

# Evaluation of the effects of caffeine in the microcirculation and edema on thighs and buttocks using the orthogonal polarization spectral imaging and clinical parameters

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## Summary

Gynoid lipodystrophy, also known as cellulite, is a common multifactorial entity that affects millions of women around the world. There have been few scientific articles dealing with its physiology and treatment in the past few years, and vascular changes seem to play an important role in its pathophysiology. Skin microvascular alterations can be observed noninvasively with a new method called orthogonal polarization spectral imaging, which was used to evaluate the effectiveness of an anticellulite drug composed mainly of a 7% caffeine solution. Microcirculatory parameters evaluated were functional capillary density (FCD; number of flowing capillaries per unit area), diameter of the dermic papilla (DPD), and capillary diameter (CD). The clinical parameters analyzed were centimetrical measurements of thighs and hips and the influence of tobacco, alcohol, and physical activities on the efficacy of the treatment. After 1 month of treatment, statistical application of chi-squared and Z approximation tests showed, in treated patients, statistically significant reduction of thigh circumferences in more than 80% of the cases and reduction of hip circumference in 67.7%. FCD, DPD, and CD did not change significantly after treatment. Smoking as well as alcohol consumption and regular physical activity were not significantly related to the centimetrical reduction observed in treated thighs and hips.

*Keywords:* cellulite, gynoid lipodystrophy, treatment

## Introduction

Gynoid lipodystrophy, also known as cellulite, is characterized by orange peel, cottage cheese-type, or mattress appearance dimpling of the skin, seen most commonly on thighs and buttocks.<sup>1,2</sup> The word "cellulite" first appeared in the French medical literature more than 150 years ago.

Cellulite can be found in any area of the body that contains subcutaneous adipose tissue. However, certain areas are more susceptible than others, such as upper outer thighs, posterior thighs, and buttocks. Cellulite affects 85% to 98% of post-pubertal females of all races. Although there is no morbidity or mortality associated, it is regarded as an issue of cosmetic concern to millions of women.<sup>3,4</sup>

There are several theories to explain the etiology and physiology of cellulite, all related to structural characteristics of subcutaneous fat lobules and connective tissue septa, vascular changes, and inflammatory factors. In this article, the authors employ the concept originally proposed by Merlen<sup>5</sup> and reformulated by Ciporkin and

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Paschoal,<sup>6</sup> in which predisposing factors (genetic), hormonal factors (hyperestrogenism), and coexisting conditions (inactivity, food intake, associated disease, and iatrogenic factors) act on two functional units of the fatty tissue: the matricial-interstitial and the microcirculatory units where the primary alterations in the physiopathology of cellulite take place.

The matricial-interstitial unit is formed by the extracellular matrix and by cells (especially fibroblasts). The extracellular matrix includes fibrous tissue (collagen, reticular, and elastic fibers) and ground substance (basically hyaluronic acid, proteoglycans, and glycoproteins). The fibrous tissue is responsible for resistance and structure. The ground substance allows the diffusion of nutrients, metabolites, and hormones from the circulatory system through the interstitial tissues. The glycosaminoglycans have hydrophylic properties and help to keep the interstitial osmotic pressure. The proteoglycans are important in the production of collagen by fibroblasts and their tridimensional distribution. They help to increase collagen storage and to rebuild the extracellular matrix.<sup>5,7</sup>

Fibroblast alterations, mainly caused by estrogen, create structural modifications in the glycosaminoglycans of the dermis and in the perivascular connective tissue followed by hyperpolymerization that increases their hydrophilicity and consequently the interstitial osmotic pressure. This process causes water retention (edema), increases viscosity of the interstitial matrix, produces cellular changes, and, consequently, compresses vessels, provoking tissue hypoxia.<sup>6,7</sup> The hypoxia leads to an alteration in the aerobic glucose metabolism, generating an exaggerated production of lactic acid. This alteration activates proline hydroxylase (the enzyme that facilitates the conversion of proline to hydroxyproline), producing procollagen and consequently increasing collagen production, resulting in fibrosis of the tissue.

The microcirculatory unit is formed by arterioles, venules, capillaries, and microlymphatics. Merlen<sup>5</sup> has described an alteration of the arteriolar precapillary sphincter in affected areas, raising capillary pressure. Together with elevation of interstitial pressure (by hyperpolymerization of the glycosaminoglycans) and reduction in plasma flow (by vascular compression), this process can cause an increase in capillary and venular permeability leading to ectasia. Ectasia causes edema of the dermis, interadipocyte, and interlobular septae. A reduction in venous tone occurs simultaneously with an increase of the capillary fragility, causing perivascular connective tissue alterations leading to rupture and microhemorrhage.<sup>5-7</sup>

There are several therapies that have been advertised or employed to "treat" cellulite. Despite numerous therapeutic modalities, only a few present strong evidence in

the improvement of cellulite. These include a few drugs that act on fat metabolism and a surgical technique called subcision, done with local anesthesia.<sup>8-11</sup> Most of the studies found use only thigh measurement and photography to assess improvement, both far from accurate and reproducible.

