

## Review Article

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# Gynoid lipodystrophy and clinical therapy: a critical analysis of scientific papers

## *Lipodistrofia ginoide e terapêutica clínica: análise crítica das publicações científicas disponíveis*

### ABSTRACT

Gynoid lipodystrophy (cellulite) is a common, unattractive dermatosis that affects many women around the world. Depending on the severity of the appearance, the condition may cause important psychosocial disorders. Many therapies have been clinically tested, and many have been proscribed, not only for their therapeutic inefficiency, but also for their risk to patients' health. Other treatments, notwithstanding their weak scientific basis, are still in vogue. Medical devices, few of which are backed by actual scientific evidence, also currently claim to help treat this condition. This paper provides an extensive scientific literature review and analysis, and aims to help dermatologists decide what specific therapies to recommend and provide assurances regarding the clinical rationale of results when treating patients with this condition.

**Keywords:** cellulitis; lipodystrophy; adipose tissue.

### RESUMO

*A lipodistrofia ginoide (celulite) é dermatose inestética comum que aflige muitas mulheres ao redor do mundo. Dependendo da intensidade do quadro estabelecido, essa condição pode ser responsável por relevantes distúrbios psicossociais. Na prática clínica, muitas formas terapêuticas já foram tentadas; muitas foram colocadas no cenário das terapêuticas proscritas não só por sua ineficiência terapêutica, mas também pelo risco que impõem à saúde do paciente. Outras, ainda em voga, têm fragilidades científicas que não sustentam sua utilização; no panorama médico atual, encaramos, também, as promessas dos aparelhos médicos, sendo poucos os que realmente apresentam substrato científico de sustentação. Este artigo faz ampla revisão da literatura médica, analisando estudos presentes na literatura científica, tentando fornecer ao leitor argumentos que possam embasá-lo na indicação de uma dada terapêutica em detrimento de outra, a fim de confortá-lo no discurso clínico de resultados junto ao paciente portador de tal enfermidade.*

**Palavras-chave:** celulite; lipodistrofia; tecido adiposo.

## INTRODUCTION

Gynoid lipodystrophy (GL), more commonly known as cellulite, is a common, physiological and undesirable dermatosis that is an important cosmetic concern. However its etiology and management are controversial.<sup>1</sup>

GL affects 85-98% of women of all ethnicities after the onset of puberty, which suggests a hormonal component of its pathogeny.<sup>1</sup> In spite of its high prevalence, there are few scientific studies on the pathophysiology of GL, which makes it difficult to find the right therapeutic approach.<sup>1</sup>

It can occur on the surface of any part of the body that contains subcutaneous adipose tissue. The superior and posterior regions of the thighs and buttocks are the most susceptible areas. Less frequently, it can also be found in the breasts, lower abdomen, and back of the neck.<sup>1</sup>

Nurnberger-Muller has proposed a degree-based scale to rate the severity of GL:<sup>2</sup>

**Stage 0:** not evident in the standing or lying positions. The pinch test results in the appearance of "folds and furrows," however there is no "mattress" appearance.

**Stage 1:** not evident in the standing or lying positions, however pinch test results in a dimpled appearance.

**Stage 2:** spontaneously evident in the standing position, but not in the lying position.

**Stage 3:** spontaneously evident in the standing and lying positions.

The main hypotheses that purport to explain GL's pathophysiology include: the architecture of the skin, alterations in the connective tissue septa, vascular alterations, and inflammatory factors.<sup>1</sup>

Using magnetic resonance imaging, it was determined that 96.7% of gluteal areas with depressions caused by GL present fibrous septa perpendicular to the skin's surface, most of which are branched. The thickness of these areas is twice that of GL-free areas, on average.<sup>2</sup>

The literature describes a great number of therapies that have been applied in the treatment of GL. Although some data indicates that these treatments are beneficial, much of the evidence is subjective and based on individual medical cases or patient-reported satisfaction. Moreover, many of the studies contain methodological biases.<sup>1,3</sup> Therefore, this article undertakes a critical analysis of the therapeutic studies published in the international medical literature regarding the approach to GL.

### Topical therapies

Many topical treatments have been declared to be effective in reducing GL, however few studies evaluate active ingredients separately and most lack an appropriate clinical design. As a result, the treatments are not scientifically validated.

### Retinol

Kligman and colleagues compared a retinol-based cream, applied twice daily for six months in one thigh versus a placebo, applied on the other thigh. Of a total of 20 patients, 13 reported significant improvement in the area treated with retinol, which aligned with the physician evaluators' assessments.<sup>4</sup> The improve-

ment was credited to the increase in the dermis' thickness, the improved blood flow, and the reduction of dermal fat.<sup>4,5</sup>

Another study analyzed 14 women (26-44 years old) who planned to undergo mild to moderate GL liposuction.<sup>6</sup> They used a stabilized retinol-based cream on one thigh (posterior face) once a day, and a common hydrating cream on the other thigh, for six months prior to the procedure. After the application period, there was a 10.7% increase in the elasticity of the skin in the area treated with retinol, while the viscosity decreased by 15.8%. There was no improvement in the "orange peel" appearance of the skin. There were no significant histological differences between the two groups. However, in the area treated with retinol, there was an increase of two to five times in the number of XIIIa+ factor dendrocytes (collagen synthesis and degradation controller) and in their relationship with CD4+, both in the dermis' and in the hypodermis' fibrous septa.<sup>5</sup> Those alterations probably improved the resting tension of the skin, which in turn would have made its surface smoother.<sup>6</sup>

Both studies were adequately designed, using the patients' own contralateral body area as a control, and evaluated pure formulations of retinol, which makes the results more reliable and reproducible. The second study carried out histological studies that showed no statistical differences between groups, which can be attributed to the multifactorial character of GL. Nevertheless, since retinol is used to increase the dermis' septa thickness, the alterations that took place in the dermal collagen regulator dendrocytes – exactly where the retinol was applied – may be a sign that this substance affects the dermal microstructure.

