Consensus Document on LIPEDEMA 2018 Includes current status of Lipedema 2019

Consensus Document on LIPEDEMA 2018

Includes current status of Lipedema 2019

MEMBRES OF THE CONSENSUS GROUP

ALCOLEA J.M.
Higher Specialization Master's in Aesthetic Medicine. Co-Director and Professor at the Master's in Aesthetic and Wellbeing Medicine, and Professor at the Master's in Laser and Phototherapy in Dermatological Aesthetic Pathology at the University of Barcelona. Scientific advisor of the Spanish Society of Aesthetic Medicine. Medical Director of Clínica Alcolea. Barcelona.

ALONSO ÁLVAREZ B.
Doctor of Physical Medicine and Rehabilitation. Head of section of Rehabilitation at the University Hospital Ram?n y Cajal and Member of the Breast Pathology Unit at the hospital. Member of the working group on Lymphedema of the Spanish Society of Rehabilitation and Physical Medicine (SERMEF). Rehabilitation Doctor at the Health and Body Aesthetics Unit of Pedro Ja?n Dermatology Group.

ARROYO BIELSA A.
Specialist in Angiology and Vascular Surgery. Head of Service of the Angiology, Vascular and Endovascular Surgery Unit at the Hospital Vithas Nuestra Se?ora de Am?rica. Madrid. Member of the Scientific Committee of the Spanish Chapter of Phlebology and Lymphology (CEFyL). Director of Medivas Vascular Studies.

DOMINGO P.
Vice President of the Spanish Association of Lymphedema and Lipedema (AEL). Graduated in Nursing and Physical Therapy. Post Graduate Teacher specialized in Manual Lymphatic Drainage and Oncology Physical Therapy. Director of the Vodder Center of Physical Therapy.

GALINDO GARCÍA A.
Specialist in Angiology and Vascular Surgery. Service of the Angiology, Vascular Surgery Unit at the Clinical Hospital San Carlos. Madrid.

GRACIA GRAELLS M.
Vascular Specialist from the French University of Montpellier. Director of the Center for Vascular Diseases (Vascular Medicine and Phlebology) Dr. Maya Gracia Graells, in Barcelona.

IGLESIAS URRACA C.
Doctor of Medicine and Surgery at the Universidad Aut?noma de Madrid. Specialist in Plastic, Aesthetic and Reconstructive Surgery. Head of section of Plastic Surgery of the Plastic Surgery and Burn Unit at the University Hospital La Paz. Madrid.

INSUA NIPOTI E.
Doctor of Medicine and Surgery at the Universidad Aut?noma de Madrid. Coordinator of the Lipedema area of AEL. Co-Director of the Master's in Aesthetic Medicine and Antiaging at the Complutense University of Madrid. Medical Director of Pineal Medical Center.

MARTÍN CASTILLO E.
Doctor of Physical Medicine and Rehabilitation. Rehabilitation Doctor of Grupo ICOT. Rehabilitation Doctor at Hospital de La Paloma. Member of the working group on Lymphedema of the Spanish Society of Rehabilitation and Physical Medicine (SERMEF).

MARTÍNEZ ÁLVAREZ JR.
Professor at Complutense University of Madrid and President of the Scientific Committee of SEDCA.

NOVOA RODRÍGUEZ M.
Specialist in Plastic Surgery. Plastic, Reconstructive and Aesthetic Surgery Service of Povisa de Vigo Hospital. Public Health Spokesperson of SECPRE.

RÍO-GONZÁLEZ A.
Doctor of Physical Therapy. President of the Spanish Association of Lymphedema and Lipedema (AEL). Graduate and post graduate Teacher at the European University, specialized in Lymphatic Therapy and Oncology Physical Therapy. Director of Fisioterapia Sanamanzana.

VILLARINO MARÍN AL.
Professor at the School of Nursing, Physical Therapy and Podiatry (UCM) and President of SEDCA.

Acknowledgements:

Spanish Association of Lymphedema and Lipedema **(AEL)**:
www.aelinfedema.org

Spanish Chapter of Phlebology and Lymphology **(CEFyL)**:
www.capitulodeflebologia.org
from the Spanish Society of Angiology and Vascular Surgery **(SEACV)**:
www.seacv.es

Spanish Society of Plastic, Reconstructive and Aesthetic Surgery **(SECPRE)**:
www.secpre.org

Spanish Society of Dietetics and Food Science **(SEDCA)**:
www.nutricion.org

Spanish Society of Aesthetic Medicine **(SEME)**:
www.seme.org

Edition: April 2018 / Update september 2019

Design, layout and printing: LITOGAMA S.L. info@litogama.com

ISBN: 978-84-09-02085-0

SUMMARY.

INTRODUCCIÓN.

Lipedema is a little-known alteration or disorder in the distribution of body fat, which affects almost exclusively women and primarily involves the lower extremities.

Epidemiological data are currently scarce and not helpful to determine the exact incidence of lipedema in the general population; its etiology and physiopathology are not clear enough; its diagnosis is basically clinical, since there are no specific diagnostic tests or enough scientific evidence to support it. However, its clinical manifestations imply deterioration in patients' quality of life due to the physical, psychological and social impact it entails.

Since about 70% of cases are associated with pain in extremities, these are usually referred to phlebology and lymphology specialists. Treatments to control the edema are not usually successful in reducing the volume of the extremities.

This is in addition to determinants of fashion from the 21st century that demand most women to have slender bodies, while the reality is that overweight and obesity are alarmingly increasing. About 80% of obese patients do not admit to have excess weight, complicating its early diagnosis and prevention of its evolution and, consequently, delaying treatment in patients with this disease.

Due to the clinical presentation and symptoms associated with lipedema, patients are often misdiagnosed with lymphedema, obesity, lipodystrophies or chronic venous insufficiency, and therefore they are not correctly and effectively treated; in the best case scenario, they are administered symptomatic treatments.

In the absence of unified criteria for lipedema, and given the national and international controversy surrounding the term, the Spanish Association of Lymphedema and Lipedema (AEL) has put together a multidisciplinary working group of health professionals from different fields involved in the diagnosis and treatment of this disorder to draft this Consensus Document.

The aim was to answer multiple questions using the documentary evidence and clinical experience available to date.

Is the currently described physiopathology enough to explain lipedema?

Is it a progressive alteration? Does it always get worse?

When you have lipedema, is the progressive increase in body fat percentage normal?

If the main symptom is not the edema: Is manual lymphatic drainage an essential tool for the treatment?

Is it correct to prescribe compression garments in all cases?

What are the most effective treatments?

This working group included the participation of: The Spanish Association of Lymphedema and Lipedema (AEL), the Spanish Chapter of Phlebology and Lymphology (CEFyL) from the Spanish Society of Angiology and Vascular Surgery (SEACV), the Spanish Society of Aesthetic Medicine (SEME), the Spanish Society of Plastic, Reconstructive and Aesthetic Surgery (SECPRE), the Spanish Society of Dietetics and Food Science (SEDCA), the Complutense University of Madrid, and doctors specialized in Physical Medicine and Rehabilitation from the Spanish Society of Rehabilitation and Physical Medicine (SERMEF).

This document includes several chapters on the definition and physiopathology of lipedema, its diagnostic methods, differential diagnosis, classification and treatment using physical, pharmacological and surgical means. It is hoped that it can help people with lipedema and health professionals caring for them.

However, there is still a lot to learn about the etiopathogenesis, diagnosis and treatment of lipedema, so research must continue and be completed with epidemiological studies of its incidence and prevalence, always using an interdisciplinary approach.

CURRENT STATUS OF LIPEDEMA 2019.

Until May of 2018, the World Health Organization (WHO) did not consider lipedema a disease, as has been stated in the Spanish Consensus Document on Lipedema of 2018.[1] As recommended by the **International Classification of Diseases (ICD 11),**[2] **"lipoedema"** and **"cellulite"** have been included in the section on non-inflammatory pathologies of superficial fat tissue, in the skin disorders chapter, with a specific four-digit code as suggested by the new classification (TABLE 1).

On May 2019, the 72nd World Health Assembly ADOPTED the eleventh revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11), which will **come into effect on January 1st, 2022.** We request that temporary provisions are established as of that date, and for a minimum of five years and for as long as needed, so Member States can gather and report statistics using previous reviews of the International Classification of Diseases. Likewise, we request the WHO Executive Board to inform the 76th World Health Assembly in 2023, the 80th World Health Assembly in 2027 and the 85th World Health Assembly in 2032 about the progress made with the implementation of this decision, and that they include an assessment of the need to review the ICD-11 in the 2032 report.

Therefore, when this Consensus Document is printed, ICD-11 will not be in effect yet.

TABLE 1

Diseases of the skin: Code range starts with EA00

Diseases of the skin incorporate conditions affecting the epidermis, its appendages (hair, hair follicle, sebaceous glands, apocrine sweat gland apparatus, eccrine sweat gland apparatus and nails) and associated mucous membranes (conjunctival, oral and genital), the dermis, the cutaneous vasculature and the subcutaneous tissue (subcutis).

Inclusions:

- Diseases of the epidermis
- Diseases of the dermis
- Diseases of the epidermal appendages (hair, hair follicle, sebaceous glands, apocrine sweat gland apparatus, eccrine sweat gland apparatus and nails
- **Diseases of subcutaneous tissue**
- Diseases of cutaneous vasculature

Diseases of subcutaneous tissue are included:

EF02 Certain noninflammatory disorders of subcutaneous fat:

- EF02.0 **Fat hypertrophy:** Focal hypertrophy of subcutaneous adipose tissue. It is a common sequela of long-term insulin injection into the skin.

- EF02.1 **Subcutaneous lipomatosis:** Diffuse infiltration of the subcutis by non-encapsulated adipose tissue.

- EF02.2 **Lipoedema:** Lipoedema is characterized by non-pitting diffuse "fatty" swelling, usually confined to the legs, thighs, hips and upper arms. It may be confused with lymphoedema. Lipoedema may also occur in the scalp.