Certain drugs act on fatty and connective tissues and on the microcirculation. They can be used topically, systemically, or transdermally. Drugs that have a lipolytic effect on fatty tissue include methylxanthines, such as caffeine, which act through phosphodiesterase inhibition, stimulating lipolysis and reducing the size of adipocytes.<sup>7,9,10</sup>

Imaging of human microcirculation using reflected light has been limited to vascular beds where the vessels are visible and close to the surface (e.g., nailfold and conjunctiva). Direct observation of vascular beds of other organs in humans has been prohibitive because of toxicity (fluorescent dyes for contrast enhancement), or the size of the instrumentation required to acquire images (transillumination).<sup>12</sup>

Using a similar basic technique described by Slaaf *et al.*, who reported on intravital microscopy technique with two orthogonal polarizers, Groner *et al.*<sup>13</sup> developed a hand-held portable instrument, based on the orthogonal polarization spectral imaging (OPS) technique, allowing easy access to a variety of vascular beds in patients.<sup>9,10</sup> OPS is a noninvasive measurement technique that can allow us to observe and record many microcirculatory parameters that can be analyzed to evaluate the degree of interstitial edema that is important in cellulitis. The most important parameters in this evaluation are functional capillary density (FCD), that increases in proportion to the reduction of interstitial edema, the measurement of the diameter of the dermic papilla (DPD), which decreases when edema of the interstice decreases, and also the measurement of the capillary diameter (CD), which also increases with reduction of edema in the interstice.<sup>9,10</sup>

In OPS imaging, the tissue is illuminated with linearly polarized light, wavelength of 538 nm reflected through a polarizer oriented orthogonally to the plane of the light. Because polarization is preserved in reflection, only photons scattered from relatively deep in tissue contribute to the images. Using OPS devices, with special optics, we can create a virtual light source that penetrates 1 mm inside the tissue. When the light is absorbed by hemoglobin (Hb), an image of the illuminated Hb-carrying structures in negative contrast is created. This patented "virtual backlighting" technology lets us visualize and measure real-time images of the microcirculation without the use of fluorescent dyes or transillumination.<sup>13</sup>

When reflected light is used, it is quite difficult to obtain a good image contrast and detail due to the surface

scattering and the turbidity of the surrounding tissue. In OPS imaging, the phenomenon of cross-polarization mitigates these effects. The method has been validated for quantitative measurements of microcirculatory parameters in an animal model against intravital fluorescence microscopy.<sup>13,14</sup>

## Objective

The aim of the study was to determine, based on microcirculatory parameters and centimetric measurements, the efficacy of a 7% caffeine solution (Elancyl® Chrono-Active) to treat cellulite. The parameters evaluated were changes of perivascular dermic edema and of centimetrical diameter of thighs and hips, in treated vs. nontreated areas.

## Material and methods

One hundred thirty-four women were selected according to the following criteria:

### Inclusion criteria:

- Clinically apparent cellulite (orange peel or mattress appearance dimpling of skin)
- Fitzpatrick phototype I to IV: melanin in excess (patients with dark or tan skin) does not allow the visualization of the microcirculation
- Body mass index between 20 and 24
- No diet during the study period
- Age between 20 and 39

### Exclusion criteria:

- Alteration in physical activity level during the evaluation
- Gain or loss of more than 1.5 kg during the study
- Use of other products on their legs except the one being tested
- Interruption of treatment
- Missed visits during the study period

In this study, after signing an informed consent form, each patient went through three visits. On the first one, the authors made an interview and a complete physical exam, when height, weight, and the larger diameter of the superior part of the thigh were measured followed by the first evaluation using the OPS technique. For this procedure, the authors chose a region on the external face of the thighs. These areas were plotted in a plastic sheet used like a map. It was important to exclude possible alterations in the microcirculation in different areas. The first measurement was made in both legs and was used as a reference point. The OPS imaging probe was applied to eight separated round targeted areas at the edge of the previously marked area, for ~30 s each. The images of the microcirculation were video recorded and stored into VHS format. The working distance of the OPS imaging

probe, which was covered with a disposable sterile plastic cap, was ~3 mm. Sterile mineral oil was applied between the probe and the skin in order to improve the coupling and, consequently, the reliability of the readings. The analysis of the parameters was done using the commercially available CapImage® computer program.<sup>15</sup>

Each patient received a commercially available box of medication for 30 days of treatment. They were told to apply it in just one leg (thigh and hip) in order to keep the other one as control. The solution was applied twice daily (morning and night), and the dose was ~15 mL per leg (thigh).

