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Evidence-based treatment for gynoid lipodystrophy: A review of the recent literature

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Summary

Gynoid lipodystrophy (GLD) is a structural, inflammatory, and biochemical disorder of the subcutaneous tissue causing alterations in the topography of the skin. Commonly known as "cellulite," GLD affects up to 90% of women, practically in all stages of the life cycle, beginning in puberty. It is a clinical condition that considerably affects the patients' quality of life. It is a frequent reason for consultation, although the patients resort to empirical, improvised, nonevidence-based treatments which discourage and can be a source of frustration not only because of the lack of results but also due to the complications derived from those treatments. In this article, a panel of experts from different specialties involved in the management of this clinical skin disorder presents the results of a systematic literature search and of the consensus discussion of the evidence obtained from different treatments currently available. The analysis was divided into topical, systemic, noninvasive, and minimally invasive treatments.

Resumen

La lipodistrofia ginoide (LDG) es una alteración estructural, inflamatoria y bioquímica del tejido subcutáneo que causa modificaciones topográficas en la piel. Conocida comúnmente como "celulitis", la LDG afecta hasta a 90% de las mujeres, prácticamente en todas las etapas de la vida, iniciando en la pubertad. Se trata de una condición que afecta considerablemente la calidad de vida de quien la padece. Es motivo frecuente de consulta aunque las pacientes recurren a tratamientos empíricos, improvisados, sin bases ni evidencia científica, los cuales desmotivan y producen frustración no sólo por su falta de resultados, sino por complicaciones derivadas de dichos tratamientos. Un grupo de expertos de diversas especialidades involucradas en el manejo de este problema presenta en este artículo el resultado de una búsqueda bibliográfica sistemática y de la discusión consensuada de la evidencia obtenida de diversos tratamientos disponibles actualmente. El análisis se dividió en

tratamientos tópicos, tratamientos sistémicos, tratamientos no invasivos y tratamientos mínimamente invasivos.

KEYWORDS

cellulite, diagnosis, etiopathogenesis, gynoid, lipodystrophy, skin, treatment

PALABRAS CLAVES

lipodistrofia, ginoide, piel, celulitis, etiopatogenia, diagnóstico, tratamiento

1 | INTRODUCTION

Gynoid lipodystrophy (GLD) is a structural, inflammatory, and biochemical disorder of the subcutaneous tissue that causes alterations in skin topography. Such changes derive in skin protrusions and depressions, mainly localized in the buttocks, lower limbs, pelvic region, and abdomen.¹

Commonly known as "cellulite," GLD occurs predominantly in up to 90% of adult women. It may begin after puberty, but it is more evident in women over 30 years old, overweight, and thin patients; men rarely have it.^{2,3}

Even though it is not a life-threatening clinical condition, GLD affects most women's psychosocial sphere because it is directly and inexorably related to the physical appearance, self-esteem, and, consequently to the well-being perception and social acceptance. Thus, the main reason to look for a treatment for GLD is its esthetic appearance.⁴

2 | ETIOPATHOGENESIS

Gynoid lipodystrophy is a complex and multifactorial condition that includes triggering, perpetuating, and exacerbating factors. It may be the result of structural, biochemical, metabolic, inflammatory, and morphological alterations, but a unique etiopathogenic explanation is not yet determined.⁵ The main hypothesis are detailed below.

2.1 | Genetics

One of the main hypotheses of GLD etiopathogenesis is genetics. Friedman et al found that *ACE* rs1799752 and *HIF1A* rs11549465 polymorphisms in the subcutaneous tissue are related to GLD. The former increases the activity of the angiotensin converting enzyme (ACE) and the disturbances in tissue oxygenation, whereas the latter protects against the microhypoxic and fibroinflammatory tissue responses.²

Another revision study conducted by Emanuele et al found that women carrying the D allele of *ACE* increases the risk of developing GLD because it is related to the production of angiotensin II in the fat subcutaneous tissue. This fosters the disturbance of the bloodstream and enables the adipocyte oxygenation (high deposition of extracellular matrix and the formation of complex networks of subcutaneous fibrous tissue).^{6,7}