Coded Elsewhere: Lipo-lymphoedema (BD93.1Y)

- EF02.3 **Cellulite:** Cellulite is a common architectural derangement of subcutaneous adipose tissue which results in dimpling and nodularity of the overlying skin. It is seen most commonly in postpubertal women and affects principally the pelvic region, lower limbs, and abdomen. It is thought to result from herniation of multiple small aggregates of subcutaneous fat through the fibrous tissue at the dermohypodermal junction. Obesity predisposes to but is not necessary for its development. The term is in widespread use but is misleading as it has nothing to do with cellulitis. The condition is asymptomatic but may cause considerable embarrassment.

The Working Group on the Consensus Document on Lipedema of 2018 would like to show through this note that, despite that the totality of items analyzed was not unanimous, a few conclusions, stated as "Key Points," were reached, emphasizing the following:

✓ That in the absence of a clear definition for lipedema, there is great confusion in the literature at an epidemiological, diagnostic and therapeutic level.

✓ That the term “lipedema” is not very accurate, since there is not a real edema in all cases, being, essentially, a fat disorder.

✓ That there are multiple etiopathogenic theories of lipedema but, to date, none of them have enough scientific evidence to support it.

✓ That elements like obesity, immobility, and lymphatic and venous insufficiency are aggravating-not etiopathogenic-factors of lipedema.

✓ That cellulite (FEP) and lipedema share some elements, although it cannot be said to be the same entity, but they may coexist.

✓ That lipedema is known to get worse with overweight and obesity, but they are different entities.

✓ That it is not clear if lipolymphedema is a clinical entity or an evolution of lipedema when there are no associated aggravating factors.

✓ That there are currently no classifications of lipedema with clinical criteria that may be quantified, and enable an objective analysis of therapeutic results.

✓ That patients with lipedema that maintain a normal weight and exercise regularly show fewer symptoms, better functional capacity and fewer complications that patients who don't.

✓ That the surgical treatment of lipedema is indicated in all cases, especially when the patient does not improve with the conservative treatment.

Members of the Working Group on the Consensus Document on Lipedema of 2018 maintain that there is still a lot to investigate, and they are currently working on a Clinical Practice Guideline on lipedema based on consensual criteria, pointing out that any diagnostic and therapeutic approach to lipedema must always be multidisciplinary.

1. https://www.who.int/classifications/icd/en/ <https://www.who.int/classifications/icd/en/>

2. Spanish Consensus Document on Lipedema of 2018, Alcolea JM., Alonso Álvarez B., Arroyo Bielsa A., Domingo P., Galindo García A., Gracia Graells M., Iglesias Urraca C., Insua Nipoti E., Martín Castillo E., Martínez Álvarez JR., Novoa Rodríguez M., Río-González A., Villarino Marín AL. April, 2018. ISBN: 978-84-09-00505-5.

CHAPTER I
DEFINITION. EPIDEMIOLOGY.

DEFINITION.

Lipedema is a chronic, poorly known, underdiagnosed clinical entity, typical of the female sex, specially involving the lower extremities and often confused with lymphedema, lipodystrophies or obesity.

Despite the recent request from the European Society of Lymphology, the World Health Organization (WHO) does not currently consider it a disease, and therefore it is not included in the International Classification of Diseases (CIE-10-ES), available in its Spanish electronic version at: *http://eciemaps.msssi.gob.es/ecieMaps/browser/index_10_mc.html>.*

In said index of diseases, the term "lipedema" appears on page 264, referring the reader to the term "edema". Upon checking the term "edema" on page 142 (edema, edematous), it is only considered as "edema in legs" (R60.0) and has two possible etiologies: "due to venous obstruction" (I87.1) or "hereditary" (Q82.0), which is related to "congenital and hereditary (chronic) (idiopathic) lymphedema" (Q82.0 on page 263). The term "elephantiasis" appears on page 143. The classification does not include the concept of lipolymphedema.

Therefore, when this Consensus Document is published, lipedema will not be considered a disease by the WHO yet, although ICD 10 is under review (ICD 11), with the final version being released in May of 2018. This will include, among others, a suggestion to consider "lipoedema" and "cellulite" (FEP) under fat tissue pathologies: *https://icd.who.int/dev11/f/en*.

Considering that the WHO defines 'disease' as the "alteration or deviation of one or several parts of the organism from its physiological state due to causes that are usually known, manifested by characteristic signs and symptoms, and the evolution of which is somewhat predictable," lipedema would qualify as a disease, just as patients' associations believe and demand. However, **this group of experts believe that lipedema, when it is not associated with diseases or aggravating circumstances (obesity, venous or lymphatic insufficiency, osteoarticular disorders, immobility, etc.), may not fulfill all the criteria to be considered a disease.**

Since there are currently no consensual and accepted diagnostic criteria by the scientific community to confirm the presence of lipedema, **more studies and new lines of investigation are required to determine if this entity meets the criteria to be a disease, or it's an aesthetic alteration causing psychological and social discomfort to its sufferers.**

It has been considered a rare disease of the adipose tissue; however, there is certain confusion in the literature when it comes to lipedema, morbid obesity, lipodystrophies and rare syndromes of the adipose tissue. In the list of Rare Diseases and synonyms published in the Orphanet journal -in alphabetical order- in December of 2016, lipedema appears with number 77243: *http://www.orpha.net/orphacom/cahiers/docs/ES/Lista_de_enfermedades_raras_por_orden_alfabetico.pdf.*

It was first described by Allen and Hines in 1940 as "Lipedema of the legs". They published that lipedema is a generalized, symmetrical volume increase of the extremities, commonly associated with a progressive increase in body weight, affecting women in many cases with similar family histories, and which can cause stress and be of great concern due to leg appearance (Allen and Hines, 1940).

The increase in volume is due to the symmetrical accumulation of adipose tissue, usually in the lower extremities, occurring almost exclusively in women and barely responding to weight loss strategies. It is also characterized by pain upon palpation and capillary fragility, with ecchymosis or hematoma associated with minimum trauma or even of spontaneous occurrence. It typically affects thighs and legs (except the feet), and sometimes the arms.

Moreover, these patients may show edema, which can have several causes:

- **Orthostatic edema:** most common; it gets worse throughout the day and improves when lying down.

- **Edema associated with venous insufficiency:** despite existing in the analyzed literature, this Group doesn't think the term "phlebolipedema" is appropriate, since it adds to the already existing confusion. According to the recommendation of the Clinical Practice Guidelines on Chronic Venous Disease (Abbad M, 2015) and the VEIN-TERM Interdisciplinary Consensus (Eklof B, 2009), chronic venous disorders that may be associated with lipedema must be named following the CEAP classification.

- **Edema due to lymphatic insufficiency:** There is controversy about whether this edema is a lymphedema associated with lipedema (the so-called lipolymphedema, a term that will be discussed later on), or it is a lymphedema secondary to obesity. Since it doesn't always occur in patients with high Body Mass Index (BMI), it is considered it may happen in both situations.

Although there is an important aesthetic component, lipedema can affect the sufferer at a physical, psychological and social level, remarkably reducing his/her quality of life.

The term "lipedema" is not very accurate and can be confusing, since there isn't real edema in all cases, being, essentially, a fat pathology. Even though in Europe it's called "lipoedema", it's used here as "lipedema" because it's the term used in Spain in the usual clinical practice. Terminology confusion is explained by the multiple words used in the literature to refer to it.

TERMS USED FOR LIPEDEMA IN THE LITERATURE:

Adipocyanosis

Adiposalgia

Segmentary or regional adiposis

Adipositas (or adiposis) dolorosa

Adipositas (or adiposis) edematosa

Adipositas (or adiposis) spongiosa

Dercum's Disease

Lipalgia

Lipedema

Lipodystrophy

Lipoedema (like it is known in Europe)

Lipohyperplasia/Lipohypertrophy dolorosa

Lipomatosis dolorosa of the legs

Massive obesity of the lower legs

Painful column legs

Riding breeches syndrome

Painful fat syndrome

Stovepipe legs

Despite the existing terminology, this Group considers the use of "lipedema" as the most appropriate one to refer to this entity.

Conditions like Dercum's Disease and Lipodystrophies cannot be considered synonyms of lipedema because they are well-defined diseases; and as for the terms: "lipohyperplasia" and "lipohypertrophy dolorosa", these are not appropriate because they are not exactly clinical cases, but histological definitions.

KEY POINTS

- Lipedema is a chronic clinical entity, typical of the female sex, involving the lower extremities.
- In the absence of a clear definition for lipedema, there is great confusion in the literature at an epidemiological, diagnostic and therapeutic level.
- The term “lipedema” is not very accurate, since there isn’t real edema in all cases, being, essentially, a fat disorder.
- Despite the existing terminology, this Group considers the term "lipedema" as the most appropriate one to refer to this entity.
- Despite existing in the analyzed literature, concepts like "phlebolipedema" and "lipolymphedema" are arguable.
- This Group of experts believes that lipedema may not fulfill all criteria to be considered a disease.

EPIDEMIOLOGY.

Epidemiological data are currently insufficient and heterogeneous. Since diagnostic criteria are not standardized or consensual, prevalence data (most coming from hospitals or lymphedema units) vary between publications.

Langendoen SI. et al. (2009) have found 10-15% of lipedemas in patients inquiring about edema in lower extremities.

In Germany, F?ldi E. (2006) reported a prevalence of 11% in women, a fact obtained after estimating the number of patients seeking medical attention at the clinic.

In 2012, Forner-Cordero I. et al., from the Lymphedema Unit at the University Hospital La Fe of Valencia, Spain, reported that 18.8% of 843 patients that visited their unit from 2005 to 2011 had lipedema. This is currently the only record of prevalence that has been published in Spain.

This number ranged from 8 to 17% of patients seen in different lymphedema clinics in Germany (Gregl A., 1987 and Herpertz U., 1997).

Researchers from the Regional Department of Dermatology of the St. George's Hospital (London, United Kingdom) estimated that less than 0.1% of women that visited their facilities had lipedema. However, they underscore that this percentage is probably underestimated due to wrong diagnosis, and scarce and inappropriate referral of patients by primary care physicians (Child AH et al., 2010).

