

# Caffeine phonophoresis versus shock wave therapy for adult women with cellulite: a randomized controlled trial

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## Background

Cellulite is a widespread problem involving women's buttocks and thighs (85% of postadolescent women). It is characterized by an irregular, dimpled skin surface with thinning of the epidermis/dermis and presence of nodular clusters of fat cells. Caffeine has anticellulite effect owing to its lipolytic activity in fatty cells. Moreover, shock wave therapy treats cellulite through improvement of cell permeability.

## Objective

To compare between the effects of caffeine phonophoresis and shock wave therapy in the treatment of women with cellulite.

## Participants and methods

A total of 41 women with bilateral cellulite grade 2 and 3 at their thighs (ages 30–45 years) were randomly assigned into two groups. The caffeine phonophoresis group received caffeine 5% gel phonophoresis with an intensity of 0.2 W/cm<sup>2</sup> at a rate of 1 min/cm<sup>2</sup>, three times/week. The shock wave group received shock wave therapy for two times/week. The treatments were conducted to a randomly selected side (the contralateral side serving as an untreated control). The cellulite grade and skin fold thickness were measured before and after 4 weeks of intervention.

## Results

There was a significant decrease in the cellulite grade and skin fold thickness of the treated side of both groups ( $P=0.001$ ). There was no significant difference between the pretreatment values of both groups ( $P=0.724$  and  $0.341$ , respectively), and no significant difference between the posttreatment values of cellulite grade and skin fold thickness of both groups ( $P=0.149$  and  $0.268$ , respectively).

## Conclusion

Caffeine phonophoresis and shock wave therapy were equally effective in improving the cellulite grade and skin fold thickness in adult women with cellulite.

## Keywords:

caffeine phonophoresis, cellulite, shock wave therapy, skin fold caliper

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## Introduction

Cellulite is defined as a localized metabolic disorder of subcutaneous tissue that alters the local body shape, leading to an unaesthetic appearance of the skin called 'orange peel' or 'cottage cheese-like' [1,2]. It is important to distinguish between cellulite and cellulitis, which is an inflammation of the adipose tissue. Cellulite affects 80–90% of all women [3]. It is not considered as a pathological condition but as esthetically disturbing dimpling of the skin seen most commonly on the thighs and buttocks [4].

The cause of cellulite is still an issue of controversy. It is considered an endocrine-metabolic microcirculatory disorder that causes interstitial matrix alterations and structural changes in subcutaneous adipose tissue. Cellulite is a physiological phenomenon with the coexistence of a number of factors that trigger or exacerbate it. The outstanding factors include connective tissue architecture, estrogen action, microvascular alterations, and certain genetic and hormonal characteristics [5].

Cellulite represents a condition in which fibrosis arises with the proliferation of fibroblasts around adipose cells in association with progressing peripheral circulatory failure and metabolic failure in normal tissue, thereby leading to progressive enhancement of metabolic failure in adipose tissue and eventually leading to adipose tissue degeneration and advanced fibrosis in the surrounding tissues [6]. A number of different classification systems have been used to categorize cellulite, according to its clinical and histopathologic changes [7].

A variety of treatment options have evolved, ranging from topical retinol to interstitial laser [1,2,8–11]. Caffeine is used as an anticellulite product, because it prevents excessive accumulation of fat in cells and has potent antioxidant properties. It protects the cells

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against the ultraviolet radiation and slows down the process of photoaging of the skin. Moreover, it increases the microcirculation of blood in the skin [12]. The main action of caffeine is to antagonize the adenosine receptors, also inhibiting the phosphodiesterase that degrades cAMP to inactive 5'-AMP, thus stimulating lipolysis and consequently reducing the fat accumulation that occurs in the cellulite, which in turn improves the skin appearance [13]. Furthermore, caffeine-loaded solid lipid nanoparticles are promising carriers for improvement of caffeine efficiency in treatment of cellulite following topical application on the skin of rats [10].

Difficulties are found in the absorption of medications such as caffeine through the skin. So, physical methods such as ultrasound had been used to facilitate its penetration through the skin in a process known as phonophoresis or sonophoresis [14]. Both thermal and mechanical effects of this ultrasound, as well as the chemical alterations of biological tissues caused by it, have been found to accelerate the diffusion of the active ingredients present in such topical medications [15,16].