In a controlled study, Emanuele et al found that the adiponectin mRNA expression is low in the subcutaneous fat tissue of areas affected by GLD, whereas there are no adiponectin changes in plasma.⁶

Even, some controlled clinical studies have found a significant correlation between tobacco use and a genetic component which may favor the development of GLD. ACE converts angiotensin I into angiotensin II and degrades bradykinin, which contributes to the decrease in the local bloodstream. ACE activity is genetically determined by an insertion/deletion polymorphism in thin women. Tobacco smoking induces oxidative stress and may promote the release of a proteolytic enzyme which alters the production of the connective tissue of the skin. In other words, there is a synergy between such genetic polymorphism and tobacco use.⁸

2.2 | Hormones

The estrogenic hormone processes play an important role on GLD etiopathogenesis. Evidence shows that such processes elicit lipogenesis and inhibit lipolysis which results in hypertrophy of the fat tissue. This mechanism may partially explain a higher prevalence of GLD in women and a casual correlation due to an exacerbation of this condition during high-estrogen periods, that is to say, during pregnancy, breastfeeding, menstruation, and oral contraceptives use.⁹ In other words, estrogens expose the sites where GLD is more common because such places have more hormone activity.

2.3 | Vascular and low-grade chronic inflammation

An extensively studied theory about GLD etiopathogenesis is the disturbance of the microvascular and lymphatic circulation of the subcutaneous fat tissue. In buttocks and thighs (sites where the lymphatic drainage and the vascular circulation are low), there is a higher predisposition to microedema increase in the subcutaneous fat layers, which fosters abnormalities in the skin.¹⁰

Rossi proposed four evolutionary stages in the GLD pathophysiology⁹:

- Modifications in the capillo-venular-lymphatic permeability, as well as capillary ectasia and intercapillary and interadipose edema.
- Edema that causes metabolic changes and results in hyperplasia and hypertrophy of the reticular structure.
- Collagen fibers joining around the adipocytes and form adipose micronodules.
- Sclerosis development that induces the formation of adipose macronodules.

Based on some cases reporting dermal and subdermal sensibility when pressing areas with GLD, inflammatory processes are

suspected. According to the evidence, macrophage and lymphocyte have been reported in the fibrous septa of biopsies of tissue with GLD, which shows the potential development of low-grade chronic inflammation and dermal atrophy.¹¹

2.4 | Morphology

Magnetic resonance imaging has confirmed that topographic modifications and clinic appearance of GLD are related to a significant increase in the presence and thickness of the subcutaneous fibrous septa.¹² The cutaneous depressions observed in GLD are the result of tension the fibrous septa execute downwards in a perpendicular direction to the surface of the skin, while the protruded areas are the projection of adipose chambers delimited by fibrous septa.¹ Another study reported that women with GLD have a higher percentage of fibrous septa, compared with men or women without GLD.¹³

3 | EVALUATION AND CLASSIFICATION

Evaluation and grading of GLD are crucial to determine the best treatment and to follow up the results. Nevertheless, it is important to take into account that some methods to assess GLD may be regarded slightly objective as the anthropometric measures (weight and body circumference) because they indirectly measure the adipose panicle.¹⁴

In any case, one of the main tests is performing a clinical examination while the patient is in a standing position and tightens the skin because that increases defects and it is useful during evaluation. The pinching test may be performed to make the lesions visible.¹ It is recommended to take and record digital photographs before and after the treatment. Taking the pictures should follow the same standards, including the light patterns, position, and adjustment of the camera.¹

De la Casa et al suggest that the pictures of co-occurrence matrices (glcm, *gray-level co-occurrence matrices*) should measure energy (textural uniformity), entropy (disorder, complex images, inversely related to uniformity), contrast (gray-scale variations in the image pixels), homogeneity (consistency of the local image), and their correlation with the texture of the site to be evaluated in relaxation and in contraction. This technique differentiates benign melanocytic nevus in normal skin.¹⁴

Another method to confirm GLD diagnosis is 2D magnetic resonance image because it shows the lipid composition of the normal and adipose tissues.¹³ It also shows the specific changes in the subcutaneous architecture caused by cellulite.¹⁵

Ultrasound is also useful to examine thickness, quality of the connective tissue, and to observe the edematous component of cellulite.¹ Image by ultrasound reveals dermal thinning and subcutaneous fat pushing it upwards. At 20 MHz frequency, ultrasound shows that adipose protrusions in the dermis are related to cellulite severity. This technique allows seeing the fat layers, but it is not routinely recommended.