The short duration of the follow-up was a limitation in both studies. It cannot be established if the improvement was sustained or whether prolonged use (longer than six months) would yield more significant increases in the clinical and histological responses.

### Methylxanthines

Methylxanthines are obtained from botanical extracts; caffeine, theobromine, and theophylline have been found to be the most effective in treating GL.<sup>6</sup> Their mechanism of action is what makes them effective: they apparently penetrate up to the subcutaneous layer, where they promote lipolysis, dissolve fat nodules, and reduce the number of fat cells.<sup>7</sup>

Collis and colleagues<sup>7</sup> studied patients (n = 17) with GL for 12 weeks. A combination of 2% aminophylline and 10% glycolic acid was compared with placebo, used twice a day. In the subjective analysis, three patients reported clinical improvement with the use of the active product.<sup>7</sup> Although the study was adequately designed, the addition of glycolic acid obscured the study's real objective: to assess the benefit of using aminophylline in the treatment of GL. Although there has been no additional response, this alpha-hydroxy acid could interfere with the evaluation if this improvement was evident. Thus the authors concluded that none of the therapy's substances was effective in improving the skin's appearance. Other authors have also not found favorable clinical responses with the use of aminophylline in the treatment of GL.<sup>7,8</sup>

The most widely used methylxanthine is caffeine, yet there are few adequately designed studies that evaluate its effectiveness separately; the studies seem to produce prior studies' methodological flaws.

In one such study, the cutaneous microrelief was observed using the orthogonal polarization spectral imaging method. The functional capillary density, dermal papilla's diameter, capillaries' diameter, diameters of the thighs and hips, and the influence of smoking, alcohol consumption, and physical activity of the volunteers were assessed.<sup>9</sup> After one month of treatment with a product containing 7% caffeine, there was a significant decrease in the circumference of the patients' thighs and hips (80% and 67.7%, respectively). Nevertheless, the microscopic parameters did not change. As a result, the authors concluded that the reduction was not linked to modifications in the patients' lifestyles, but rather to the use of the active principle.<sup>9</sup>

That study sought an objective evaluation by using the imaging method and thigh and hip metrics, and observed improvement after the treatment. Nonetheless, the various concomitant therapeutic measures instituted in the study prevented the improvement from being attributed to the caffeine-based cream alone.

Another author evaluated the efficacy of a product containing retinol, caffeine, ruscogenin extract, and alcohol in a double-blind, randomized, placebo-controlled trial with 46 women. All patients had mild to moderate GL in the thighs and a body mass index of 20–25. In the placebo, only alcohol was kept in order to simulate the application's cosmetic sensation. The product was applied twice daily for three months on one thigh, and the placebo was applied on the other. Patients were evaluated at baseline and after 28, 56, and 84 days.<sup>10</sup> Non-invasive, objective methods were used to perform a clinical assessment: digital analysis was used to assess the cutaneous microrelief, structural dermo-hypodermic characteristics were assessed using 20 MHz 3D ultrasound, cutometry was employed to evaluate the skin's mechanical properties, and laser Doppler was used to assess cutaneous flowmetry.<sup>10</sup>

Of the possible responses, only improvement in the cutaneous microrelief was observed, with a 53.1% reduction in the "orange peel" appearance on day 84, compared to 14% with the placebo.<sup>10</sup> The authors explained that the findings were statistically irrelevant when comparing the study product and placebo, since the circular movement used for the topical application – which exerts a positive action on GL, accelerated blood circulation, and prevented fat fibrosclerosis (perhaps due to the liberation of noradrenaline) – produced a qualitative change in the non-esterified fatty acids.<sup>10</sup>

Based on that hypothesis, the authors concluded that the combination of the various substances only benefited the cutaneous microrelief. It was inferred that mechanical action, such as massage, should be included in all treatments because it has an intrinsic benefit. Therefore, once again the combination of different extracts prevented the isolated analysis of the active principles. Since retinol is the only substance that features in these studies as a monotherapy with potentially positive responses, it

is possible to hypothesize that such improvement is due exclusively to that substance.

### Mesotherapy

Mesotherapy is a popular method for treating GL in Europe. It comprises intradermal injections containing a variety of solutions that are designed to stimulate lipolysis and reduce local fat, thus improving the appearance of cellulite.<sup>11</sup>

An *in vitro* trial using human fat attempted to verify the presence of lipolysis through the generation of glycerol using substances often used in lipolytic mesotherapy combinations: isoproterenol, aminophylline, yombine, and melilotus, 11 which when used in isolation provided a greater stimulus of lipolysis compared to the control. The addition of aminophylline to isoproterenol and melilotus produced a significant increase in lipolysis compared to the isolated use of those agents. By contrast, the addition of lidocaine to the isoproterenol, aminophylline, and yombine combination inhibited lipolysis.<sup>11</sup>

An interesting finding in this study was the demonstration that topical anesthetics inhibit lipolysis, in light of the fact that nearly all mesotherapy solutions usually contain procaine, lidocaine, or some other local anesthetic. Indications can be found in the medical literature that local anesthetics inhibit lipolysis in human fat cells.<sup>11</sup>

It is important to emphasize that the results presented in that study were obtained *in vitro*, and might not correspond to the clinical results. The paper proves the tested substances' lipolytic effect and demonstrates that combining them produces better results.<sup>11</sup>

In Brazil, mesotherapy was employed in the treatment of GL with the use of phosphatidylcholine in an off-label manner. However, Brazil's National Health Surveillance Agency issued a regulation that forbid the import, distribution, trade, and use of injectable phosphatidylcholine throughout Brazil. There have been no studies of the clinical efficacy and safety standards for injectable phosphatidylcholine. The practice of mesotherapy with this substance in Brazil can lead to sanctions to the physicians that are not limited to the ethical scope.<sup>12</sup>

## THERMAL, LIGHT, SOUND, AND MECHANICAL ENERGY-BASED THERAPIES

### Radiofrequency (RF)

RF is used to treat GL; it acts by heating the dermis and, potentially, the subcutaneous tissue.<sup>13–22</sup> A summary of the various clinical studies on RF can be found in table 1.<sup>14–22</sup>

Although these studies demonstrate improvement in the appearance of GL with the use of RF, several methodological flaws, such as small sample sizes and subjective assessments, can be identified in their designs. The studies have important flaws in the process of obtaining objective instrumental answers, and do not use standardized photographic images to define and analyze acceptable response levels.