Lipedema affects almost exclusively women. Considering it manifests at puberty and that it can be aggravated during pregnancy and/or menopause, an estrogenic dependency is presupposed. Only two cases have been described in men, one with hypogonadism and the other with liver cirrhosis (Chen SG, 2004; Langendoen, 2009).

Between 15-64% of family cases have been described (Halk AB., 2017).

KEY POINTS

- Epidemiological data are currently insufficient and heterogeneous.
- Due to the absence of clear diagnostic criteria, its real prevalence is unknown.
- It is considered an under-, poorly diagnosed disorder.
- New studies are required to determine the true prevalence of lipedema in general population.

CHAPTER I

BIBLIOGRAPHY.

Abbad CM, Rial Horcajo R, Ballesteros Ortega MD, García Madrid C. Guías de Práctica Clínica en Enfermedad Venosa Crónica. ID Médica Ed., 2015. P. 9-11.

Allen EV, Hines EA. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic oedema. Proc Staff Mayo Clin. 1940; 15:1984-7.

Chen SG, Hsu SD, Chen, TM, Wang HJ. Painful fat syndrome in a male patient. Br J Plast Surg. 2004;57(3): 282-86.

Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, et al. Lipedema: an inherited condition. Am J Med Genet A. 2010 Apr;152A (4):970-6.

Eklof B, Perrin M, Delis KT, Rutherford RB, Gloviczki P. Updated terminology of chronic venous disorders: The VEIN TERM transatlantic interdisciplinary consensus document. Journal of vascular surgery. 2009; 49 (2): 498-501.

Földi E, Földi M. Lipedema. In: Foldi M, Foldi E, editors. Foldi's textbook of lymphology. 2nd ed. Munich, Germany: Elsevier;2006. p. 417-427.

Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis, and treatment of the disproportional fatty deposition syndrome - systematic review. Clin Obes. 2012; 2:86-95.

Gregl A. Lipedema (in German). Z Lymphol 1987; 11:41-3.

Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. Phlebology. 2017 Apr;32(3):152-159.

Herpertz U, Das Lipödem und seine Kombinationen. Vasomed. 1997; 9:301-307.

Langendoen SI, Habbema L, Nijsten TE, Neumann HA. Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol. 2009 Nov;161(5):980-6.

CHAPTER II

ETIOPATHOGENESIS.

Most etiopathogenic theories proposed for lipedema try to explain the characteristics of fat deposits affecting the lower half of the body, as well as some associated clinical manifestations, such as pain and capillary fragility, among others.

Many etiopathogenic mechanisms have been described, some lacking sound scientific support and therefore not analyzed by this Group, such as intestinal dysbiosis, improper clearance of the interstitial space, acidified diet and the use of tight clothes.

LYMPHATIC AND BLOOD MICROCIRCULATION MECHANISMS

The existence of lipedema-related alterations of the lymphatic circulation has been proposed, although lymphoscintigraphy alterations described in the literature are variable. Whereas Bilancini S (1995) describes a delay in lymphatic emptying in patients with lipedema compared with normal subjects, he cannot explain why findings are asymmetrical, although lipedema is always bilateral and symmetrical. However, Van Geest AJ (2003) rules out said alterations in a later study.

Experimental studies like the one carried out by Blum K.S. (2014) describe a decrease in the frequency of the contractions of lymph vessels and a decreased response to mechanical stimulation in mice exposed to a fat-rich diet. In this case, the alteration of the lymph vessels would be secondary to the fat deposit, whereas authors like Godoy J.M.P. and Godoy M.F.G., in 2011 and 2012, believe the cause of lymphatic stasis is a mechanism enabling adipogenesis related with the etiopathogenesis of fibrosclerotic edematous panniculopathy (FEP).

The lymphatic stasis mechanism is also supported by authors like Curri SB (1984, 1985, 1986) and Bacci PA (1997), who explain the enzyme and/or inflammatory action leading to hypoxia as the cause of excess fat deposits, and attribute it to this mechanism *(Figure 1*).

Amann-Vesti BR (2001) describes the existence of microlymphatic aneurysms in patients with lipedema both in thighs and ankles, while they are hardly found in the back of the foot. The author himself admits that microaneurysms can be secondary to lipedema instead of its cause. Authors like Fife CE (2010) suggest the existence of blood microcirculation alterations with the formation of new capillaries in the thickness of adipose tissue, which, through the mechanisms of capillary fragility, would result in tissue hypoxia, the formation of hematomas and pain associated with lipedema. However, the pain of the lipedema has also been attributed to other mechanisms, such as nerve compression of adipocyte hypertrophy/hyperplasia, or inflammatory or central mechanisms related with chronic pain (Langendoen S.I., 2009; Peled W., 2016).

Authors like Siems W (2005) associate capillary fragility with angiogenesis, which in turn causes tissue hypoxia, and find Vascular Endothelial Growth Factor (VEGF) values 5 times higher in patients with lipedema and/or FEP compared with normal subjects.

Szolnoky G (2008) uses a suction method to study capillary fragility and describes that complex physical therapy enables to decrease capillary fragility expressed by the number of petechiae in the treated group versus the control group. No subsequent studies validating these results, as well as the reproducibility of the method, are known.

Authors like F?ldi E (2006) make mention of a reduced venoarterial reflex that can contribute to the formation of ecchymosis and hematomas associated with lipedema.

Clinical perception leads to the belief that mechanisms increasing capillary fragility can also be associated with functional phenomena related to menstrual cycles and mediated by hormonal mechanisms. There is evidence of hemodynamic changes affecting vein diameter and valve closure throughout the menstrual cycle (Asbeutah AM, 2014).

Blood microcirculation alterations have also been described by Curri SB in her thermographic classification of "cellulite" (Curri SB; Merlen JF, 1986). Already in the 80s, these authors believed that the etiopathogenesis of FEP was the cause of blood microcirculation alterations, like hypoxia and skin hypothermia, but the lipedema review shows that more recent publications (Fife CE, 2010; F?ldi E, 2006; Szolnoky G, 2008) have extrapolated these microcirculation alterations explaining lipedema-related hypoxia as the cause of hypothermia, pain, capillary fragility, fat deposits and presence of telangiectasia.

Harvey NL (2008) and White MH (2001) also suggest the existence of alterations in the structure and function of the lymphatic system.

Even though this Consensus Group (CG) thinks that FEP can coexist with lipedema, there is not enough scientific evidence to support microcirculation alterations as etiopathogenic of both entities, and these should not be considered the same pathology.

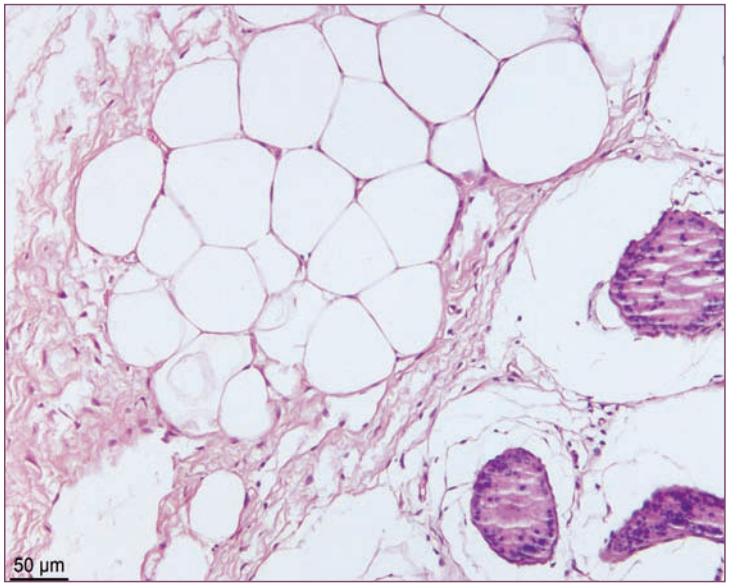


Figure 1.
White adipose tissue of a Wistar rat. Technical microphotography with hematoxylin-eosin and transmitted light microscope (40x zoom).

MECHANISMS ASSOCIATED WITH THE GENESIS OF THE EDEMA

The 2017 British Clinical Practice Guidelines on lipedema (Coppel T, 2017) mention that lipedema may be accompanied by edema, just as it was described in the original work by Allen EV (1940), caused by the overload of a normal functioning lymphatic system.

Therefore, edema would not be an etiopathogenic mechanism of lipedema, but it may be associated to orthostatic edema due to immobility or a systemic or circulatory (venous and/or lymphatic) pathology that might worsen the symptoms (Krijnen RM, 1997; Madeleine P, 1998; Rossi G, 2007; Schmeller W, 2007; Uda S, 1997). Based on authors such as Schmeller W (2007), it is important to emphasize the involvement of mechanisms like immobility in the genesis of lymphedema, since the lymphatic system requires movement and exercise to create the initial lymphatic transport through changes in tissue pressure. A clinical case is that known as "couch legs", a term coined by Sneddon I and Church R (1983), where patients spend day and night seated in a couch with their lower extremities hanging. Despite the absence of lymphatic.

abnormality, immobility itself reduces lymphatic drainage and causes functional lymphedema. In time, lymphatic vessels can suffer irreversible damage and cause permanent lymphedema. This mechanism might explain the presence of lymphedema in morbid obese patients and worsening of lipedema.

ADIPOGENESIS MECHANISMS. LIPOLYMPHEDEMA

Adipocyte hypertrophy is more related with abdominal obesity (*Figure 2) a*nd its metabolic complications, being more frequent in men and post-menopausal women; whereas hyperplasia is usually observed in association with genetic factors and occurs in gluteal-femoral fat (Hirsch J, 1989, Centofanti D, 2017). In young women, fat distribution predominates in the hips (gynoid distribution), while, with age, fat tissue decreases from the lower extremities as it increases in the central region; this change is more obvious in post-menopausal women. Central fat distribution is typical of men (android distribution) and old women (Björntorp P, 1996); it is associated with co-morbidities (metabolic syndrome, hypertension, insulin resistance and type 2 diabetes) but responds well to diet and fasting, unlike fat located in the lower half of the body.

