz Dermaselect device with a special modification for dermatological purposes with 0.16 mJ/mm² energy flux densities and 1000 impulses for 3–6 sessions. A number of antioxidant parameters were assessed. They found an antifibrosclerotic effect of ESWT in their cohort trial.

3.1.2.2. Angehrn et al., 2007 [12]. Angehrn and coworkers performed a cohort study with 21 females undergoing low energy defocused ESWT using an ActiVitor Derma device with 0.018 mJ/mm², 40,000 shots for 12 sessions twice a week. Results provided evidence that low-energy defocused ESWT caused remodelling of the collagen within the dermis of the tested region using high resolution ultrasound, which was associated with collagen remodelling.

3.1.2.3. Christ et al., 2008 [13]. Christ and coworkers published in 2008 a cohort study on 59 females undergoing either six or eight sessions of planar ESWT twice a week. Device was a Storz CellActor SC1 with 0.25 mJ/mm² and 3200 impulses per session. 15 females had six sessions of ESWT, 44 females had eight sessions. Follow-up was done at three and six months. Changes in connective tissue were evaluated using the DermaScan C ultrasound system (Cortex Technology, Hadsund, Denmark). Skin elasticity measurements were performed using the DermaLab system (Cortex Technology). Photographs of treated areas were taken at each therapy session and at follow-up sessions. Skin elasticity values gradually improved over the course of ESWT and revealed a 73% increase at the end of therapy. At 3- and 6-month follow-ups, skin elasticity had even improved by 95% and 105%, respectively.

3.1.2.4. Adatto et al., 2011 [14]. Adatto and coworkers published a study of 14 females who underwent eight focused ESWT sessions using a Storz Cellactor SC1 device. Energy flux densities were 0.45–1.24 mJ/mm² with 1500 impulses per session with the focused ESWT and 3–4 bar and 3000 impulses with the radial ESWT handpiece. Two control patients were included, randomization as highlighted in the title of the paper could not be proven based on a through analysis of the full paper. Measurements with the ultrasound system clearly demonstrate a significant diminution in the subcutaneous fat layer thickness and a reduction of the averaged circumference of thighs.

3.1.2.5. Ferraro et al., 2012 [15]. Ferraro and coworkers published a cohort analysis of 50 females with localized fat and cellulite who were treated in a combination of ESWT and cryolipolysis using a unique probe combining both therapeutic options. The probe called Proshockice from Promoitalia had 50–500 bar, 1–6 Hz, and was incorporated in a freezing probe. Four sessions every two weeks were scheduled. Follow-up was 12 months later. The procedure significantly reduced the circumference in the treated areas, significantly diminishing fat thickness. The mean reduction in fat thickness after treatments was 3.02 cm. Circumference was reduced by a mean of 4.45 cm. Weight was unchanged during the treatment, and no adverse effects were observed.

3.1.3. Case studies

3.1.3.1. Kuhn et al., 2008 [16]. Kuhn and coworkers published a case study on a 50-year-old female with cellulite grade 3, who underwent four focused ESWT using an ActiVitorDerma electrohydraulic device (0.155 mJ/mm², 4 Hz, 800 impulses on a 2 × 2 cm sample, which was later biopsied). Related to a scheduled hip surgery, she was biopsied in the treated as well in an untreated region. Histopathological evaluation found an induction of neocollagen-genesis and neoelastino-genesis in the ESWT treated region (Table 1).

3.2. Quality assessment scores

Based on the quality assessment scores from the quality index tool we found a high range of 22–82 quality points for the eleven studies included in this trial with a mean of 57 points (Table 2). The five included RCTs were assessed with 63/82/82/63/48 quality points, respectively. Based on this assessment, a large heterogeneity in terms of reporting quality was evident in the published ESWT cellulite trials.

4. Discussion

This metanalysis included a total of 11 clinical trials on the effects of extracorporeal shock wave therapy (ESWT) on cellulite with a total of 297 included females to date. Among the 11 clinical trials, 5 randomized controlled trials on ESWT in cellulite with a total number of 123 females have been published so far.

Given the very short history of a decade of using ESWT in cellulite with the first cohort study published by Werner Siems from Germany in 2005, in 2015 we have substantial body of evidence that ESWT is able to improve cellulite in females affected based on 5 randomized-controlled trials published to date.