A pressure to circulate their results in the international medical community, with little concern for compliance with scientific rigor or, in particular, confirming whether those res-

Table 1: Summary of studies that use RF in the approach of GL

Authors and year of publication	Methodology	Results	Comments
Del Piño ME, Rosado RH, Azuela A, Guzmán MG, Argüelles D, Rodríguez C, Rosado GM, 2006 <sup>14</sup>	Accent® RF in the unipolar mode, penetration energy up to 2 cm beneath the skin's surface. Energy used was 100-200 W, allowing the heating of the dermis and hypodermis. Women (n = 26, 18-50 years old), weight " 20% of ideal weight. Assessed buttocks' and thighs' subcutaneous tissue's thickness using ultrasound with multifrequency linear transducer (2-5 MHz) for soft tissue. Three consecutive passes applied in each area at each session. Treatment performed in two sessions (15-day interval). Ultrasound assessments carried out at baseline (T0) and 15 days after the second session (T45). Clinical and photographic records taken at baseline and after each session.	<ol style="list-style-type: none"> <li>1) organization of pre-existing fibrous lines;</li> <li>2) increase in fibrous tissue (53%) and in the thickness of fibers (57%); and</li> <li>3) volumetric contraction and improvement of thighs' and buttocks' contour, confirming action in the connective and subcutaneous tissues.</li> </ol>	<ol style="list-style-type: none"> <li>1) does not mention statistical significance of results;</li> <li>2) does not show correlation between energy level used and connective tissue contraction; and</li> <li>3) does not assess long-term results.</li> </ol>
Alster TS, Tehrani M, 2006 <sup>15</sup>	VelaSmooth™ system (wide spectrum infrared, with 20 W/700-2,000 nm combined with 20 W/1MHz RF and 200 mbar/750 mmHg vacuum mechanical bearing). Twenty volunteers, 4-6 passes in each area in 30-minute sessions, 2 times/week, 8	<ol style="list-style-type: none"> <li>1) significant improvement in the skin's texture and progressive GL reduction in the following weeks and months.</li> </ol>	<ol style="list-style-type: none"> <li>1) small sample; and</li> <li>2) cellulite and its intensity evaluated subjectively.</li> </ol>
Wanitphakdeedecha R, Manuskiatti W, 2006 <sup>16</sup>	VelaSmooth™ applied until erythema and radiant heat in the skin. Twelve patients, 8-9 sessions of 30-45 minutes each, twice per week. Results photographed and analyzed by two dermatologist physicians. Calibration of treated sites' circumference and weight measurements at baseline, immediately after final treatment, 4 weeks after and one year after.	<ol style="list-style-type: none"> <li>1) clinical improvement in the abdomen (25%) and thigh (50%); and</li> <li>2) body, weight, and shape did not influence the average degree of clinical improvement and circumference reduction.</li> </ol>	<ol style="list-style-type: none"> <li>1) can be considered a therapeutic option in GL, however requires a larger sample, objective evaluation, and better photographic records of results.</li> </ol>
Goldberg DJ, Fazeli A, Berlin AI, 2008 <sup>17</sup>	Unipolar RF. Patients (n = 35) with GL stages III-IV treated in six sessions. Assessed using photographs, clinical measurements, biopsy, MRI, and blood lipids measurement.	<ol style="list-style-type: none"> <li>1) 27 volunteers presented clinical improvement;</li> <li>2) 2.45 cm mean reduction in thigh circumference;</li> <li>3) fibrosis in the upper dermis achieved; and</li> <li>4) resonance showed no alterations.</li> </ol>	<ol style="list-style-type: none"> <li>1) does not produce electrical current within the tissue; and</li> <li>2) improvement seems greater than previously reported studies that used bipolar system and low-energy laser.</li> </ol>
W Manuskiatti C, Wachirakapha N, Lektrakul S, 2009 <sup>18</sup>	Tripolar RF. Patients (n = 39, 23-41 years old) with stage I-II GL, once per week, 8 total sessions. Before and after measurement of circumferences; subcutaneous fat thickness measured using ultrasound. 20,0-28.5 W energy, 1 MHz frequency, 40-42° C max temperature. Skin elasticity was measured with Cutometer® 580 MPA, photographs taken before, immediately after treatment, and a few weeks after the end of the study.	<ol style="list-style-type: none"> <li>1) 3.5 cm reduction in abdominal circumference.</li> </ol>	<ol style="list-style-type: none"> <li>1) tripolar RF more effective than bipolar RF and low-energy laser; and</li> <li>2) longer follow-up and larger sample size would strengthen findings.</li> </ol>
Sadick N, Magro C, 2007 <sup>19</sup>	VelaSmooth™: 16 women with GL in thighs and buttocks, using contraceptives. One side treated, the other used as control. Total of 3 weekly of c. 30-minute sessions, six passes, energy 1-3 J/cm <sup>3</sup> .	<ol style="list-style-type: none"> <li>1) 0.44 cm average reduction in circumference of lower thighs and 0.53 cm of upper thighs; and</li> </ol>	<ol style="list-style-type: none"> <li>1) further studies with larger samples and longer duration of device use are necessary to better assess sustained response; and</li> </ol>

Continued...