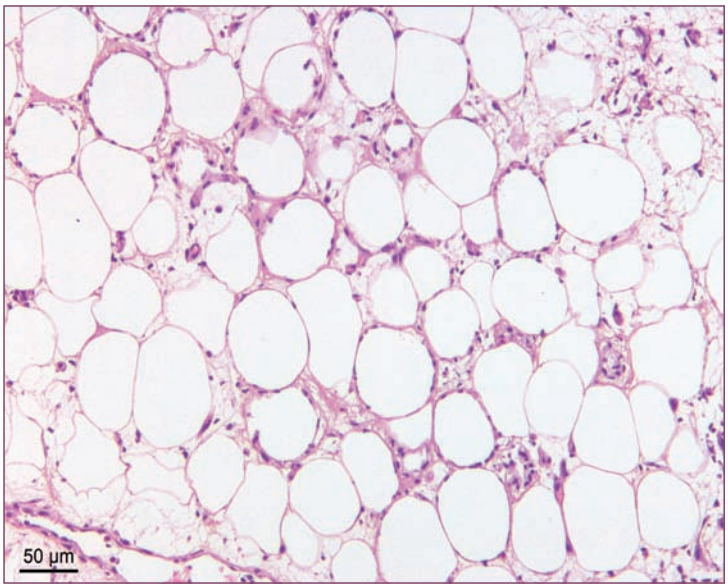


Figure 2.
Microphotography of visceral adipose tissue of Wistar rat, stained with hematoxylin-eosin and examined under transmitted light microscope (40x zoom).

According to these genetic (female sex) and hormonal (estrogens) mechanisms and those related to embryonic development, there is a larger fat deposit in women compared to men, which is distributed in the lower half of the body as a secondary sexual character. The fact that adipocyte hyperplasia is more frequent in gluteal-femoral fat of young women would explain its little response to diet.

Suga H (2009) and Schneble N (2016) believe that the increase of subcutaneous fat tissue in lipedema may be due to adipocyte hypertrophy and/or hyperplasia, but they think hyperplasia is more likely because fat deposits in the extremities with lipedema don't respond to diet. No histological studies in large populations have been found confirming whether lipedema shows adipocyte hypertrophy or hyperplasia, so it is only considered an etiopathogenic theory by this group.

As it was mentioned before, authors such as Blum KS (2014), Godoy JMP and Godoy MFG (2011, 2012) hold there are lymphatic microcirculation mechanisms that stimulate localized adipogenesis in lipedema, while authors such as Hosogai N (2007), Trayhurn P (2008) and Halberg N (2009) attribute fat hypertrophy/hyperplasia mechanisms to hypoxia.

The increase of certain markers (Ki67 and CD34), associated with the proliferation of pluripotent cells and adipose progenitor cells, has also been described, which suggests a fast increase of adipogenesis that in turn could condition tissue hypoxia. In this case, hypoxia would be a consequence of excess fat and not its cause.

High levels of plasma malondialdehyde (MDA) and protein carbonyl groups have been proven in patients with lipedema, compared with healthy subjects, which were reduced after shock wave therapy (Siems W, 2005). These markers of oxidative stress are found increased in many other chronic diseases, including obesity, although it is possible that biochemical mechanisms associated with adipokines production and increase of inflammatory phenomena favoring adipogenesis still remain to be known (Arner E, 2010; Dalle-Donne I, 2003; Ezquerro S, 2016; Jung UJ, 2014).

However, several authors (Buck DW, 2016; Fuster JJ, 2016; Herbst KL, 2012; Jeffery E. 2016) do not associate lipedemas with metabolic diseases, such as diabetes or hypertension. This could be explained by the fact that co-morbidities are more related with central obesity than with gluteal-femoral fat.

Adipogenesis occurs with angiogenesis, where macrophages play an important role. It has been observed that, whereas in normal adipose tissue they make up between 5-10% of all cells, in obese people, the number of macrophages reaches up to 40%. The study carried out by Cho CH (2007) on distal adipose tissue of mice epididymides showed that macrophages induce angiogenesis through secretion of metalloproteases and activation of the VEGF-VEGFR2 system.

There is probably still a lot to be known about the mechanisms associated with adipogenesis, and whether these are related with the etiopathogenesis of lipedema or they respond to obesity-related changes (Mc Gillicuddy FC, 2011; Tan BK, 2009).

More recent studies have found a correlation between fibrosis in subcutaneous adipose tissue and an increased difficulty to lose weight after bariatric surgery (Bel Lassen P, 2017).

Experimental studies connecting lymphatic stasis with adipogenesis and fibrosis of adipose tissue, which also show inflammatory phenomena, have been found (Maruyama K, 2005; Hardford KA, 2011; Rosen ED, 2002).

Other authors consider lipedema as masking obesity, the clinical diagnosis of which is relatively simple but with physiopathological mechanisms that are not entirely known (Langendoen SI, 2009; Sz?l E, 2014).

This association between lipedema and overweight and obesity can be seen in the work of Khalaf M (2013), who studied 20 female patients enrolled in a program involving diet, decongestive physical therapy and pressotherapy, resulting in a significant decrease of Body Mass Index (BMI) and of the extremities volume. It should be noted that the patients treated had overweight and obesity, so they were expected to improve through diet.

This Group believes it's necessary to open new lines of investigation to study adipose tissue as a cytokine-producer endocrine organ, as well as to confirm that the lymphatic and blood circulation mechanisms described in the bibliography are involved in the etiopathogenesis of lipedema, despite the limitations surmised by in-vivo functional studies at the level of microcirculation.

This CG rules out lipolymphedema as an evolution of lipedema, although functional lymphatic alterations may coexist, explaining the occurrence of edema associated with lipedema or organic alterations, since the incidence of primary lymphatic alterations of lower extremities in the general population is unknown.

GENETIC AND HORMONAL FACTORS

Lipedema is a chronic alteration of adipose tissue, affecting almost exclusively women (Coppel T, 2017; Lontok E, 2017), so a gender-related etiopathogenesis could be presumed.

Even though the studies available are insufficient, there is certain evidence of genetic predisposition affecting family members in 15-64% of patients (Child AH, 2010; Földi E 2006; Schmeller W, 2007).

The genetic variants involved have not been fully identified, but research suggests that there would be an autosomal dominant pattern with incomplete penetrance (Herbst KL, 2012).

Since lipedema affects almost exclusively women starting at puberty, this condition could also be explained both by the effect of estrogens on the early stages of fat (caudal outline) and by puberty.

Isolated cases of lipedema described in men (Chen SG, 2004; Langendoen SI, 2009) might be explained as secondary to hormonal disorders, since these subjects have shown low levels of testosterone.

Intake of anovulatories, pregnancy and menopause should be considered aggravating factors and not causes of lipedema.

Hormone factors, such as hypothyroidism, Cushing's or adiposogenital syndrome, could also be aggravating factors when associated with overweight/obesity, mobility limitations and other manifestations like myxedema.

KEY POINTS

- There are multiple etiopathogenic theories of lipedema but, to date, none of them have enough scientific evidence to support it.
- It is considered that elements like obesity, immobility, and lymphatic and venous insufficiency are aggravating-not etiopathogenic-factors of lipedema.
- FEP and lipedema share some elements, although it cannot be said to be the same entity, but they may coexist.
- Lipedema is known to get worse with overweight and obesity, but they are different entities.
- The term "lipolymphedema" is used in the literature to define the connection between lipedema and lymphedema. However, it is not clear if this association is a clinical entity Or an evolution of lipedema, or if the lymphedema is primary or secondary.

CHAPTER II

BIBLIOGRAPHY.

Allen EV, Hines EA. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic oedema. Proc Staff Mayo Clin 1940; 15: 1984-7

Amann-Vesti BR, Franzeck UK, Bollinger. A Microlymphatic aneurysms in patients with lipedema. Lymphology. 2001;34(4):170-5.

Arner E. Westermark PO, Spalding KL, Britton T, Rydén M, Frisén J et al. Adipocyte turnover: relevance to human adipose tissue morphology. Diabetes. 2010; 59(1):105-9.

Asbeutah AM, Al-Enezi M, Al-Sharifi NM, Almajran A, Cameron JD, McGrath BP et al. Changes in the diameter and valve closure time of leg veins across the menstrual cycle. J Ultrasound Med. 2014 33(5):803-9.

Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. Angiology. 1995;46(4):333-9.

Bacci PA. Il lipolinfedema. Correlazione tra lipodistrofia e linfostasi. Flebologia Oggi. 1997; 1:51- 62.

Bel Lassen P. Charlotte F, Liu Y, Bedossa P, Le Naour G, Tordjman, J et al. The FAT Score, a Fibrosis Score of Adipose Tissue: Predicting Weight-Loss Outcome After Gastric Bypass. J Clin Endocrinol Metab. 2017; 102:2443-2453.

Björntorp P. The regulation of adipose tissue distribution in humans. Int J Obes Relat Metab Disord. 1996; 20(4): 291-302.

Blum KS, Karaman S, Proulx ST, Ochsenbein AM, Luciani P, Leroux JC et al. Chronic high-fat diet impairs collecting lymphatic vessel function in mice. PLoS One. 2014; 9 (4): e94713.

Buck DW, Herbst KL. Lipedema: a relatively common disease with extremely common misconceptions. Plast Reconstr Surg Glob Open. 2016;4(9): e1043.

Centofanti D. Ferreiro AM. Gender-specific development and distribution of adipose tissue depots: a literature review. Aesthetic Medicine, 2017 (3):18-22.

Coppel T, Cunnen J, Fetzer S, Gordon K, Hardy D, Jones K, et al. Best practice guidelines: the management of lipoedema [Internet]. London: Wounds UK; 2017. Available from:
http://www.wounds-uk.com/best-practice-statements/best-practice-guidelines-the-management-of-lipoedema

Curri SB. Linfedema, lipedema, liposclerosi: una questione nosológica. La Medicina Estetica 1984; 8:9-33.