Naturally, the published clinical trials vary substantially in terms of the devices used, the type of ESWT (radial or focused), the device parameters (energy flux densities, impulses, pressures) as well as the number and timing of session, the follow-up period and the outcome parameters applied in the studied.

Albeit these shortcomings of the published cellulite ESWT trials to date, a number of practical implications may be derived by this thorough metanalysis:

- Both, focused as well as radial ESWT devices have been found effective in treating cellulite so far
- Typically, one or two sessions per week and 6–8 sessions overall were studied in the published clinical trials
- Follow-up typically ranged between three and six months
- Overall, outcome parameters mainly focused on digital standardized photographs, circumference measurements and specific ultrasound examinations
- Only one RCT to date used a non-validated patients' questionnaire to assess the patients' evaluation of the treatment

4.1. Mechanisms

In terms of the “mechanical” perspective one might speculate that the focused extracorporeal shock wave has somewhat disrupted either the fat components or the septae or both, which might led to a smoothening of the afflicted skin. MR imaging has shown that fibrous septa are visualized in 97% of the area with cellulite depressions, which are markedly thickened in cellulite afflicted areas [17]. Shockwave energy might have weakened the fibrous septae and thus, smoothened the afflicted skin.

Reduction of lymphedema is a second potential underlying mechanism. Potentially, a direct effect on the associated

Table 2

Quality index items published by Sara Downs and Black [5] for the published clinical trials focusing on the effect of radial and/or focused extracorporeal shock wave therapy (ESWT) on cellulite.

Quality index items	Siems 2005	Angehrn 2007	Kuhn 2008	Christ 2008	Adatto 2010	Adatto 2011	Ferraro 2012	Knobloch 2013	Russe-Wilfing. 2013	Schlaudraff 2014	Nassar 2015
Reporting											
1. Study hypothesis/aim/objective	1	1	0	1	1	1	0	1	1	1	1
2. Main outcomes	1	1	0	1	1	1	1	1	1	1	1
3. Participants characteristics	1	1	0	1	1	1	1	1	1	1	0
4. Interventions of interest	1	1	1	1	1	1	1	1	1	1	1
5. Distribution of principal confounders	0	0	0	0	0	0	0	0	0	0	0
6. Main findings	1	1	1	1	1	1	1	1	1	1	1
7. Estimates of random variability	0	0	0	1	1	0	0	1	1	0	0
8. Adverse events described	0	1	1	1	1	1	1	0	1	1	1
9. Participants lost to follow-up reported	0	0	1	1	0	1	1	1	1	0	0
10. Actual probability values reported	0	0	0	1	1	1	1	1	1	1	1
External validity											
11. Were subjects asked to participate representative of population of which they were recruited?	0	0	0	0	0	0	0	0	0	0	0
12. Were subjects prepared to participate representative of the entire population from which they were recruited?	0	0	0	0	0	0	0	0	0	0	0
13. Were the staff, places and facilities where the patients were treated, representative of the treatment patients received?	1	1	0	1	1	1	1	1	1	1	1
Internal validity											
14. Was an attempt made to blind study subjects to the intervention they have received?	0	0	0	0	0	0	0	1	1	0	0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0	1	0	0	0	1	1	0	0
16. If any of the results of the study were based on „data dredging“ was this made clear?	1	1	1	1	1	1	1	1	1	1	1
17. Does analysis adjust for length of follow-up or is the time period between intervention and outcome the same?	1	1	0	1	1	1	1	1	1	1	1
18. Were the statistical tests used to assess the main outcomes appropriate?	0	0	0	0	1	1	1	1	1	1	0
19. Was the compliance with the intervention reliable?	1	1	1	1	1	1	1	1	1	1	1
20. Were the main outcome measures used accurate (valid and reliable)?	1	1	0	1	1	1	1	1	1	1	1
Internal validity (selection bias)											
21. Were cases and controls recruited from the same population?	0	0	0	1	1	1	0	1	1	1	1
22. Were cases and controls recruited over the same period of time?	1	0	0	0	1	0	0	1	0	1	1
23. Were study subjects randomised to intervention groups?	0	0	0	0	0	1	0	1	1	1	0
24. Was randomized intervention assignment concealed from participants/researchers until recruitment complete?	0	0	0	0	0	0	0	1	1	0	0
25. Was there adequate adjustment for confounding in the analysis from which the main findings were drawn?	0	0	0	0	0	0	0	0	0	0	0
26. Were losses to follow-up of patients taken into account?	0	0	1	0	0	1	1	1	1	0	0
Power											
27. Did the study have sufficient power to detect a clinically important effect?	0	0	0	1	1	1	1	1	1	1	0
Total Score %	40.7	40.7	22.2	63.0	63.0	66.7	55.6	81.5	81.5	63.0	48.1