Table 1: Summary of studies that use RF in the approach of GL

Authors and year of publication	Methodology	Results	Comments
		2) significant visual improvement in skin texture and GL.	2) the authors of the present review suggest the use of higher energy levels and parallel research on the combination of other adjuvant factors in the treatment of GL (physical activity and topical retinol, for example).
Trelles MA, Mordon SR, 2009 <sup>20</sup>	Histology condition of buttocks with GL assessed before and 2 hours after VelaSmooth™ treatment.	1) treated skin histopathology: normal epidermis, areas of moderate edema in the dermis. Adipocytes with integrity alteration and ruptured membranes (with negligible necrosis) in the subcutaneous.	1) lacks post-treatment follow-up to assess sustained histopathologic alterations.
Lugt C, Romero C, Ancona D, Al-Zaroun M, Perera J, Trelles MA, 2009 <sup>21</sup>	Bipolar RF (ThermaLipo™): 50 patients (aged 24-58) with GL stage III in buttocks; 12 sessions of 12 min in each thigh. Evaluated using photographs, body measurements, satisfaction questionnaires, before, at the end of treatment, and 2 months after. Used 6J/cm <sup>3</sup> energy, 0.6 - 2.4 MHz.	1) dermis inflammation, with neocollagenesis, achieved; and 2) dermis became more compact with aligned and parallel fibers; subcutaneous tissue appeared to be pushed downwards.	1) only 15 of 50 study patients underwent biopsy.
Kulick MI, 2010 <sup>22</sup>	SmoothShapes: 15 minutes on side of thighs, twice per week, for 4 weeks, 1 W (650 nm) to 10 W (915 nm) energy in each session. Volunteers assessed at 1, 3, and 6 months after treatment. Analysis based on 3D and digital images, BMI, weight, body fat percentage, and patient questionnaire.	1) 94% of volunteers who completed the study (17 of 20) experienced improvement in cellulite. 3D images show 82% improvement at 1 month, 76% in 3 months, and 76% in 6 months. n.a.	1) small sample; and 2) more robust device-based analysis that is not restricted to surface imaging methods (e.g., MRI, skin biopsy), would make results more conclusive.

ponses can be sustained over time, is evident in those studies' methodologies.

### Intense Pulsed Light (IPL)

IPL is a therapeutic modality that uses the emission of light in the visible spectrum. Studies have demonstrated that it also stimulates the production of collagen.<sup>23</sup> A summary of the research on IPL in the treatment of GL is compiled in table 2.<sup>23</sup>

A study with IPL (510-1200 nm) was performed with 20 patients aged 23-56 years who had visible cellulitis both when standing and lying down. The patients were divided into two groups: Group 1 used IPL after applying retinyl palmitate cream for five nights before the procedure (suspended the night before the procedure), Group 2 received IPL only.<sup>23</sup>

After three months, based on the patients' personal evaluation, 60% experienced improvement greater than 50% in their

cellulite, and this improvement was sustained for eight months in 43% of the patients. There were no clinical and ultrasound differences between the groups, however the group using the retinyl palmitate cream sustained the improvement over the long term.<sup>23</sup>

That study evaluated a small population sample and used very wide energy fluence parameters, which undermined the veracity of its conclusions. In addition, the maintenance of long-term clinical affects in the group that used retinyl palmitate was not statistically significant when compared to the group that received IPL only, implying that it is not possible to confirm the superior efficacy of that therapeutic combination. Finally, the clinical confirmation of the neocollagenesis theory would be better supported if there had been cutaneous biopsies before and after the treatment.

### LED (light-emitting diode)

A summary of the studies involving LED treatment of GL are compiled in table 3.

The effectiveness and safety of topical phosphatidylcholine cream combined with LED (semiconductor diode that emits red light, which is meant to increase the synthesis of collagen) was evaluated in women with cellulite.<sup>24</sup> Nine women aged 39–64, with cellulite stages II and III, had one thigh treated with placebo (control) and the other with a cream containing a combination of 7% *Blupearum falcatum* extract (plant of the *Apiaceae* family that has anti-inflammatory action), the coenzyme A at 100 ppm, 15% phosphatidylcholine, and 1% caffeine. The creams were applied twice a day for three months. Both thighs were also treated at the same time with LED (660 nm +950 nm) twice a week for 15 minutes, during the same months. The study's results were recorded through clinical, photographic, and ultrasonographic (USG) evaluations of all patients, in addition to cutaneous biopsy in six participants (weeks 0, 6 and 12).<sup>24</sup>

After 12 weeks, eight of the nine patients who used the active cream presented a reduction in cellulite. The USG evaluation showed decreased fat and evagination of the subcutaneous tissue; half of the biopsied patients (three of six) presented decreased evagination of the cellular subcutaneous tissue. Eighteen months later, three patients still showed signs of clinical improvement. Five participants who demonstrated improvement later regressed to the cellulite stage they presented at the beginning of the study, which suggests that maintaining the treatment is key to obtaining good results.<sup>24</sup>

This randomized, double-blind, controlled study did not rely on the opinions of patients or evaluators; the results were therefore more reliable. The fact that each patient used different therapies (one on each thigh) also helped in the evaluation of results by mitigating the influence of different lifestyles. Furthermore, the sample was small, and biopsies were not performed on all volunteers, meaning that additional studies are needed to better evaluate these results.

### Ultrasound

Ultrasound has been developed to treat cellulite by inducing volumetric heating and, secondarily, lipolysis. Although some analysis has been carried out, additional well-designed clinical studies, with long-term follow-up of clinical outcomes, are necessary.<sup>13</sup>

### Shockwave therapy

Already used to treat nephrolithiasis, treatment with extracorporeal shockwaves is an effective therapeutic means for non-invasive treatment of GL. The shockwaves reach the tissue's surface and cross the homogeneous barrier without damaging other areas, which increases the blood flow in the target site.<sup>25</sup>

Cellulite's etiology involves the deterioration of the dermal vasculature, which causes edema and tissue hypoxia. Subsequently, there is a thinning and sclerosis of the fibrous septae, which are permeated by a chronic inflammatory infiltrate.<sup>25</sup> Based on those histopathological findings, the clinical possibilities of using this technology to treat cellulite were extrapolated. A summary of several clinical studies on ultrasound treatment is compiled in Table 4.<sup>25–29</sup>