In the second and third visits, a complete dermatological exam of the treated area was done, and the measurements mentioned above were repeated. The authors also did the second and third evaluations using the OPS device, just like the first one. At the end of the third visit, the patient answered a questionnaire about the smell and dispersibility of the product.

Microcirculatory parameters analyzed were FCD (number of capillaries with flowing red cells per unit area), DPD, and CD.

Clinical parameters evaluated were circumference of upper and lower portions of the thighs, circumference of hips and influence of alcohol ingestion, smoking, and physical exercise on the efficacy of the drug.

The main evaluation criterion was the reduction of the perivascular dermic edema in the treated region, observed through the OPS exam. The secondary evaluation criterion was the measurement of the circumference of the superior third of the thighs. Other ones were control of body weight, local tolerance, and patient's opinion on the cosmetic aspects of the drug.

After 1 month of treatment, chi-squared and Z approximation tests were applied in order to study the statistical significance of the results, which was achieved when  $P < 0.05$ .

## Results

At the end of the study, from the first 134 patients selected, only 99 completed the protocol. Thirty-five patients were excluded based on the criteria mentioned above. The results were the following.

### Microcirculatory parameters

One of the parameters considered in the analysis of the microcirculation was the evaluation of the FCD in the treated area. FCD increases in proportion to the reduction of interstitial edema, making it easier to visualize the capillaries. In the patients studied, the medication did not



**Figure 1** Evaluation of FCD in a cellulite area before treatment; four capillaries are observed and a great amount of interstitial edema. OPS examination ( $\times 100$ ).



**Figure 2** Evaluation of FCD of the same patient after 1-month treatment. Increase of the number of functional capillaries to seven and reduction of the interstitial edema. OPS examination ( $\times 100$ ).

significantly increase FCD in the treated leg when compared with the nontreated one (Figs 1 and 2). Evaluation of FCD in smokers vs. nonsmokers did not show a significant difference either ( $P = 0.560$ ). Evaluation of the effect of regular physical activity on FCD pointed out, however, a  $P = 0.04$  using chi-squared test. The results did not show an association between FCD and history of alcohol ingestion ( $P = 0.958$  also using chi-squared test).

Another study parameter related to the microcirculation was DPD, which decreases when edema of the interstice decreases. Table 1 shows that 40.4% of papilla had their diameters reduced in the sample, against 59.6% that increased or remained unchanged (Figs 1 and 2).

**Table 1** Alteration in DPD in 99 patients treated with a 7% caffeine solution for 30 days (LPM/UERJ: August 2003/April 2004).

	Papilla diameter	
	Count	%
Reduction	40	40.4
Rise	59	59.6

$P = 0.70$ .

The application of Z-test approximation did not detect significant differences between the two groups ( $P = 0.70$ ). Evaluation of DPD in smokers and nonsmokers was also not significant ( $P = 0.170$ ). The evaluation of the effect of regular physical activity on DPD also showed no statistical significance ( $P = 0.489$ ) as well as alcoholic ingestion ( $P = 0.250$ ).

The last evaluated microcirculatory parameter was CD, which also increases with reduction of edema in the interstice. There was no statistical significance between the two groups ( $P = 0.228$ ) and in the CD of the treated and nontreated legs in patients that referred regular practice of physical activity ( $P = 0.123$ ) or alcoholic ingestion ( $P = 0.303$ ).

Statistical significance was observed in the comparison between CD in treated and nontreated legs in smoking patients ( $P = 0.011$  using the chi-squared test).

#### Clinical parameters

The clinical evaluation of the drug, made possible through centimetrical measurement of thigh and hip under treatment, as well as the contralateral leg (control), showed a reduction in more than 80% of the patients treated, in the upper and lower portion of the thighs.

Regarding the measurements obtained in the thicker portion of the right thigh, when treated and nontreated ones were compared, a reduction of the circumference was noticed in 80.8% ( $P < 0.0001$ ) of the patients, after 30 days. The reduction of the circumference in the lower portion of treated thighs was statistically significant ( $P < 0.0001$ ) in the third visit (after 30 days of treatment), when compared with nontreated ones, in the same period.

A reduction of the circumference of the inferior portion of the left thigh, in the treated ones, was observed in 83% of the patients ( $P < 0.0001$ ) after 30 days. The reduction of the circumference in the upper part of treated left thighs was statistically significant ( $P < 0.0001$ ) when compared with the nontreated thighs and was observed in 77.7% of the patients.