Doppler laser flowmeter is also useful to establish a GLD diagnosis because it assess cutaneous microcirculation of the skin to obtain data of the blood flow and eritema.¹

Likewise, cellulite may be confirmed by thermography and infrared thermal camera because GLD areas are characterized by low blood flow and low temperatures.¹

Hexsel's and Dal'forno's alphanumeric classification *Cellulite Severity Scale* (CSS) has become a selection tool to graduate GLD severity because it is based on five clinical and morphological aspects: (1) number of evident depressions, (2) depth of depressions, (3) morphological appearance of the skin surface, (4) grade of flaccidity, and (5) GLD grade. Each of them is ranked from 0 to 3. The sum of all the items shows GLD severity: mild, moderate, or severe¹⁶ (Table 1).

In any case, the more simplicity and reproducibility the scale has, it is preferred.

Kaminer et al have described a CSS simplified classification (Table 2) which was developed and validated for a clinical study. It includes two clinical-morphological items: (a) number of evident depressions and (b) depth of depressions. The severity of each item is classified from 0 to 3 based on the definition and on the set of photographs taken at baseline. The total score is calculated from the sum of A and B values and the later subtraction of 1. The result shows a qualitative measure converted into a severity scale from 0 to 3, which is equivalent to none, mild, moderate, and severe (Table 2).¹⁷

TABLE 1 Severity scale of GLD (Hexsel's and Dal'forno's, *Cellulite Severity Scale*, CSS)

Number of evident depressions
0 = No depression
1 = Small quantity (1-4 depressions)
2 = Moderate quantity (5-9 depressions)
3 = Large quantity (10 or more depressions)
Depth of depressions
0 = No depressions
1 = Superficial
2 = Median depth
3 = Depth
Morphological appearance of the skin alterations
0 = No protrusions
1 = Orange peel
2 = Cottage cheese
3 = Mattress phenomenon
Grade of laxity, flaccidity, or sagging skin
0 = The absence of laxity, flaccidity, or sagging skin
1 = Mild draped appearance
2 = Moderate draped appearance
3 = Severe draped appearance

Adapted from Hexsel and Dal'forno.¹⁶

TABLE 2 GLD severity according to independent testers

Score	Description		
A. Number of evident depressions			
0	None		
1	Mild (≤ 4 depressions)		
2	Moderate (≥ 5 to ≤ 9 depressions)		
3	Severe (≥ 10 depressions)		
B. Average depth of the depressions			
0	None		
1	Mild (1-2 mm)		
2	Moderate (3-4 mm)		
3	Severe (≥ 5 mm)		
Severity grade			
Severity scale (A + B—according to testers' scores)		Classification	Severity
0		None	0
1-2		Mild	1
3		Moderate	2
4-5		Severe	3

Adapted from Kaminer et al¹⁷

4 | TREATMENT

It is a common recommendation to change lifestyle to reduce GLD; that is to say, to modify diet and do exercise regularly with the purpose of controlling body weight and, consequently, to reduce cellulite.

The food industry has conducted research to analyze how conjugated linoleic acid decreases GLD signs because it is a powerful PPAR- α activator that improves the epidermal differentiation, reduces inflammation (which increases the extracellular matrix components), and favors bright in the skin. Nevertheless, there is scarce evidence showing the unquestionable and long-term efficacy of these measures in the GLD treatment.¹⁸

The available therapeutic options for GLD are numerous and range from conventional modalities (topical applications and massages, intense pulsed light, acoustic waves, and radiofrequency) to minimally invasive approaches such as subcision, laser therapy, and injections. Their objectives are improving the esthetic appearance of the skin and maintaining treatment response as long as possible.