One study investigated the effects of low energy extracorporeal shockwaves (ActiVitorOrthoDerma®). It is similar to ultrasound lithotripsy, with a 2.5 cm x 2.5 cm area of cutaneous action, and emits 0.018 mJ/mm<sup>2</sup>.<sup>23</sup> Of the 21 volunteers, seven noticed significant clinical improvement, ten observed slight improvement, and four reported no improvement. Two months after the end of treatment, a new questionnaire was administered, in which six patients reported that improvement was maintained; ten did not notice any changes since the end of treatment, and five described the recurrence of cellulite. According to the ultrasound results, there was a remodelling of the skin's collagen.<sup>25</sup>

Another report describes the clinical results obtained by using shockwaves to treat the skin of a 50-year-old woman. The histologic examination demonstrated the presence of neocollagenesis and the formation of elastin in the dermis and subcutaneous, with the thickening of those two tissues. There was also

Table 2: Summary of studies that use IPL in the approach of GL

Authors and year of publication	Methodology	Results	Comments
Fink JS, Mermelstein A, Thomas A, Trow R, 2006 <sup>23</sup>	IPL (510-1,200 nm) combined with retinyl palmitate cream in one group and isolated in the other group: 20 volunteers, once per week, for 12 weeks. Used fluence 8-14 J/cm <sup>2</sup> , depending on skin type and individual tolerability.	<ol style="list-style-type: none"> <li>1) 60% of patients reported GL improved more than 50%;</li> <li>2) absence of between-group clinical and ultrasound differences; and</li> <li>3) long-term improvement sustained in group using retinyl palmitate cream.</li> </ol>	<ol style="list-style-type: none"> <li>1) small population sample;</li> <li>2) energy and fluence parameters excessively wide, affecting conclusions;</li> <li>3) absence of statistical significance in long-term maintenance of clinical response in retinyl palmitate cream group; and</li> <li>4) pre- and post-treatment skin biopsies could help better define neocollagenesis theory.</li> </ol>

Table 3: Summary of studies that use LED in the approach of GL

Authors and year of publication	Methodology	Results	Comments
Sasaki GH, Oberg K, Tucker B, Gaston M, 2007 <sup>24</sup>	Randomized, double-blind, placebo-controlled study with phosphatidylcholine topical cream combined with LED, applied for 3 months to one thigh (placebo on the other). Assessed using clinical and photographic evaluation, ultrasound of all patients, and skin biopsy on 6 patients (0, 6, and 12 weeks).	<p><b>1)</b> clinical improvement of GL; ultrasound showed decreased fat and subcutaneous tissue evagination in the active cream group;</p> <p><b>2)</b> recurrence of GL in some volunteers after the study suggested the importance of maintaining treatment.</p>	<p><b>1)</b> biased final evaluation (biopsies not carried out in all volunteers);</p> <p><b>2)</b> treatment continuity is required to maintain results; and</p> <p><b>3)</b> small sample.</p>

an increase in the thickness of the dermis and subcutaneous fat. Hyperemia was observed in the treated skin immediately after and on the days following the treatment.<sup>26</sup>

With only two studies – one with a small sample, and the other a case report of a single patient – further investigations are necessary in order to demonstrate whether shockwave therapy is an effective option to treat cellulite.

Another shock therapy modality – extracorporeal activation pulse therapy, which, according to the authors, transmits energy from the point of generation to the target treatment area – stimulates cellular activation and improvements in metabolism.

A study of 59 females with GL stages 2 and 3, and senile conjunctiva fragility, 27 were divided into two groups and were given the same number of pulses at each session. Ultrasound (DermaScan C, 20 MHz) and cutaneous elasticity, whose standardization of measurement methods has been criticized, measurements were taken. Photographs were also taken at each session. An improvement in elasticity of around 70% in both groups, as well as improvement in the skin's appearance and strengthening of the connective tissue, were reported. Those outcomes were described during a six-month follow-up period, mainly in elderly women.<sup>27</sup>

Another study also evaluated extracorporeal pulse activation therapy (D-ACTORR200®, Storz Medical AG): 25 female volunteers underwent treatment with six sessions distributed over four weeks. Three thousand pulses were applied in a 10 cm x 15 cm area of the thighs, with a frequency of 15 Hz and energy of 2.6–3.6 bar. Evaluations were carried out before and after one week of treatment using 3D images (DermaTOP®, Eotech, Paris, France) that allowed the evaluation of the skin's structure through the observation of its morphology and surface, in addition to cutaneous elasticity measurements (DermaLab).<sup>28</sup>

Five parameters were evaluated: volume of the depressions, volume of elevations, cutaneous roughness, elasticity, and viscoelasticity. The results were as follows:<sup>28</sup>

Depressions: 50% in treated thighs versus 29% in untreated thighs ( $p = 0.0160$ ).

Elevations: 55% in treated thighs versus 15% in untreated thighs ( $p = 0.0021$ ).

Roughness: 30% in treated thighs versus 5% in untreated thighs ( $p = 0.0371$ ).

Elasticity: 33.3% in treated thighs versus 5.5% in untreated thighs ( $p = 0.0348$ ).

Viscoelasticity: 16.7% in treated thighs versus 11.1% in untreated thighs ( $p = 0.6520$ ).

The above evaluations were conducted after one week of treatment. Surprisingly, the final outcomes (12 weeks after the treatment's end) were not described in the study results. Also, no photographic record of the patients' analyzed region, nor the cellulite stage classification according to Muller-Nurnberg, were kept.

In a randomized controlled study, 50 female volunteers aged 18–65 were divided into two groups. They exercised their gluteal region twice a day (two exercises with 15 repetitions each) and underwent six shockwave sessions of 2,000 pulses in the gluteal region and thighs every 1–2 weeks. The energy used in the control group was 0.01 mJ/mm<sup>2</sup>, while in the intervention group it was 0.25 mJ/mm<sup>2</sup>. The evaluation was carried out at baseline and after 12 weeks using photographic imaging, anthropometric measurements, laser Doppler, spectrophotometry, and cutometry. Surprisingly, the article was published without the clinical results, given that the study is still in progress.<sup>29</sup>

Several methodological flaws have been observed in studies published on the use of extracorporeal pulse activation therapy – for instance the use of methodologies with questionable statistical confidence tests, an excessively wide age range of patients (including the young and the elderly), different numbers of volunteers in comparison groups, and excessively small samples.