Extracorporeal shock wave therapy and radial shock wave therapy have been introduced as safe and effective treatment options for cellulite [17–25]. A shock wave is an acoustic pressure wave that is produced in any elastic medium, such as air, water, or even a solid substance [26]. 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 [26]. Shock wave therapy has direct and indirect effects on tissues; the direct effect is the creation energy that being transferred to the targeted tissues, and the indirect effect is the result of the development of cavitation bubbles in the treated tissue. It has been hypothesized that both the direct and indirect effects produce a biological response in the treated tissues [26,27]. The extracorporeal shock wave has somewhat disrupted either the fat components or the septae or both, which smoothen off the afflicted skin [28]. Its second potential underlying mechanism is the reduction of lymphedema [29].

To the authors' knowledge, there is no previous study that compared between effects caffeine and shock wave therapy for cellulite. As caffeine and shock wave therapy have different mechanisms of action, the aim of this study was to compare between the effects of caffeine phonophoresis (caffeine associated with therapeutic ultrasound treatment) and shock wave therapy in the treatment of adult women with cellulite.

## Participants and methods

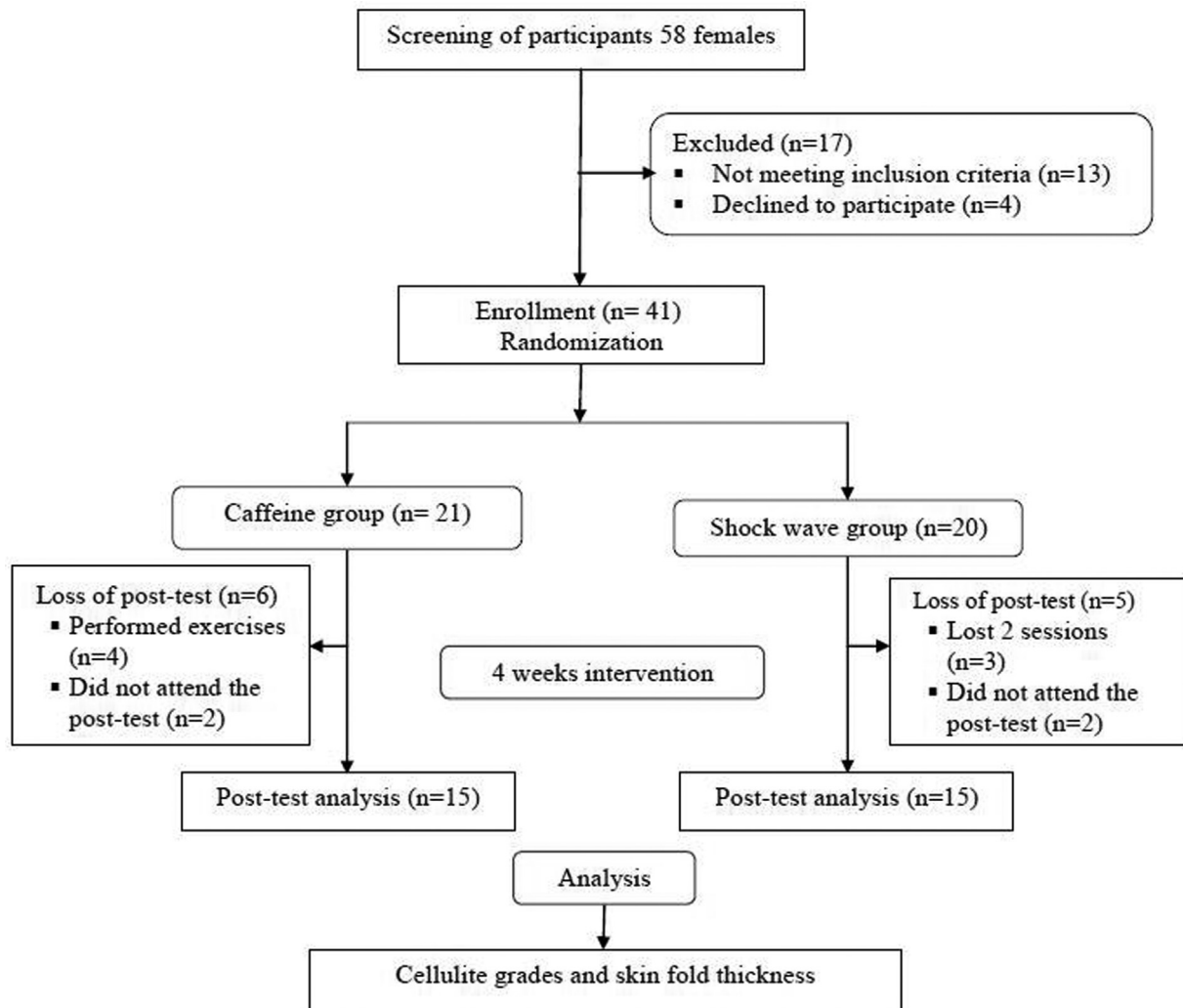
Female patients with bilateral cellulite (grades 2 and 3) at their thighs participated in this single-blind, randomized, controlled trial. A total of 58 female patients were selected from a private clinic and were assessed for eligibility. In total, 17 patients were excluded as they did not meet the inclusion criteria or were unwilling to participate in the study. The remaining 41 patients were randomly assigned into two groups: caffeine group ( $n=21$ ) and shock wave group ( $n=20$ ). A computer-generated table of random numbers was used to simply randomize the participants. Stratification and blocking were avoided during the randomization procedure. After 4-week treatment period, the outcome data were available for 15/20 patients in the caffeine group and 15/19 in the shock wave group. The estimated sample size was calculated using the formula of Pourhoseingholi *et al.* [30] that depends on the prevalence of the cellulite that was 80–90% of post-pubertal women [3], and precision of 0.05%. The recruitment and treatment allocations of the patients are shown in Fig. 1.