All questions were scored with 1 = yes, 0 = unable to determine or no.

lymphedema is a potential consequence of ESWT application in cellulite. A recent Korean prospective clinical trial evaluated the effect of four ESWT sessions (0.056–0.068 mJ/mm², 2000 impulses, Dornier AB2) within 2 weeks in patients suffering from secondary lymphedema [18]. Both, the circumference and the thickness of the skin fold of the affected region were significantly reduced by 37% in line with a pain reduction on the visual analogue scale. In animal experiments ESWT and VEGF-C hydrogel appear to exert a synergistic effect in promoting lymphangiogenesis [19]. In systemic sclerosis ESWT is able to again improve pain and the Rodnan skin score for skin wellness [20].

On the other hand, shockwave therapy might somewhat influence mesenchymal stem cells. There is evolving experimental data suggesting that shockwave therapy activation pathways in adipose derived stem cells (ADSM) [21]. Clinically, diseased skin appears to normalize following shockwave treatment such as in progressive systemic sclerosis with an upregulation of endothelial progenitor cells (EPC) and circulating endothelial cells (CEC).

4.2. Combination therapy

In regard to different techniques to positively influence cellulite, there is evolving clinical data that for example low level laser therapy (LLLT) with 532 nm wave lengths appears to improve cellulite in a double-blind, placebo-controlled randomized trial [22]. 1064 nm Nd:YAG laser appear to improve mild to moderate cellulite also [23]. Radiofrequency is able to reduce cellulite in a randomized trial [24]. A combination of radial ESWT and cryolipolysis has been included in this metaanalysis showing a substantial fat thickness reduction of 3 cm and a circumference reduction by 4.5 cm in a cohort trial from Italy [25]. In the future, one might consider combining ESWT and laser therapy and/or cryolipolysis to further enhance the beneficial effect in cellulite.

4.3. Limitations

Given our metaanalysis, some limitations have to be considered when interpreting our data. First, the heterogeneity of the published clinical trials is tremendous in terms of devices used, device parameters, timing and frequency of sessions as well as in terms of primary and secondary outcome parameters. However, among the eleven clinical trials evaluated in this metaanalysis, as much as five randomized trials on ESWT in cellulite were included with a total number of 123 patients. Three of the five trials were with an intra-individual control, in other words a cross leg study design. Among the five RCTs, three were performed with radial ESWT, on with focused ESWT only and one with a combination of radial and focused ESWT.

Publication bias is a major problem in evidence based medicine [26]. As well as positive outcome studies being preferentially published or followed by full text publication authors are also more likely to publish positive results in English-language journals. This unequal distribution of trials leads to a selection bias in evidence I level studies, like systematic reviews, meta-analysis or health technology assessments followed by a systematic failure of interpretation and in clinical decisions. Publication bias in a systematic review occurs mostly during the selection process and a transparent selection process is necessary to avoid such bias. For systematic reviews/meta-analysis the PRISMA-statement (formerly known as QUOROM) is recommended, as it gives the reader for a better understanding of the selection process. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement published in 2009, which includes a 27-item checklist and flow diagram, was developed principally for systematic reviews and meta-analyses of randomized trials that use

aggregate data, generally extracted from published reports [27]. Our quality assessment revealed a substantial heterogeneity in terms of trial reporting quality from 22 to 82 points based on a validated assessment tool.

5. Conclusions

This metaanalysis identified eleven published clinical studies on ESWT in cellulite with five randomized-controlled trials among them. There is growing evidence that both, radial as well as focused ESWT and the combination of both are able to improve the degree of cellulite both in terms of appearance as well as in terms of ultrasound improvement of the subcutaneous fat. Typically, six to eight treatments once or twice a week have been studied so far. Long-term follow-up data beyond one year is lacking as well as details on potential combination therapies with low level laser, cryolipolysis and others.

Ethical approval

Metaanalysis only.

Funding

None.

Author contribution

KK did the study design, the study assessment, data analysis and writing.

RK did the study assessment, the data analysis and writing.

Competing interests

None.

Guarantor

Karsten Knobloch and Robert Kraemer.

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