### Laser

A study was carried out with 52 female patients with cellulite stages III and IV to demonstrate the efficacy and safety of a combination of two methods to treat GL: the application of Nd:YAG laser (to cause lipolysis) and autologous fat transplantation. The following parameters were used in the Nd:YAG laser sessions: 1,064 nm wavelength and energy ranging from 2,000–12,000 J, depending on the size of the area and the clinical severity. The lipolysis' product was removed with a 2 mm aspiration cannula.<sup>30</sup>

Table 4: Summary of studies that use shock waves in the approach of GL

Authors and year of publication	Methodology	Results	Comments
Angehrn F, Kuhn C, Voss A, 2007 <sup>25</sup>	Low-energy extracorporeal shockwaves (ActiVitor-Derma) applied on the side of the thighs: 21 GL patients (aged 20-60), twice per week for 6 weeks. Cellulite measured using high-resolution ultrasound, before and after treatment, to detect collagen remodelling in the dermis.	<ol style="list-style-type: none"> <li>1) 7 volunteers reported significant clinical improvement; 10 reported slight improvement;</li> <li>2) ultrasound revealed remodeling of collagen in the skin.</li> </ol>	<ol style="list-style-type: none"> <li>1) excessively small sample;</li> <li>2) absence of histological results and more robust image-based evaluations (e.g., MRI).</li> </ol>
Kuhn C, Angehrn F, Sonnabend O, Voss A, 2008 <sup>26</sup>	Low-energy extracorporeal shockwaves: 4 applications in a patient's left thigh, 21-day intervals. High-resolution ultrasound evaluation before and after treatment. Skin samples of treated area and contralateral area taken for histopathological analysis.	<ol style="list-style-type: none"> <li>1) histopathology revealed: neocollagenesis, elastin formation in the dermis and subcutaneous tissue, and thickening of the dermis and subcutaneous fat.</li> </ol>	<ol style="list-style-type: none"> <li>1) clinical study with one patient only.</li> </ol>
Christ C, Brenke R, Sattler G, Siems W, Novak P, A Daser, 2008 <sup>27</sup>	Extracorporeal pulse activation therapy: 59 female patients, two groups (Group A: 15 volunteers, 33-59 years, 18.2- 30.0 BMI), 6 sessions in 3 weeks. Group B (44 volunteers, 45-47 years, 16.2-40.0 BMI), 8 sessions in 4 weeks.	<ol style="list-style-type: none"> <li>1) c. 70% improvement in elasticity in both groups.</li> </ol>	<ol style="list-style-type: none"> <li>1) groups with different numbers of volunteers; and</li> <li>2) excessively wide patient age ranges, young and elderly volunteers included.</li> </ol>
Adatto M, Adatto-Neilson R, Servant JJ, Novak P, Krotz A, 2010 <sup>28</sup>	Extracorporeal pulse activation therapy in a 10 x 15 area of the thighs: 25 volunteers, six 4-hour sessions over 4 weeks. Assessed using 3D imaging and skin elasticity measurement (DermaLab) at baseline and one week after treatment.	<ol style="list-style-type: none"> <li>1) statistically significant improvement in both the treated and untreated thighs.</li> </ol>	<ol style="list-style-type: none"> <li>1) small sample; and</li> <li>2) device-based analysis results reported at one week after first session. The results originally sought by the study were not described at the end of the trial (12 weeks after the beginning of the study).</li> </ol>
Knobloch K, Joest B, Vogt PM, 2010 <sup>29</sup>	Randomized, controlled clinical trial: 50 volunteers divided into 2 groups. Different extracorporeal shockwave energies (25x stronger in the intervention group than the control); 6 sessions, 1-2 week intervals. Measurements taken at baseline and after 12 weeks. Skin elasticity assessed using Cutometer®. Microcirculation alterations assessed using laser Doppler and spectrophotometry. Other parameters used: photonumeric severity score, Nurnberger-Muller classification, thigh circumference measurement, and self-assessment.		<ol style="list-style-type: none"> <li>1) study is incomplete, lacks definitive results.</li> </ol>

The depressed areas were corrected using autologous fat transplantation. The results showed significant clinical improvement. Adverse effects were mild and temporary, and the post-operative period was well tolerated. The histopathological findings from the analysis of the samples of treated tissue revealed ruptured adipocytes (focal lipolysis), fibrous tissue coagulation, and degenerative alterations in the septae's connective tissue.

Most patients (84.6%) rated the results as good or excellent.<sup>30</sup>

According to the authors, laser-induced lipolysis has the advantages of inducing neocollagenesis and stimulating cutaneous contraction in the post-operative period, and this treatment should be established as a new therapeutic combination. However, the authors also conclude that further studies are necessary to perfect the technique, demonstrate its reproducibility.



lity, and consolidate the conclusions.<sup>30</sup> According to the preliminary results, this study looks promising.

### Endermologie

Endermologie is a mechanical method of mobilizing subcutaneous fat through the negative suction of the skin. The technique combines lymphatic drainage and ultrasound massage.<sup>7</sup>

A 12-week study assessed endermologie as an isolated treatment (twice a week for ten minutes) and combined with a cream based on 2% aminophylline and 10% glycolic acid applied on one thigh (a placebo cream was applied on the other). In the isolated endermologie group, while five of 17 patients reported improvement in the treated thigh, the evaluator physician found a difference in only two patients, and photographic records verified improvement in only one. In the endermologie combined with creams group, five of 18 patients reported improvement in both thighs.<sup>7</sup>

In another study, 33 women with GL (stages 1–3) underwent endermologie sessions twice a week, in a total of 15 sessions. The clinical evaluation was conducted using photographs (hips and thighs) and perimetric measurements of eight body sites (arms, chest, waist, hip, subgluteal region, thigh, knee, and calf). According to the authors, significant differences were found regarding the cellulite stage before and after treatment, which coincided with the volunteers' own opinions. Notwithstanding, improvement in appearance occurred in only five women (15%). It is worth noting that the clinical improvement was verified in women who lost weight during the study period.<sup>31</sup>