Curri SB. Rapporti vasculo-tessutali. In: Ribuffo A, Bartoletti CA, editors. La cellulite. Roma: Salus Int Ed; 1985. p. 37-46.

Curri SB, Merlen JF. Troubles microvasculaires du tissu adipeux. J Mal Vasc. 1986; 17:303-309.

Chen SG, Hsu SD, Chen, TM, Wang HJ. Painful fat syndrome in a male patient. Br J Plast Surg. 2004;57(3): 282-86.

Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S et al. Lipedema: An inherited condition. Am J Med Genet. 2010; Part A 152A:970–976.

Cho CH, Koh YJ, Han J, Sung HK, Jong Lee H, Morisada, T et al. Angiogenic role of LYVE-1-positive macrophages in adipose tissue. Circ Res. 2007;100(4): e47-57.

Dalle-Donne I, Rossi R, Giustarini D, Milzani A, Colombo R. Protein carbonyl groups as biomarkers of oxidative stress. Clin Chim Acta.2003; 329(1-2):23-38.

Ezquerro S, Frübeck G, Rodríguez A. El tejido adiposo, protagonista en las alteraciones metabólicas de la obesidad. Revista de la Sociedad Española de Bioquímica y Biología Molecular; 2016;190: 23-8.

Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. Adv Skin Wound Care. 2010;23(2)81-92.

Földi E, Földi M. Lipedema. In: Foldi M, Foldi E, editors. Foldi's textbook of lymphology. 2nd ed. Munich, Germany: Elsevier;2006. p. 417-427.

Fuster JJ, Ouchi N, Gokce N, Walsht K. Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease. Clin Res. 2016;118(11):1786-807.

Godoy JMP, Godoy MFG. Treatment of cellulite based on the hypothesis of a novel physiopathology. Clinical, Cosmetic and Investigational Dermatology:2011;4 55–59.

Godoy MFG, Buzato E, Franco Brigidio PA, Godoy JMP. Is Lymphostasis an aggravant of lipedema? Case Rep Dermatol. 2012; 4(23):222-6.

Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, et al. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in White adipose tissue. Mol Cell Biol. 2009;29(16):4467-83.

Hardford KA, Reynolds CM, Mc Gillicuddy FC, Roche HM. Fats, inflammation and insulin resistance: insights to the role of macrophage and T-cells accumulation in adipose tissue. Proc Nutr Soc. 2011;70(4):408-17.

Harvey NL. The link between lymphatic function and adipose biology. Ann N Y Acad Sci. 2008; 1131:82-8.

Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. Acta Pharmacol Sin.2012;33(2):155-72.

Hirsch J, Fried SK, Edens NK, Leibel RL. The fat cell. Med Clin North Am. 1989;73(1): 83-96.

Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K et al. Adipose tissue hipoxia in obesity and its impact on adipocytokine dysregulation. Diabetes 2007;56(4):901-11.

Jeffery E, Wing A, Holtrup B, Sebo Z. Kaplan JL, Saavedra-Peña R et al. The adipose tissue microenvironment regulates depot-specific adipogenesis in obesity. Cell Metab. 2016;24(1):142-50.

Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and non- alcoholic fatty liver disease. Int J Mol Sci. 2014; 14(4):6184-223.

Khalaf M, Ashem HN. Suggested physical therapy protocol for reduction of lipomatosis dolorosa of the leg. The Egyptian Journal of Medical Human Genetics. 2013; 14, 103-108.

Krijnen RM, de Boer EM, Ader HJ, Bruynzeel DP. Venous insufficiency in male workers with a standing profession. Part 2: diurnal volume changes of the lower legs. Dermatology. 1997; 194(2):121-6.

Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM. Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol. 2009;161(5): 980-86.

Lontok E, Briggs L, Donlan M, Kim Y, MosleyE, Riley EAU et al. Lipoedema: a giving smarter guide. Milken Institute; 2017 Santa Monica (CA), USA.

Madeleine P, Voigt M, Arendt-Nielsen L. Subjective, physiological and biomechanical responses to prolonged manual work performed standing on hard and soft surfaces. Eur J Appl Physiol. 1998;77(1-2):1-9).

Maruyama K, Ii M, Cursiefen C, Jackson DG, Keino H, Tomita M et al. Inflammation-induced lymphangiogenesis in the cornea arises from CD11b-positive macrophages. J Clin Invest. 2005; 115(9):2363-72.

Mc Gillicuddy FC, Harford KA, Reynolds CM, Oliver EF, Claessens M, Mills KHG et al. Lack of interleukin-1 receptor I (IL-1RI) protects mice from high-fat-diet-induced adipose tissue inflammation coincident with improved glucose homeostasis. Diabetes. 2011;60(6):1688-98.

Peled W, Kappos EA. Lipedema: diagnostic and management challenges. Int J Womens Health. 2016; 11(8): 389-95.

Rosen ED. The molecular control of adipogenesis, with special reference to lymphatic pathology. Ann N Y Acad Sci.2002; 979:143-58.

Rossi G. Diagnóstico diferencial de los edemas del miembro inferior. Flebología y Linfología / Lecturas Vasculares. Lecturas Vasculares. 2007; 4:157-220.

Schmeller W, Meier-Vollrath I, Weissleder, Schuchhardt. Lymphedema. Diagnosis and Therapy. 3rd edition. Viavital Verlag GmbH, 2007.Germany: Cap 7
https://es.scribd.com/document/54037242/Lipoedema-Chapter#

Schneble N, Wetzker R, Wollina U. Lipedema lack of evidence for the involvement of tyrosine kinases. J Biol Regul Homeost Agents. 2016;30(1):161-63.

Siems W, Grune T, Voss P, Brenke R. Anti-fibroesclerotic effects of shock wave therapy in lipedema ad cellulite. Biofactors. 2005;24(1-4):275-82.

Sneddon I, Church R. Practical Dermatology 4th ed. London, UK: Edward Arnold;1983.

Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodelling in lipedema: adipocyte death and concurrent regeneration. J Cutaneous Pathol. 2009; 36:1293-98.

Szél E, Kemény L, Groma G, Szolnoky G. Pathophysiological dilemmas of lipedema. Med Hypotheses. 2014; 83(5):599-606.

Szolnoky G, Nagy N, Kovács RK, Dósa-Rácz E. A. Szabó, K. Bársony et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. Lymphology. 2008; 41:161-166.

Tan BK, Adya R, Chen J, Farhatullah S, Heutling D, Mitchell D et al. Metformin decrease angiogenesis via NF-kappaB and Erk1/2Erk5 pathways by increasing the antiangiogenic thrombospondin-1. Cardiovasc Res. 2009;83(3):566-74.

Trayhurn P, Wang B, Woos IS. Hypoxia in adipose tissue: a basis for dysregulation of tissue functionin obesity? Br J Nutr.2008;100(2):227-35.

Uda S, Seo A, Yoshinaga F. Swell-preventing effect of intermittent exercise on lower leg during standing work. Ind Health. 1997;35(1):36-40.

Van Geest AJ, Esten SC, Cambier JP, Gielen EG, Kessels A, Neumann HA et al. Lymphatic disturbances in lipoedema. Phlebologie. 2003; 32:138–42.

Witte MH, Bernas MJ, Martin CP, Witte CL. Lymphangiogenesis and lymphangiodysplasia: from molecular to clinical lymphology. Microsc Res Tech 2001, 55: 122–45.

CHAPTER III

CLINICAL DIAGNOSIS. DIFERENTIAL DIAGNOSIS. CLASIFICATION.

CLINICAL DIAGNOSIS.

e responde escasamentThe authors of this study agree with Herbst KL (2012) and Coppel T (2017) that the diagnosis of lipedema is essentially clinical and based on anamnesis and physical examinations, since there are no specific supplementary tests.

The main findings of anamnesis and physical examination are:

There is often a genetic predisposition, since it can affect several women from the same family.

As of puberty, it affects the female gender almost exclusively.

It occurs bilaterally and symmetrically in the lower extremities.

There is a disproportion of fat distribution between the lower and upper halves of the body, with little response to diet and exercise *(Figure 3*).

Figure 3.
Body disproportion and leg morphology shaped as "stove pipes".

Lipedema's main sign is a fat deposit increase in the lower extremities, except the feet (Chen SG, 2004; Child AH, 2010), with disappearance of normal concavities at both sides of the Achilles tendon (Todd M, 2016) *(Figure 4)*, and legs assuming a typical morphology shaped as Egyptian columns, stove pipes or baggy pants.

Figure 4.
Bilateral and symmetrical involvement of the lower extremities.

Lipedema is characterized by fat distribution above the malleoli, except the feet (adipose ring or fold) *(Figure 5)*.

It may coexist with an increase of fat deposit in buttocks or the trochanteric region ("saddlebag sign" or "riding breeches"), as well as with FEP and/or flaccidity.

Stemmer's sign is negative *(Figure 6)*.

5a

5b

Figures 5a and 5b.
Adipose ring or fold except the foot and ankle.

Figure 6.
Negative Stemmer's sign in patient with lipedema.

This Group inquires whether there is lipedema of upper extremities, or if this location is more appropriate for entities like lipodystrophies or morbid obesity. No evidence of clinical cases has been found in the literature about the presence of lipedema in the upper extremities or about its prevalence in the general population. *(Figure 7)*.

Figures 7a and 7b.
Involvement of the upper extremities in patient with lipodystrophy

It is characterized by pain and/or hypersensitivity to slight touch and palpation. The cause of the pain is multifactorial.

Lipedema is usually accompanied by heaviness of the legs, a symptom that normally increases similarly to Chronic Venous Insufficiency (CVI): when a person is on his/her feet for too long, in excessive heat conditions, during long trips by plane or bus, etc.

Another characteristic is increased sensitivity to cold. Colder skin areas (hypothermia) and with different texture (usually softer) may be detected upon palpation.

The occurrence of ecchymosis associated with minimum trauma is frequent. But since said finding is common in women, this Consensus Group (CG) believes it is necessary to quantify it to have a clinical sign that can be objectively assessed.