**Table 2** Evaluation of the alteration of diameter of the hip in 99 patients treated with a 7% caffeine solution for 30 days (LPM/UERJ; August 2003/April 2004).

	Hip	
	Count	%
Rise	32	32.3
Reduction	67	67.7

$P < 0.0001$ .

The median circumference reduction in the thicker portions of treated thighs was 2.1 cm. When considering the lower portion (10 cm above the patella), the difference between the first and last evaluation was 1.7 cm, in treated thighs.

Regarding hip measurements, it was observed that among 99 patients in the study, 67.7% (Table 2) showed centimetrical reduction after the treatment period, which was also significant ( $P < 0.0001$ ).

The influence of tobacco use on the therapeutic response to caffeine solution was not possible to determine because no association between the habit of smoking and the alterations of circumference of thighs and hips under treatment were detected. Regular physical activity was also not significantly related to the centimetrical reduction observed in treated thighs. Finally, occasional or frequent alcohol consumption did not show any statistically relevant association with the efficacy of the drug under study.

All patients were questioned about signs or symptoms of adverse reactions including allergic or irritant contact dermatitis. There was no evidence of adverse reaction, local or systemic, in any patient in the study.

## Discussion

Evaluation of therapeutic modalities for cellulite is very difficult due to confounding factors, such as diet and exercise (exclusion criteria in this study), as well as the absence of standard and objective criteria used to assess treatment response. Treatment categories include attenuation of aggravating factors, physical and mechanical methods, pharmacologic agents, and laser therapy.<sup>4,8</sup>

Pharmacologic agents used for the improvement of cellulite include xanthines, retinoids, lactic acid, and herbs. Although there are several topical treatments that are available over the counter at drugstores, there are no large-scale studies showing the effectiveness of any of these therapies. Only two of these drugs, aminophylline (xanthine) and retinoids, have been critically evaluated, with poor results.<sup>4,16,17,18</sup>

Some new devices have been introduced that use the combination of different technologies to treat cellulite, such as the combination of low-energy laser diodes that stimulate microcirculation and neoangiogenesis, a localized cooling system that can reduce edematous collections, and a rhythmical suction massage that can stimulate the lymphatic drainage.<sup>19</sup> The effects of a bioceramic-coated neoprene garment to enhance the penetration of topical agents to treat cellulite were already evaluated; warmth and external pressure from wearing the garment likely improves absorption, which allowed the anticellulite cream that was under evaluation to penetrate the dermis.<sup>20,21</sup> The topical agent applied was associated with a great improvement of cellulite with or without occlusion; among the active ingredients of such formulation was caffeine that is associated to a stimulation of lymphatic and microvascular flow and lipolysis of adipose tissue.

In this study, using the OPS imaging system, the use of the 7% caffeine solution did not modify significantly the microcirculation in the three studied parameters: FCD, DPD, and CD. This outcome suggests that a 30-day treatment might not be enough to show significant dermic microcirculation effects of the drug, or that its action might not be measurable in the dermic microcirculation.

Statistically, the treatment was more efficient in the diameter reduction of dermic capillaries in nonsmoking patients, suggesting that tobacco use is a negative influence in the patient's response to the drug.

Regular practice of physical activities showed a significant association with the rise of capillary density in patients treated with caffeine solution, suggesting a benefit for patients that exercise.

A 30-day treatment with this caffeine solution showed statistical significance concerning the reduction of circumference in treated thighs. This reduction was observed in more than 80% of the patients and was of about 2.1 cm in the thicker portion of the thigh and 1.7 cm in the lower portion. The use of 7% caffeine solution was also statistically significant in the reduction of hip circumference in 67.7% of the treated patients.

Weight loss, diet, and regular practice of exercise are considered means of improving cellulite, although there are few studies that confirm this theory. Many patients confuse weight gain with the appearance of cellulite. However, obesity alone does not create cellulite, as it affects nearly all lean females and very few obese males. On the other hand, weight loss does diminish the clinical perception of cellulite even if it does not alter the physiological reasons that created it.<sup>4,7</sup>

In this study, clinical parameters were not influenced by alcohol ingestion, tobacco use, or regular physical activities, suggesting that the efficacy of the drug might

not be influenced by those variables. However, diet and exercise should be encouraged as an initial step in the treatment of cellulite as they improve microcirculatory parameters and, consequently, the nutrition of the tissue.

In conclusion, 7% caffeine solution showed significant clinical improvement (diameter of the hip) and poor correlation to microcirculatory parameters after 30 days of treatment.

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