All participants were nonpregnant women, free from any pathological condition that might affect the results, received a good explanation of treatment and measurement devices. The exclusion criteria were age under 30 or above 45 years, breastfeeding, diseases of the skin, thrombosis or post-thrombosis syndrome, known malignoma or chemotherapy, anticoagulation therapy, cortisone-therapy, known metabolic disorders (i.e. diabetes mellitus and hyper-cholesterolemia), inflammation within the treatment area, other simultaneous treatment of cellulite, and morbid obesity ( $BMI>40$ ). Their demographic data are illustrated in Table 1. The faculty ethics committee approval (approval no. P. T.REC/012/002146) and the patient's written informed consent were obtained. Moreover, this study was clinically registered by the Pan African Clinical Trial Registry (PACTR201902473450574).

## Treatment procedures

The caffeine phonophoresis group received caffeine 5% gel phonophoresis three times/week. The affected area was cleaned with cotton soaked with alcohol for sterilization. The ultrasound device (ULS-1000, Taiwan) was set and calibrated for a frequency of 3 MHz [31], and an intensity of  $0.2\text{ W/cm}^2$  at a rate of  $1\text{ min/cm}^2$ , with continuous emission [32]. An application time of  $1\text{ min/cm}^2$  was used [33], with the transducer being moved slowly and continuously until the end of the application [16]. The caffeine gel

Figure 1



Study flow chart.

was prepared by adding 5% (w/w) of anhydrous caffeine (Sigma Chemical Company, St Louis, Missouri, USA) to the gel.

The shock wave group received shock wave therapy for two times/week. The shock wave equipment (Storz Medical AG, Tägerwilten, Switzerland) with D-Actor applicator (radial waves) at energy levels of 0.1–8.0, with mean energy level 3.5, was used. This level corresponds to an energy flux density of 0.16 mJ/mm<sup>2</sup>. The treatment region was scanned with 2000 shots using D-actor applicator in both horizontal (1000 shots) and vertical (1000 shots) directions for 15 min [34]. All treatments were delivered to a randomly selected upper posterolateral thigh (using the contralateral side as a non-treated comparative control).

#### Assessment procedures

Cellulite grading scale is a simple grading scale of cellulite by inspection that was adopted by

Nurnburger and Muller [35], and Mirrashed *et al.* [36] as follows: grade 0: smooth surface of the skin while lying down and standing and wrinkles upon pinch-test; grade 1: smooth surface of the skin while lying down and standing, the mattress-phenomenon upon pinch-test, and smooth surface of the skin while lying down; grade 2: mattress-phenomenon spontaneously appears while standing; and grade 3: mattress-phenomenon spontaneously appears while standing and lying down.