Telangiectasia may occur in a variable manner and more often in patients with lipedema. Its coexistence with telangiectasia is not considered a characteristic of lipedema, but more of a coincidence, since class C1 (telangiectasia and reticular veins) of the CEAP classification is present in over 50% of women. (Álvarez-Fernández LJ, 2008). *(Figure 8).*

Figure 8.
Patient with lipedema and telangiectasia (C1 of the CEAP classification)

Puede asociarse a edema ortostático, tal como fue descrito originIt may be associated with orthostatic edema, as originally described by Allen EV (1940), although there is minimal or no presence of fovea. It can also be associated with lymphedema. *(Figure 9).*

Figure 9.
Lipedema in obese patient with signs of lymphatic stasis (lymphangitis and skin thickening). "Lipolymphedema".

Other lipedema-related findings are: decrease in skin elasticity and connective tissue, less mobility due to pain and joint dysfunction, and alterations of arch support and joint hyperlaxity, all of which are factors that alter the dynamic of the lower extremities and the muscle pump, affect the venous drainage, overload the function of the lymphatic system and favor the edema. This CG considers that all these findings are not typical of lipedema, but they can coexist with it.

In 2013, Smeenge J describes a certain degree of muscle weakness, which makes physical activities even harder.

Special mention should be made of the psychological involvement and stress associated with lipedema as factors affecting the patient's self-esteem, particularly these days due to the importance given to fashion and slender bodies. Due to size disparity between the upper and lower halves of the body, these patients usually have difficulties to find clothes they feel comfortable in. A survey performed in the United Kingdom in patients with lipedema has allowed to gather the following, very significant data (Fetzer A, 2016):

95% showed difficulties to find appropriate clothes.

60% had a limited social life.

60% felt desperate.

50% felt they had a limited sexual life.

40% believed they could have had a different professional career if it hadn't been for lipedema.

This discouraging fact should be added: that, as much as patients follow strict diets and periods of intense exercise, the areas with lipedema do not decrease in volume. Repercussions in the personal and work environments may sometimes cause mental disorders like depression, anxiety and alteration of body image.

Lipedema deteriorates patients' health-related quality of life; although no specific validated scales to measure it in this population are currently available, there are surveys like the SF-36 Health Questionnaire *(ANNEX 5).*

CLINICAL CRITERIA FOR LIPEDEMA

- Female gender.
- Occurrence at puberty.
- Family history.
- Bilateral and symmetrical increase in volume of the lower extremities, except the foot (adipose ring or fold).
- Disproportion between the lower and upper halves of the body, with no response to diet or exercise.
- Negative Stemmer's sign, and minimum or no fovea
- Pain with hypersensitivity to slight touch and palpation.
- Psychological involvement is common.
- Occurrence of ecchymosis associated with minimum trauma is common.

AGGRAVATING/CONCOMITANT FACTORS

Lipedema may condition a worst quality of life when associated with other pathologies of the extremities, although it should be noted that there are no validated questionnaires available to determine the degree of involvement.

It is important to use clinical examinations to rule out the coexistence of concomitant factors that might aggravate symptoms such as:

Chronic Venous Disease

It is commonly associated with telangiectasia (C1), venous reflux-related varicose veins (C2*), (Figure 10*) and venous edema (C3), from the CEAP classification, that may worsen the symptoms in lower extremities, particularly those related with standing up, heat, etc. Its coexistence with Chronic Venous Disease must be treated based on clinical stages and results of hemodynamic studies according to the Clinical Practice Guidelines (Abbad CM, 2015).

Figure 10.
Lipedema associated with varicose veins in the area of the great saphenous vein (C2)

Obesity and Overweight

Although normal-weight, low-weight, and even anorexic patients can show lipedema, the existence of overweight/obesity aggravates the symptoms in the extremities, especially if it is associated with immobility. It is essential to use anthropometric measures (weight, height, BMI, index of waist and hip circumference) and bioimpedance techniques to properly diagnose overweight/obesity.

Sedentary Lifestyle/Immobility

Lack of mobility is usual in patients with lipedema, due to the mechanical limitation typical of an increase in volume of the extremities, pain and joint restrictions, especially in hip and knees, and particularly in older patients. This, combined with aggravating factors like obesity and psychological involvement, results in patients limiting their social life.

Patients with lipedema that maintain a normal weight and exercise regularly show fewer symptoms, better functional capacity and fewer complications than patients who don't (Coppel T, 2017).

Other causes of edema of lower extremities

In general, systemic edema is characterized by presence of fovea, and it can be detected through interviews and physical examinations. In case of coexistence in patients with lipedema, it must be properly analyzed to receive specific treatment. Due to the life risk they entail, systemic acute edemas (of renal, cardiac or hepatic origin, by hypoproteinemia, drug edema) or acute loco-regional edemas, such as those caused by deep vein thrombosis, become important.

DIFFERENTIAL DIAGNOSIS.

Lipedema must be mainly distinguished from two entities with which it is usually confused, lymphedema and obesity, despite that it can coexist with both (Fife CE, 2010).

Obesity shows some clear differences with lipedema, although it cannot be ignored that over 50% of patients with lipedema may have associated overweight/obesity.

- Obesity affects both men and women.
- Fat distribution in obesity is symmetrical, although, unlike lipedema, its distribution is generalized. It should be noted that, if fat is of gynoid distribution (buttocks and legs) it is harder to diagnose with lipedema.
- BMI is increased (≥30 in obesity and ≥25 in overweight), while it can be normal in patients with lipedema.
- Diet treatments enable weight loss and a progressive and uniform reduction of body fat, especially in the abdominal area; this is not the case with lipedema, which doesn't usually decrease with diet.
- Hematomas and ecchymosis are not common in obesity.
- There is no special pain or skin sensitivity.

The following clinical-epidemiological features help distinguish lymphedema from lipedema (Child AH, 2010; Fife CE, 2010; Langendoen SI, 2009):

- It affects both men and women (lipedema occurs almost exclusively in women).
- It usually affects the back of the foot. Stemmer's sign is positive.
- It can start during childhood, particularly in the case of premature congenital lymphedema, while lipedema usually starts during adolescence.
- Except for a few cases of primary lymphedema, in general there isn't a family history (however, lipedema is frequently related with the mother).
- It can be unilateral or bilateral, but generally asymmetrical (lipedema is bilateral and symmetrical).
- Postural measures with the extremity raised can decrease lymphatic edema, especially during the initial phases (this is not the case with lipedema). In lipedema, when the patient is lying down, the orthostatic edema disappears, but the volume of the extremities barely varies.
- Concomitant hematomas are rare.
- In lymphedema, pain shows different characteristics, not so hypersensitive to touch.
- Skin is usually thickened in lymphedema (especially in advanced stages), while, in lipedema, skin is thin and soft.

Reviewing the published bibliography can also be confusing when cases consistent with localized adiposities at the bitrochanteric level, the buttocks area and inner knees are considered lipedema, or when skin alterations are reported as "orange peel" *(Figure 11)*. These entities are different from lipedema, but they can coexist.

Figure 11.
Patient with lipedema and FEP with "orange peel" and adiposity in buttocks and thighs.

This Group considers it necessary to clearly differentiate between lipedema, lymphedema, FEP and gynoid obesity/overweight *(Table 1)*.

CHARACTERISTIC	LIPEDEMA	LYMPHEDEMA	OBESITY	FEP
Physiopathology	Multifactorial	Lymphatic alteration 1st or 2nd	Multifactorial	Multifactorial
Family history	YES	Only some primary	YES / NO	NO
Appearance of the skin	Light ans soft	Depends on the state	No alterations	"Orange peel"
Gender	Womwn	Men / Women	Men / Womwn	Women
Age of onset	Puberty	Any age	Any age	Puberty
Symmetry	Bilateral and simmetrical	Uni- or bilateral	Symmetrical	Bilateral and simmetrical
Response to diet	NO	YES / NO	YES	NO
Pain	YES	YES / NO	NO	YES / NO
Stemmer's sign	NO	YES	NO	NO
Tendency to ecchymosis	YES	NO	NO in men	YES / NO
Disproportion of body upper and lower half (gynoid)	YES	NO	YES (Gynoid obesity) No (Central obesity)	YES

Table 1. *Differential diagnosis of lipedema*

Other differential diagnoses should be determined with:

Rare diseases of the adipose tissue and/or lipodystrophies: There are some rare diseases of the adipose tissue that occur with fat deposits and an increase in body volume, but which constitute entities of their own and should not be confused with lipedema, including, among others: Dercum's disease or adiposis dolorosa, characterized by the occurrence of localized subcutaneous fat accumulation with painful skin plaques; Madelung disease or multiple symmetrical lipomatosis, with occurrence of masses of adipose tissue in nape, neck, shoulders, trunk and proximal part of the extremities, preferably in men with history of chronic ethylism; and also ovarian polycystosis, with increase of androgenic production and generalized obesity, and Cushing's syndrome.

CLASIFICATION.

There is not an appropriate classification of lipedema and, if there are, they're insufficient and not universally accepted. They don't have much clinical use, because no clear correlation between the different groups and the seriousness, symptoms, or impact of lipedema on patients' quality of life has been observed. They don't provide a diagnostic or follow-up value of the therapeutic results either.

Furthermore, it is still under debate whether it is a progressive pathology or not, or if clinical worsening is mainly due to its association with obesity and venous and/or lymphatic insufficiency.

Changes or evolution of some types of lipedema have not been described either, so, for diagnostic purposes, no useful classifications are available.

Some of the classifications available to date are:

- **Classification of Schingale** (Schingale FJ, 2003)

Schingale distinguishes 5 types of lipedema:

- Type I: the adipose tissue is increased on buttocks and thighs.
- Type II: the lipedema extends to the knees, especially on their inner side.
- Type III: the lipedema extends from the hips to the ankles.
- Type IV: the lipedema affects the arms and legs.
- Type V: lipolymphedema.