Clinical evidence for most of the modalities provides positive results in efficacy; however, it is still scarce and slightly consistent; thus, more research is needed to confirm such results. In any case, we can classify GLD treatments into topical, pharmacological, noninvasive, and minimally invasive.

4.1 | Topical

Numerous are the ingredients used in topical presentations to treat GLD. Most of the products contain caffeine, retinol, or botanical derivatives as active ingredients. The potential effects are lipolysis,

lymphatic drainage, stimulation of peripheral microcirculation, edema reduction, and stimulation of collagen production.⁹ Methylxanthines such as caffeine, aminophylline, or theophylline are the main category whose action has been documented to treat GLD. Their use is based on the potential to induce lipolysis in adipose tissue by inhibiting the activity of phosphodiesterase enzyme. Caffeine also has a stimulant effect on cutaneous microcirculation and as an antioxidant.¹⁹

Retinoic acid and vitamin A derivatives are widely used in GLD because they increase the collagen thickness, improve the elastic fibers, and function as inhibitors of the differentiation of human adipocyte precursor cells.⁹

Extracts of Ginkgo biloba leaves are also used to improve the appearance of GLD because they contain flavonoids, bioflavonoids, and terpenes. These substances improve the local microcirculation when reducing the blood viscosity, inhibit the platelet growth factor, diminish the capillary permeability, and improve the tone of the vessel wall.⁹ Other botanical derivatives such as *Centella asiatica*, *Ruscus aculeatus*, *Carica papaya*, *Vitis vinifera*, *Glycyrrhiza glabra*, and *Aesculus hippocastanum* have been used because of their potential as promoters of microcirculation and because they improve the lymphatic drainage.^{9,20,21}

As a rule, topical treatments are intended to improve the appearance and skin texture (orange peel, cottage peel), but they only have a transient effect, that is to say, they do not improve the retraction caused by fibrous septa.

4.2 | Massage

Mechanical stimulation by massages is one of the oldest methods to treat GLD. It is thought it promotes lymphatic drainage and the microcirculation of the subcutaneous tissue, which diminishes lymphedema associated with GLD. It may be manual or performed with the assistance of devices; one of them execute positive and negative pressure to the skin and to the subcutaneous tissue, which is believed to cause a nonlethal damage to the adipocytes which are distributed and achieve a better skin contour.^{22,23}

4.3 | Pharmacological (oral)

In a systematic revision (67 clinical studies) of the current management for GLD, it was found that in spite of the contradictory views about the effectiveness of oral treatments for GLD, the commonest are considered nutritional supplements made from extracts of *Vitis vinifera* (grape), *Ginkgo biloba*, *Centella asiatica*, *Mellilotus officinalis*, *Fucus vesiculosus*, fish oil, and borage oil. Their antioxidant effects inhibit the oxidation of the tissue molecules. Another option included in this revision is drinking aronia juice because it enhances the cellular metabolism, increases collagen and elastin synthesis; reduces edema and bowel inflammation; and improves microcirculation.²⁴

Another group of researchers proposes the use of *Dioscorea opposita*, *Theobroma cacao*, *Aesculus hippocastanum*, *A. hippocastanum*, and

Solanum lycopersicum because their extract regulates the release of glycerol from the adipocytes that decrease the fat content in the tissue.^{25,26}

4.4 | Noninvasive

Noninvasive devices based on energy.

4.4.1 | Acoustic waves

The transmission of acoustic waves toward subcutaneous tissue seems to be a safe alternative in the GLD treatment.^{27,28} Evidence shows that shock waves of this technique—widely used in urology to fragment kidney stones—in GLD promote lipolysis when breaking the cellular wall of the adipocyte, improve local blood flow, and enable lymphatic drainage with the subsequent lymphedema decrease. Likewise, it seems to stimulate collagen and elastin production, which improves skin elasticity.²⁴

Nevertheless, a systematic revision does not show positive results related to the efficacy of the acoustic waves devices²⁴; thus, more clinical studies are needed to increase the consistency of the results.