In order to evaluate and compare the benefits of three non-invasive methods for treating GL, women aged 30–50 ( $n = 60$ ), with cellulite stages 2 or higher according to the Nurnberg-Muller classification, were selected and divided into three groups. Group 1 was treated with mechanical massage, Group 2 with manual lymphatic drainage, and Group 3 with a connective tissue manipulation technique. The volunteers attended four sessions a week, for five weeks (for a total of 20 sessions). The parameters used in the analysis were: standardized photographs, body composition analysis, thigh circumference measurements, and measurements of the thickness of the adipose tissue in the abdominal, suprailiac, and thigh regions.<sup>32</sup>

All groups presented a reduction of subcutaneous fat after the treatment ( $p < 0.05$ ). The volunteers' weights remained practically constant, and the thigh circumferences decreased an average of 0.5 cm in all groups. Group 1 patients showed better results regarding the reduction in the suprailiac region's fat, while Group 3 presented better results in the reduction of the thigh's circumference. According to the photographs, 30% in Group 1, 25% in Group 2, and 25% in Group 3 presented improvement in the shape of the studied regions. The study's authors concluded that all three methods are effective in reducing fat in patients with cellulite.<sup>32</sup>

Nevertheless, no follow-up was undertaken to evaluate the results' durability. In addition, the sample in each group was small, no ultrasound evaluation of the behaviour of the subcutaneous tissue was carried out after the treatment, and there

were no descriptions of possible alterations in patients' cellulite classification stages.

Although the authors are inclined towards concluding that endermologie is a well-tolerated and effective method of decreasing body circumference, given the problems in methodology, it cannot be established as an effective treatment of GL. From the analysis of the article itself it can be deduced that the metric reduction is without doubt secondary to the weight loss of the volunteers during the study, and that the clinical improvement of GL was only visually verified in 15% of patients. Perhaps a study design with a wider scope and objective methods for standardizing clinical responses would improve the understanding of the real benefits of such a methodology.

### Bio Ceramic Neoprene Shorts

Bio ceramic-lined neoprene shorts (which have a layer of rubber that is expanded under high pressure and temperature, vulcanized, and lined with a special fabric either on both sides or one side only), present the following features: flexibility, elasticity, resistance, and thermal protection.<sup>33,34</sup>

Two four-week studies evaluating the effectiveness of a topical caffeine-based cream containing green pepper, green tea, ginger root, cinnamon extracts, sweet orange peel, and capsicum resin, combined or not with the use of neoprene shorts (only one thigh was in contact with the shorts) were found in the literature. The shorts were used to promote occlusion, thus increasing local temperature to facilitate the cream's absorption and penetration and enhance its efficacy. In both studies, patient evaluations were carried out after four weeks of use; four independent dermatologists assessed pre- and post-treatment pictures.<sup>31,33</sup>

The first study evaluated 17 women. The shorts and the cream were used on one thigh, while the cream only was applied on the other.<sup>34</sup> In the second study, 34 women used the study cream and shorts on one thigh and a placebo cream and shorts on the other.<sup>31</sup>

In the first study, 76% of volunteers reported clinical improvement; of those, 54% reported improvement in the thigh that had contact with the shorts. In the second study, 62% (21 of 34 patients) reported improvement; of those, 62% (13 of 21) observed improvement in the thigh that had contact with the active cream and the shorts. In the objective evaluation regarding the average reduction of the thigh's circumference, in the first study, the thigh with shorts presented a 1.3 cm reduction while the thigh without shorts presented a 1.1 cm reduction. In the second study, the thigh with the active cream presented a reduction of 1.9 cm, while the one treated with placebo reduced by 1.3 cm. In the dermatologists' evaluation, in the first study, the thigh with shorts improved by 65%, while the thigh without shorts improved by 59%. In the second study, the thigh treated with the active cream presented an improvement of 68%.<sup>31,33</sup>

No statistical differences between treatment groups can be observed in these studies. Although they conclude that the topical use of the cosmetic cream could be considered effective in treating cellulite – especially when combined with the use of the shorts – a critical analysis of the study results discourages such conclusions, which cannot be proven by the statistical tools

used. Therefore, further studies must be carried out to further assess the effectiveness of this therapy in treating cellulite.

### Subcision

Subcision is a straightforward surgical procedure that was first described by Hexsel and Mazzucco in 2000 as an approach to treating GL.<sup>34</sup> It is carried out under local anesthesia with the introduction of a subcutaneous catheter, which is manually moved parallel to the skin's surface in order to sever the adhesions between the dermis and the muscular fascia. The rupture of those connections improves the appearance of cellulite.<sup>31,35</sup>

Despite reports of success with using this technique, its benefits and long-term recurrence rates are still unclear. Although the authors of the present review have had very positive results with this technique in their daily practice, they still have to compile their cases and evaluate a greater number of patients over the long term – a major challenge, as patients frequently miss follow-up appointments – in order to establish the duration of results. Only then will it be possible to verify whether the improvements are maintained over the long term.

### Carboxitherapy

Treatment with carbon dioxide (CO<sub>2</sub>) or carboxitherapy involves the transcutaneous administration of CO<sub>2</sub> for therapeutic ends. Brandi and colleagues described the efficacy of CO<sub>2</sub> in the treatment of localized fat, showing reductions in abdominal circumference and in the thigh and knee regions. In the same article, the authors presented histological evidence of the effects of subcutaneous CO<sub>2</sub> infiltration in adipose tissue. Later, they reported improvements in skin elasticity when performing carboxitherapy to correct skin irregularities caused by liposuction.<sup>36</sup>

In one study, 101 women and 10 men were divided into three groups according to their age group (20–29, 30–39, and 40–50 years old). A total of five sessions were carried out at intervals of 1–2 weeks. The infusion was administered at a 50–100 mL/min rate, with the amount of infused CO<sub>2</sub> at 500–1,000 mL in the abdomen and 800–1,000 mL in each thigh, over a period of 20–30 minutes. The analysis was based on the measurement of abdominal and thigh circumference before and two weeks after the beginning of the treatment.<sup>36</sup>