Only Schingale's Type III is considered lipedema by this CG *(Figure 12)*, where fat distribution symmetrically affects both lower extremities, specially including the infrapatellar region, characterized by an adipose ring or fold.

As for Types I and II, they may be consistent with gynoid fat distribution as a secondary sexual character and should not be included in the lipedema case, although they may coexist with it, as well as with FEP.

There is not enough scientific evidence to consider lipedema of upper extremities (Type IV) when it is not associated with obesity or lipodystrophies.

The lipedema-lymphedema association, as it was previously discussed, may occur during the different phases and stages of lipedema, so it should not be considered an independent type in the classification.

Lipedema can be observed both in patients with overweight *(Figure 12a)* and normal weight *(Figure 12b).*

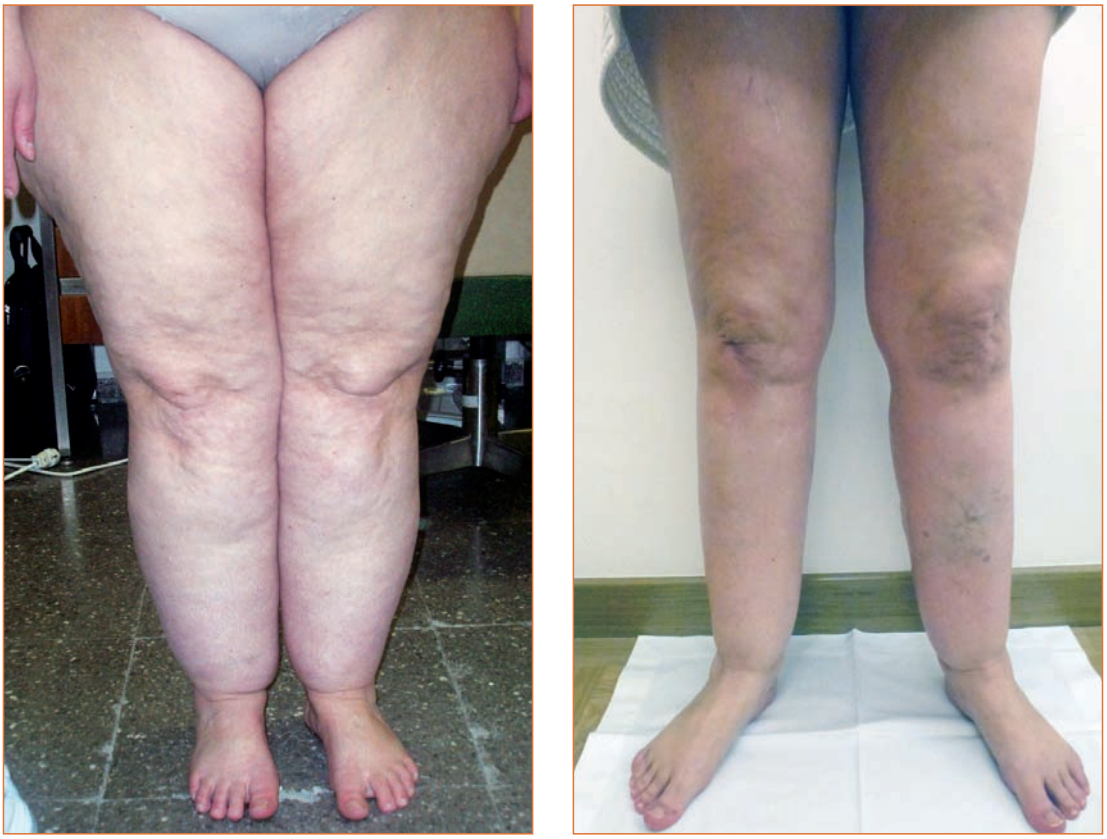


Figure 12.
Lipedema: Type III of Schingale. Figure 12a. Overweight patient. Figure 12b. Normal weight patient

- **Classification of Meier-Vollrath** (Meier-Vollrath I, 2007)

In line with Shingale's classification (Schingale FJ, 2003), other authors classify lipedema based on its anatomical location and equally define five types without considering occurrence or not of lymphedema (Meier-Vollrath I, 2007).

- Type 1: fat deposits are located in the pelvis, hips and buttocks, without affecting the rest of the lower extremity.
- Type 2: the fat is deposited in the thighs, between the buttocks and the knees.
- Type 3: the increased adipose tissue affects the lower extremities, from the buttocks to the ankle.
- Type 4: the lipedema affects the arms, but not the lower extremities.
- Type 5: the lipedema affects the legs, from the knee to the ankle, but not the foot.

Regarding this classification, and consistent with this CG's position, only Types 3 and 5 are considered lipedema.

- **Classification of Schmeller & Meier-Vollrath** (Schmeller W, 2004; Meier-Vollrath I, 2004)

These authors classify lipedema in three stages based on changes occurring on the skin and upon palpation :

- **Stage 1:** Skin surface is normal, with increase of subcutaneous cellular tissue with soft consistency, in the shape of palpable nodules

.

- **Stage 2:** Skin surface is uneven and harder, due to the presence of accumulation of fat in the shape of nodules or lipomas (liposclerosis).

- **Stage 3:** Large accumulations of fat that cause lobular deformation of the skin surface, particularly in thighs and around the knees. When pinching the skin, the "orange peel" phenomenon can be observed.

This classification does not distinguish between lipedema and other nosological entities, and causes confusion by giving it characteristics typical of FEP, such as "orange peel" or palpation of adipose micro- or macronodules, so it is not considered appropriate by this CG.

- **Classification of Fonder** (Fonder MA, 2007)

This author's classification is based on the shape of the extremities and distinguishes two groups:

- Columnar: Lower extremities shaped as columns or cylinders. *(See Figure 3).*
- Lobar: Presence of large protuberances or lobes of fat on the enlarged lower extremities, hips or arms *(see Figure 13).*

It is barely a descriptive classification about the possible morphology of extremities with lipedema, but does not provide any clinically or therapeutically useful data.

Figure 13.
Lipedema with lobar distribution of fat and overweight

The group of experts that prepared the recently published British Clinical Practice Guidelines (Coppel T et al., 2017) believes that any approach to a classification of patients with lipedema should take into account its symptoms and functional effects and should be susceptible to the treatment needs and responses. Furthermore, they suggest that the terms "mild", "moderate" or "severe" are more intuitive than stages, and that each degree could, in turn, entail or not the occurrence of lymphedema.

As suggested by the recently published Dutch guidelines on lipedema (Dutch Society for Dermatology and Venereology, 2014), perhaps the ICF (International Classification of Functioning,

Disability and Health, which the WHO uses as a conceptual framework to understand functioning, disability and health) should be applied, like it has been done to assess other chronic pathologies (Halk AB, 2017).

Based on everything that has been said, this CG believes a new classification of lipedema is necessary, taking into account the following elements:

- Localized adiposities in buttocks and thighs that don't affect the rest of the extremity cannot be considered lipedema, although they can coexist with it.
- There are not enough data to claim the existence of lipedema of upper extremities.
- The classification based on skin changes does not distinguish between lipedema and other nosologica entities, like FEP.
- It is necessary to have classifications considering objective clinical data.
- This CG suggests the introduction of clinical quantifiable criteria to classify patients with lipedema, objectifying pain and ecchymosis, among others.

KEY POINTS

- The diagnosis of lipedema is basically clinical and based on anamnesis and physical examination.
- There are basic clinical criteria (see table on page 25: CLINICAL CRITERIA FOR LIPEDEMA).
- In general, no other supplementary diagnostic methods are necessary, except for differential diagnoses.
- There are currently no classifications of lipedema with clinical criteria that may be quantified, and enable an objective analysis of therapeutic results.

CHAPTER III

BIBLIOGRAPHY.

Abbad CM, Rial Horcajo R, Ballesteros Ortega MD, García Madrid C. Guías de Práctica Clínica en Enfermedad Venosa Crónica. ID Médica Ed., 2015.

Allen EV, Hines EA. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic oedema. Proc Staff Mayo Clin 1940; 15: 1984-7.

Álvarez-Fernández LJ, Lozano F, Marinello-Roura J, Masegosa-Medina JA. (2008) Encuesta epidemiológica sobre la insuficiencia venosa crónica en España: Estudio DETECT-IVC 2006.Angiología. 2008; 60:27-36.

Coppel T, Cunnen J, Fetzer S, Gordon K, Hardy D, Jones K, et al. Best practice guidelines: the management of lipoedema [Internet]. London: Wounds UK; 2017. Available from: *http://www.wounds-uk.com/best-practice-statements/best-practice-guidelines-the-management-of-lipoedema*

Chen SG, Hsu SD, Chen, TM, Wang HJ. Painful fat syndrome in a male patient. Br J Plast Surg. 2004;57(3): 282-86.

Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S et al. Lipedema: An inherited condition. Am J Med Genet. 2010; Part A 152A:970–976.

Dutch Society for Dermatology and Venerology. Lipedema guidelines in the Netherlands 2014 [Internet]. Utrecht: NVDV; 2014. Available from: *https://diseasetheycallfat.tv/wp-content/uploads/2015/08/Dutch-lipoedema-guideline-2014.pdf*

Fetzer A, Wise C. Living with lipoedema: reviewing different self-management techniques. Br J Community Nurs. 2015; Suppl Chronic: S14, S16-9.

Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. Adv Skin Wound Care. 2010;23(2)81-92.

Fonder MA, Loveless JW, Lazarus GS. Lipedema, a frequently unrecognized problem. J Am Acad Dermatol 2007;57(2 suppl):S1-S3.

Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. Phlebology. 2017; 32(3):152-159.

Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. Acta Pharmacol Sin.2012;33(2):155-72.

Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol. 2009;161(5): 980-86.

Meier-Vollrath I, Schmeller W. Lipoedema, current status, new perspectives. J Dtsch Dermatol Ges 2004; 2: 181-6.

Meier-Vollrath I, Schneider W, Schmeller W. Das Lipodem: neue Möglichkeiten der Therapie. Schweiz Med Forum 2007; 7: 150-5.