Skin fold technique was as follows: pinch the skin on the chosen site with fingers, grasping skin and adipose tissue but not muscle (the muscle will be denser and more firm than skin and adipose tissue). Try it as many times as necessary to get a feel of the tissues. Apply the caliper on centimeter below your fingers and right angle to the skin surface. The measurement is recorded after 2 s with the calipers engaged, then released, and then another measurement is take. The average value of the two measurements was used for

data analysis [37]. The measurement was conducted by three raters who were blinded regarding the group assignment, and the average value was used for further data analysis.

### Statistical analysis

Data were analyzed using a statistical package for the social sciences (IBM Corp., Armonk, New York, USA) version 20.0. An independent *t*-test was used to compare between the demographic variables of the participants. Paired *t*-test was used to compare between pretreatment and posttreatment values of the cellulite grades and skin fold of both groups, and independent *t*-test was used to compare between both groups. The results were expressed as means and SD. The least significant difference test was used to locate the source of differences. The significance level was set at 0.05 for all tests.

## Results

There was no significant difference between both groups regarding age, height, weight, and BMI ( $P=0.253$ , 0.108, 0.073, and 0.383, respectively), as shown in Table 1.

Regarding the cellulite grading, there was no significant difference between the pretreatment values of treated and untreated side (control) of the caffeine and shock wave groups ( $P=0.481$  and 0.401,

respectively). There was no significant difference between the pretreatment and post-treatment values of the untreated side of both groups ( $P=0.082$  and 0.582, respectively). The posttreatment value of the treated side was significantly lower than that of the untreated side ( $P=0.001$ ) for both groups. For the treated side, there was no significant difference between the pretreatment values ( $P=0.724$ ) and post-treatment values ( $P=0.195$ ) of both groups. The post-treatment value of each group was significantly lower than the pretreatment value ( $P=0.001$ ), as shown in Table 2.

For the skin fold thickness; there was no significant difference between the pretreatment values of treated and untreated side (control) of the caffeine and shock wave groups ( $P=0.875$  and 0.635, respectively). There was no significant difference between the pretreatment and post-treatment values of the untreated side of both groups ( $P=0.353$  and 0.238, respectively). For the treated side, there was no significant difference between the pretreatment values ( $P=0.341$ ), and post-treatment values ( $P=0.268$ ) of both groups. The post-treatment value of each group was significantly lower than the pretreatment value ( $P=0.001$ ), as shown in Table 2.

## Discussion

The results of this study showed that there was a significant improvement in cellulite grades of both groups, with the improvement in the shock wave group being higher than that of caffeine group. The improvement of the caffeine group is supported by the findings of Velasco *et al.* [38] who found that the topical application of caffeine combined with sodium benzoate reduces the diameter of the fat cells by ~17% compared with the control. Moreover, after 30 days of cellulite treatment, the caffeine solution was effective in reducing hip circumference in 67.7% of the treated patients [39]. Furthermore, the caffeine-based

**Table 1** Participants' demographic characteristics

Groups	Caffeine group ( <i>n</i> =15)	Shock wave group ( <i>n</i> =15)	<i>P</i> value
Age (years)	34.80±3.93	36.60±4.50	0.253
Height (cm)	163.20±3.84	160.80±4.07	0.108
Weight (kg)	72.80±5.78	69.07±5.19	0.073
BMI (kg/ m <sup>2</sup> )	27.30±1.37	26.73±2.04	0.383

Data are presented as mean±SD. \* $P<0.05$ , significant.

**Table 2** The values of cellulite grading scale and skin fold thickness (mm) of caffeine and shock wave groups

Outcomes	Caffeine group ( <i>n</i> =15)		<i>P</i> value	Shock wave group ( <i>n</i> =15)		<i>P</i> value
	Treated side	Untreated side		Treated side	Untreated side	
Cellulite grading scale						
Before	2.60±0.51	2.47±0.52	0.481	2.53±0.52	2.67±0.49	0.401
After	1.13±0.55	2.67±0.49	0.001*	0.87±0.55	2.60±0.51	0.001*
<i>P</i> value	0.001*	0.082		0.001*	0.582	
Skin fold thickness						
Before	44.67±6.76	45.07±7.05	0.875	46.87±5.62	45.93±5.02	0.635
After	37.27±6.04	44.73±6.61		35.13±4.12	46.27±4.82	0.268
<i>P</i> value	0.001*	0.353		0.001*	0.238	

Data are presented as mean±SD. \* $P<0.05$ , significant.

liposome-encapsulated cream significantly reduced the thickness of the subcutaneous fat over a 2-month period [40].