Results showed significant reduction (in cm) in the measured maximum, average, and minimum abdomen circumference for the three groups:<sup>36</sup>

20–29 years old:  $1.8 \pm 0.5$  vs.  $1.6 \pm 0.4$  vs.  $2.1 \pm 0.3$

30–39 years old:  $1.6 \pm 0.4$  vs.  $2.3 \pm 0.3$  vs.  $2.1 \pm 0.3$

40–50 years old:  $2.0 \pm 0.4$  vs.  $2.5 \pm 0.4$  vs.  $2.6 \pm 0.4$

The reduction was not significant in the men who participated in the trial. For the 57 women who underwent the therapy in the thighs, the circumference was significantly reduced (in cm):

Left thigh vs. right thigh:  $1.6 \pm 0.3$  vs.  $1.5 \pm 0.2$ ;  $1.1 \pm 0.3$  vs.  $1.1 \pm 0.3$ ; and  $1.6 \pm 0.3$  vs.  $1.5 \pm 0.4$ .<sup>36</sup>

Weight loss was significant for older women who underwent abdominal therapy:  $1.3 \pm 0.2$  in the 30–39 group (n = 43)

and  $1.3 \pm 0.2$  in the 40–50 group (n = 29). Older women who underwent treatment on the thighs also reported a significant reduction in weight:  $0.9 \pm 0.4$  in the 30–39 group (n = 18) and  $1.6 \pm 0.3$  in the 40–50 group (n = 12).<sup>36</sup> The ultrasound data also shows evidence of subepidermal thinning after five carboxitherapy sessions.<sup>36</sup>

Although the objective of the study was the use of carboxitherapy in GL, it analyzed weight reduction only, and did not assess improvement in the appearance of GL. Additional methodological limitations were the different number of patients in each group, an absence of diverse types of analysis of results, and measurement calibration. The ultrasonographic evaluation was poorly described.

### Oral Therapies

Regarding oral treatments of GL, two clinical trials subjectively and objectively evaluated the effects of different oral formulations based on plant extracts.<sup>37</sup>

In the first study (prospective, longitudinal, double-blind, placebo-controlled), volunteers used a formulation combining grape seed (*Vitis vinifera*), *Ginkgo biloba*, *Centella asiatica*, *Melilotus officinalis*, and *Fucus vesiculosus* extracts, in addition to fish and borage oils. Forty-five women with GL were organized into three groups: Group A (11 patients) received capsules containing all extracts being tested, Group B (13 patients) received capsules containing all extracts except *Fucus vesiculosus*, and Group C (13 patients) received the placebo. All groups received two capsules daily for 60 days. Clinical, iconographic, and echographic imaging evaluations were performed at baseline and 20 and 60 days after treatment.<sup>37</sup>

The clinical-iconographic evaluation showed improvement of symptoms (edema and pain) in 71% of patients receiving the active treatment, with or without *Fucus vesiculosus*. Patients who presented changes in their body contour (30%) had taken the active treatment containing *Fucus vesiculosus*. The echographic evaluation showed a decrease in all signs associated with tissular edema in 70% of patients who had received the active treatment, with and without *Fucus vesiculosus*, unlike those receiving the placebo. No major alterations in the skin's architectural pattern were observed.<sup>37</sup>

In the second study (prospective, longitudinal, double-blind, placebo-controlled), 145 patients aged 18–45 (mean = 31.6 years) were randomized into three groups: Group A (58 patients) received a product containing bioflavonoids expressed as polyphenols (*Vitis vinifera*), fatty acids (essential poly-unsaturated, EPA- acids, DHA, g-linolenic acid), vitamin E, *Ginkgo biloba*, *Ruscus*, *Melilotus*, and *Centella*; Group B (29 patients) used inert substances as a placebo (natural fibers and soybean oil); and Group C (58 patients) used bioflavonoids expressed as polyphenols (*Vitis vinifera*), *Recaptacell*, *Ginkgo biloba*, *Ruscus*, *Melilotus*, *Centella*, and *Fucus*. All volunteers used three capsules a day for 47 days. Objective parameters were analyzed (height, weight, blood pressure, oxidative stress, body mass index (BMI), and abdominal, thigh and ankle circumferences) and a subjective questionnaire was administered. Some patients underwent addi-

tional tests (blood biochemistry, videocapillaroscopy, Doppler-flowmetry, ultrasound, pain test with ultrasound, echo-Doppler, light reflection, and thermography). According to the authors, there were statistically significant reductions in groups A and, especially, in Group C: decrease in BMI (average reduction Group A = 3%, Group C = 7.1%), decrease in abdominal circumference (average reduction Group A = 1.3%, Group C = 4.1%), and in the thigh and ankle (average reduction Group A = 0.2%, Group C = 0.5%).<sup>37</sup>

These studies, which were conducted by the same sponsor yet present different methodological details, have limitations. In the first study, the number of volunteers was small and the treatments were carried out in intermediary periods. Although the objective photographic evaluation captured alterations, these changes were not deemed important, and were not correlated with the volunteers' variations in weight during the study period. In the second study, although the number of volunteers was adequate, there was no uniform objective assessment (some volunteers were prioritised without clear explanation), and the study period was very short.

The methodologies of both studies should be merged and refined: volunteers should be followed up for one year, and the objective methods should be applied to all patients in clinical and instrumental monthly evaluations. As the findings currently stand, it is not possible to conclude whether oral are effective in treating GL.

## CONCLUSIONS

This article analyzes and criticizes the results of clinical studies published in the international medical literature on the various therapeutic approaches to GL. In general, the studies involved a reduced number of volunteers, short clinical follow-ups during and after the study period, as well as poor methodologies related to standardizing the acquisition of clinical responses and the objective instrumental validation of clinically obtained responses. We observed a dearth of studies that compare available medical devices and classic topical treatments in a competitive manner; the articles seemed restricted to issuing favorable opinions on therapeutic categories. Unfortunately, it is not yet possible to conclude which is the best therapy for managing GL. ●

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