4.4.2 | Radiofrequency

Radiofrequency devices (RF) heat the target area due to the resistance to the flow of electric current in the dermis and subcutaneous tissue. Such phenomenon is known as bioelectrical impedance, and its objective is decreasing the appearance of cellulite when affecting the connective septal and adipose tissue.⁵

There are mainly two types of devices emitting energy by radiofrequency: unipolar and bipolar. The most important difference between them is the depth the thermic wave reaches. The former reach deeper layers and comprise most part of the subcutaneous tissue, whereas the latter usually reach the depth of the deep dermis and the most superficial part of the subcutaneous cellular tissue.

Such mechanism is used in GLD due to its capacity to induce collagen production, tissue restructuring, and adipocyte lysis.⁵ It is believed that heat released to the subcutaneous layer is absorbed by adipocytes in order to induce cell breakage by membrane lysis. Subsequently, a process of repair by production of collagen would improve the tissue characteristics, making it firmer and improving the clinical appearance of GLD.²

RF is usually used in combination with other techniques such as ultrasound, infrared light, suction, but according to a systematic revision of evidence, RF effectiveness alone or in combination is limited. The results of clinical studies do not show systematic analysis or complete and definite resolution of GLD; thus, more randomized studies with larger samples are needed to confirm results.²⁴

4.4.3 | Infrared light and intense pulsed light

Heat generated by infrared light on the skin implies an increase in microcirculation, lymphatic drainage, and collagen synthesis. The

process of collagen denaturalization induces its contraction, thickening, and later skin tightening. It may also be combined with laser techniques and mechanical stimulation.⁵

Intense pulsed light (IPL) is based on the supposition that this technique promotes collagen generation and induces firmer dermis. Dermal damage executed by this energy promotes subsequent repair and remodeling of collagen. Hence, it is believed that IPL improves the esthetic appearance of GLD.²²

Due to the depth of these treatments (exclusively cutaneous), results are not significant or lasting, specifically for GLD.

4.4.4 | Ultrasound

Focused ultrasound is now used in GLD because of its effects in the structural alteration of tissues; mainly by dermal damage and micromechanical disruption.²⁹ The energy released by open ultrasonic waves promotes disruption of the adipocyte cellular wall. It is thought that this system (known as cavitation) reduces fat tissue volume. However, the damage it may provoke to the deep tissues has not been confirmed. Several systems using ultrasonic waves have been developed to treat GLD in combination with other techniques and procedures like radiofrequency and the results of their efficacy seem to have a basis.³⁰

4.4.5 | Criolipolysis

Technology of controlled freezing of subcutaneous cellular tissue was approved by FDA to be applied in order to reduce fat volume; its use in GLD treatment is still under research.^{31,32}

4.5 | Minimally invasive

4.5.1 | Carboxytherapy³³

Carboxytherapy is a technique or nonsurgical procedure whereby carbon dioxide (CO₂) is administered intradermally by means of a machine that regulates gas flow. This procedure is used to fight excess fat from the body, cellulite, body and facial aging, flaccidity, varicose micro-veins, and to reduce scars and stretch marks. It is also used as a postoperative treatment of liposuction or esthetic surgery to correct skin irregularities, to prevent fibrosis, and to improve results. CO₂ administration in subcutaneous tissue induces hypercapnia and reduces local pH, which derives in a considerable vasodilating response by the relaxation of the prearteriolar smooth muscle at the site of application.³³

According to the expertise of the authors of this document, carboxytherapy acts in GLD at four levels:

- Improves blood and lymphatic flows, which facilitates drainage of the retained liquid.
- Improves the tone of the skin, which restores elasticity and counters the typical sagging in GLD.
- Reduces fatty deposits and, consequently, the orange appearance of the skin.