Although the previously mentioned studies [38–40] investigated the caffeine effect without phonophoresis, the improvement of the caffeine group could be explained by the findings of Boucaud *et al.* [41] who investigated the effect of low-frequency phonophoresis on fentanyl and caffeine permeation. Their results showed that the low-frequency ultrasound increased the transdermal transport of both fentanyl and caffeine across human and hairless rat skin. Moreover, the ultrasound enhances the caffeine permeation through hairless mouse skin, especially the low-frequency, relatively high-intensity ultrasound [42]. So, the use of caffeine phonophoresis was more useful than its application without ultrasound, which agreed with the findings of Pires-de-Campos *et al.* [43] who concluded that ultrasound treatment was efficient in improving the cutaneous permeation of caffeine, as it reduces the hypodermis thickness and number of adipocytes.

It is reported that caffeine is used as an active compound in anticellulite products because it prevents excessive accumulation of fat in cells and inhibits the phosphodiesterase activity which degrades fats during lipolysis. Caffeine has potent antioxidant properties, protects cells against ultraviolet radiation, and slows down the process of photoaging of the skin. Moreover, caffeine increases the microcirculation of blood in the skin which improves the cosmetic appearance [12]. These positive effects could explain the improvement of the caffeine group.

In spite of the short intervention duration of this study, the improvement of the shock wave group concurs with the results of Russe-Wilflingseder and Russe [44] who assessed the efficacy of acoustic wave therapy in women with cellulite. They found that the radial acoustic waves are effective and safe to treat cellulite, without adverse effects. The cellulite improvement progressed up to 3 months. Moreover, there is a reduction in cellulite severity, and thickness of the subcutaneous fat tissue, and improved quality of life after 12 weeks of acoustic wave therapy [45].

Furthermore, the improvement of the shock wave group may be attributed to the physiological effect of extracorporeal acoustic wave therapy, as it stimulates the microcirculation and improves the cell permeability which improve the density and firmness in the network of

collagen/elastic fibers in the dermis and subcutis [23]. Moreover, it is noticed that the extracorporeal shock wave combined with daily gluteal muscle strength is superior to the gluteal muscle strength program alone in women with cellulite after six sessions [46]. The improvement of cellulite grade and skin thickness of the shock wave group could be attributed to that the shock waves have relevant effects on the biological tissue, which leads to restructuring of skin properties and subcutaneous tissue, thus clinically improving the aspects of cellulite and localized fat [28,47]. In addition, there is a growing evidence that the extracorporeal shock wave therapy is able to improve the degree of cellulite [48]. At the same context, the lack of improvement in cellulite grade and skin fold thickness of the contralateral side (comparative control) of both groups could explain the importance of early intervention to prevent the dramatic deterioration of cellulite that was supported by the findings of the previous studies [18,19,24,38,45].

The findings of this study are limited to the recruitment of a small number of cases owing to the restrictive inclusion and exclusion criteria. So, it is recommended to conduct this study on a larger sample for generalization of its results. The participants of the current study were adult women. So, another study conducted on elder females may distinguish between caffeine phonophoresis and shock wave therapy effects in women with cellulite. There were variations in nutritional status, physical activity, and motivation of the participants. Another limitation of this study was the shorter treatment duration (4 weeks). So, the results may vary with longer duration. Finally, a longer follow-up period (3–6 months) is needed to determine the long-term effects of caffeine phonophoresis and shock wave therapy in treating cellulite, as the maintenance of the results is an essential target of anticellulite treatment. Further research is required to examine the effect of other modalities such as low-level laser therapy, and cryolipolysis on cellulite.

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## Conclusion

After 4 weeks of treatment, caffeine phonophoresis and shock wave therapy were equally effective in controlling cellulite grade and skin fold thickness in adult women with cellulite in expression of decreasing its degree and improving the thigh appearance. The treatments offered in the current study are noninvasive treatments for cellulite and no unwanted adverse effects were observed. So, these treatments might be considered by clinicians during designing program for women with cellulite.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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