- Fight fibrosis because it improves blood microcirculation and restores skin elasticity (decrease of the characteristic dimples of the skin with GLD).

In their study, Ramalho et al found that carboxytherapy is effective to treat abdomen, thighs, and/or knees (localized adiposities) which showed circumference reduction after treatment. In that same article, it is also emphasized that the lipolytic effect of carboxytherapy increases the collagen remodeling induced by intradermal CO₂ injections. It is also described that this technique promotes vasodilation of the microcirculation, increase in peripheral blood and temperature at the injection site.³³

Notwithstanding Ramalho's sample is small, the results Lee obtained in a sample including 101 patients also confirms the effectiveness of this technique. In the case of GLD, specifically, there was reduction in GLD grades III and II.³⁴ Obviously, more controlled studies and with larger samples are required to confirm that carboxytherapy is an evidence-based treatment.

4.5.2 | Mesotherapy and enzymes

Mesotherapy is the subcutaneous injection of several compounds such as collagenases, caffeine, hyaluronidase, carnitine, aminophylline, phosphatidylcholine, lipase, amylase, catalase, cathepsin, among others. Hyaluronidase, for instance, acts as an enzyme in epithelial and connective tissues promoting depolymerization of fibrous edema in interstitial tissue and enabling local metabolic changes.³⁵

Phosphatidylcholine injections—particularly sodium deoxycholate of the formulation—model the body; it is focused on the fatty deposits in the subcutaneous tissue and induces lipolysis by the activation of cyclic monophosphate.^{36,37}

This approach is chosen because lipases catalyze numerous reactions, including hydrolysis, inter-esterification, aminolysis, lipolysis, among others.²⁹ Even though this technique has been used in different conditions, its efficacy in GLD has not been consistently demonstrated due to the substance variability and different mechanisms of action.^{22,24,38}

Another up-to-date option to treat GLD is neocollagenesis by dermal filling with biodegradable injections of calcium hydroxyapatite microspheres. This minimally invasive procedure is safe, well-tolerated, and obtains good results because calcium hydroxyapatite microspheres stimulate collagen and elastin formation, besides improving microcirculation at a local level, which generates a long-term quality of life of skin and a better appearance of GLD. This treatment may be applied alone or in combination with other therapies.

4.5.3 | Subcision

Subcision is an effective surgical technique used to divide bands or subcutaneous fibrous septa and release the underlying skin, which results in a smoother and softer cutaneous topography.

The principle sustaining its use in the treatment of cellulite is the evidence showing that fibrous septa fix and depress the skin vertically toward the subcutaneous tissue, which causes evident depressions on the cutaneous surface. The most common methods have been liposuction cannulas, laser thermal guide (Nd:Yag 1440 nm), needles, all of them manually operated. The objective is releasing the skin to obtain a uniform surface.²

The latest treatment is a subcision system (TS-GS, Tissue Stabilized Guided Subcision) developed to gain more control, precision, reproducibility, and safety. It is a device approved by FDA and CE-Marked; it treats the structural underlying cause of cellulite by an accurate release of the fibrous septa by a suction system and microblades.³⁹

The clinical improvement achieved after using this technique results from the release of the fibrous septa, performed at an exact depth of 6 to 10 mm, which allows the re-distribution of the subcutaneous tensional forces that minimize the protrusion of the fat tissue. Evidence of multicenter clinical studies show that TS-GS is effective and safe to improve GLD appearance and that it achieves wide satisfaction and a maintained, long-term response (1, 2 and 3 years) after only one session.^{17,40,41}

5 | CONCLUSIONS

Gynoid lipodystrophy is a frequent condition, whose psychological impacts affect the quality of life of the patients who suffer it. It is important to carry out regular revisions of the literature and analyze the evidence published of several treatments for GLD because thus far there are no randomized, controlled studies with proper-size samples and adequate methodology. Likewise, it is necessary that clinicians, who treat this type of patients, document and publish the results of the treatments used because some of the current procedures show promising results and it should be clearly established what treatments have not shown efficacy to avoid the expense of resources, time, and patients' expectations.

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