Schingale FJ, (ed.). Lymphoedema, Lipoedema: A Guide for Those Effected. Hannover: Schlütersche, 2003, pp. 64-71

Schmeller W, Meier-Vollrath I. Moderne therapie des lipödems: kombination von konservativen und operativen maßnahmen. Modern therapy in lipedema: Combination of conservative and surgical methods. Lymphol Forsch Prax. 2004; 8:22-6

Smeenge J. Muscle strength and functional exercise capacity in patients with lipedema and obesity: a pilot study [Master thesis] [Internet]. Utrecht: Utrecht University; 2013. Available from: *http://www.milkeninstitute.org/publications/view/846*

Todd M. Diagnosis and management of lipoedema in the community. Br J Community Nurs. 2016; 21(Suppl 10): S6-S12.

CHAPTER IV

SUPPLEMENTARY TEST.

The diagnosis of lipedema is basically clinical and, in general, no supplementary methods are necessary except when lymphedema is suspected, in which case the test of choice would be lymphoscintigraphy (Meier-Vollrath I, Schmeller W, 2004); whereas for Forner-Cordero I (2010) the ultrasound can be considered a first-line supplementary diagnostic technique for edemas of extremities of non-systemic causes.

The different supplementary diagnostic tests and their indication for the study of lipedema will be analyzed.

ANALIYSIS

There are no specific supplementary tests to diagnose lipedema, although laboratory examinations are recommended to rule out associated pathologies that may worsen the symptoms, such as obesity or systemic edema. (Herbst KL, 2012; Coppel T, 2017; Forner-Cordero I, 2012; Dutch Guides, 2014).

Therefore, the following items **will be assessed through blood and urine tests:** hemogram (to rule out anemia that would warrant asthenia or immobility), blood glucose, glycosylated hemoglobin, lipid profile, liver function, thyroid function (to rule out hypothyroidism and subclinical hypothyroidism), urea, creatinine and electrolytes, urinalysis for kidney function, determination of plasma proteins, including albumin and insulinemia.

STREETEN TEST

This test is mentioned in the study by Forner-Cordero I et al. (2012). Prior to carrying it out, conditions like heart and kidney failure and vein insufficiency must be ruled out.

The patient drinks 20 ml of water per kilogram of body weight and remains in an upright position for 4 hours. During this observational period, urine is collected. The volume of each leg is measured before and after the test. Normal healthy subjects excrete more than 60% of the ingested water and the volume of each leg does not increase more than 350 mL/leg.

Pathological results indicate the existence of more permeability of blood capillaries. This test is meant to measure orthostatic edema.

The Streeten test does not provide relevant information for the diagnosis of lipedema.

LYMPHOSCINTIGRAPHY/ISOTOPIC LYMPHOGAMMAGRAPHY (LGG)

It consists of an intradermal or subdermal injection of a macromolecule marked with a radiotracer in the interdigital space of the extremity under study. Then the tracer is followed using a gamma camera. These colloidal particles will spread out in the circulation, based on superficial load and size; small-diameter particles are absorbed by blood capillaries, while larger ones are absorbed by the lymphatic system.

The time required by the radiotracer to appear in the different lymphatic regions depends on the physical characteristics of the colloid used. For instance, human serum albumin marked with technetium 99 can appear in pelvic collections in 10 minutes; however, other agents like rhenium and colloids marked with antimony trisulfide (Sb2S3) may take 30 minutes and an hour, respectively.

The main advantage of LGG is that it enables the functional study of the lymphatic system and diagnosis of lymphedema (Forner-Cordero I, 2010; Sánchez Nevárez MI, 2014), since the qualitative interpretation of the images results in excellent sensitivity (92%) and specificity (100%) to diagnose lymphedema, but it is not useful to distinguish primary from secondary lymphedema (Sánchez Nevárez MI, 2014).

In lipedema, lymphoscintigraphic findings described in the bibliography are different. Bilancini S (1995) describes a delay in lymphatic emptying in patients with lipedema compared to normal subjects. The author cannot explain why findings are asymmetrical, although lipedema is always bilateral and symmetrical.

Br?utigam P (1998) convincingly proves that all the studied patients with pure lipedema (no obesity) showed normal findings in the lymphoscintigraphy with two cameras, after analyzing epifascial and subfascial drainage, and not just drainage asymmetry and visualization of lymph nodes, like in Bilancini's study. Furthermore, he stresses the importance of recognizing that lymphoscintigraphy is not enough to detect differences between normal lymphatic functioning and slight or functional lymphatic alterations. This author also analyzes idiopathic cyclical edema in women attributed to an increase of microvascular permeability with microangiopathy (in the study with electron microscopy), and in general with a positive Streeten test. This Group has shown an increase in the speed of the radiotracer consistent with dynamic lymphatic insufficiency. The author concludes that lymphoscintigraphy is not essential, but it is a useful tool when it is hard to perform a diagnosis.

There are forms of edema where individual etiological components cannot be easily distinguished, so morphological changes described by authors such as Herpetz U (1995) are not necessarily indicative of functional abnormalities, since no alterations in the lymphatic function of pure lipedema have been observed.

This technique has the following limitations:

- Although it may distinguish between different lymphatic failure mechanisms, especially in primary lymphedema, it doesn't necessarily identify a cause for lymphatic obstruction (Sanchez Nevárez MI, 2014; Meier-Vollrath I, 2004).

- Different protocols are described and followed (Williams WH, 2011), which cannot always be reproduced.

- Interpretation may vary based on the molecule used and infiltration route (intradermal, subcutaneous), which could explain the different findings with this technique in lipedema that have been published (Andrade M, 2011).

Therefore, the forms of edema must be clinically defined, and clear diagnostic criteria must be established (Piller N, 2017) before indicating supplementary studies, like lymphoscintigraphy.

Several authors agree that lymphoscintigraphy is important in the diagnosis of lymphedema, but it has variable results for lipedema and other edemas.

The lack of systematization of protocols, as well as ignoring the incidence of asymptomatic primary lymphatic alterations in the general population, are important limitations for the systematic indication of LGG in the diagnosis of lipedema; also, LGG findings may not be interpreted in the same way by the different professionals *(Figure 14)*. Although Forner-Cordero I (2016) makes reference to lymphoscintigraphic alterations in up to 40% of patients with lipedema, these are more common in advanced stages.

Prospective studies in this field should be suggested to unify LGG protocols (colloids and radiotracers used, infiltration technique, dynamic studies, interpretation results, etc.), and assess findings in pure lipedema (not associated with obesity and/or venous insufficiency), female cyclical edemas and the general population.

This CG considers that LGG must be prescribed by the specialist physician when there is suspicion of a lymphatic pathology, or when selecting candidate patients for surgical treatment (liposuction) to rule out coexistence of lymphatic insufficiency.

Figure 14.
Lymphoscintigraphy reported as normal in a patient with lipedema.

IMAGING METHODS

Conventional systems based on X-rays and advanced technologies, like computed tomography (CT) scans, ultrasounds (echographies, Doppler ultrasounds, elastography), magnetic resonance imaging (MRI) and bone densitometry (DEXA), are the most widely used diagnostic means for the study of cutaneous and subcutaneous cellular tissue conditions, especially those related with tumor and circulatory processes.

The DEXA (Dual-Energy X-Ray Absorptiometry) technique, based on the use of low-kilovoltage photons, besides studying bone densitometry, enables to analyze the amount and distribution of body fat in the study of overweight and obesity.

Computed Tomographies (CT) or Magnetic Resonance Imaging (MRI) can help diagnose lymphatic alterations associated with tumor pathologies, or through images characteristic of superficial adipose tissue with a beehive pattern, typical of lymphedema.

Exceptionally, MRIs help analyze body fat distribution and edemas, being the technique of choice for the non-invasive study of arteriovenous and lymphatic malformations. It also provides information about lymph nodes.

ULTRASOUNDS (US)

Ultrasounds (US) used for diagnostic purposes don't have any negative biological effects on the tissues studied, being a non-invasive technique that can be repeated.

Ultrasound-based studies include, among others:

- **Two-Dimensional or B Mode Ultrasound:** Based on the emission and reflection of ultrasound waves through the different tissues, which are transformed in grayscale images.

- **Color Doppler Ultrasound:** Echographies include the analysis of vascular flow through the application of the Doppler effect, which is based on the change in frequency of the US beam as it passes through moving structures, such as blood corpuscles inside vessels; these changes in frequency are proportional to the speed of blood flow at the point studied. It is the diagnostic test of choice for vascular studies, since it allows to obtain anatomical and functional data about the arterial and venous systems. It does not provide information about the lymphatic system.

- **Elastography:** Ultrasound-based diagnostic technique that provides information about the elastic properties of soft tissues. Tissues are subjected to a mechanical vibration and react to these compression waves with a response that can be visualized in a color scale, determining the rigidity degree of the studied tissue (Ophir J, 1991).

Mode B ultrasounds and elastography are non-invasive techniques that allow to study the skin and hypodermis, and are useful for the differential diagnosis of lymphedema and lipedema. These require high-definition ultrasound machines and high-frequency probes (18-22 MHz). The great variability of machines, as well as being operator-dependent, might limit the reproducibility of these techniques.

Color Doppler ultrasound (with 7-12 MHz linear probes) is currently the gold standard for vascular studies, being indicated for edemas of extremities, especially acute edemas with suspicion of deep vein thrombosis, and it also allows to measure fat tissue thickness in the leg.

TWO-DIMENSIONAL OR B MODE ULTRASOUND

High-resolution ultrasound with 18-22 MHz probes enables to study the characteristics of the dermis and subcutaneous cellular tissue, which help to distinguish lipedema from lymphedema. (Suehiro K,2013; Naouri M, 2010).

When performing this test, it is important not to exert any pressure on the patient with the probe, since it notably alters the results. Limitations include the difficulty to reproduce these ultrasound patterns, since they require high-resolution ultrasound machines and great experience.

The use of 7-12 MHz linear probe ultrasound machines enables to quantify fat tissue thickness in the leg, and provide quantitative data on lipedema, although with limitations in obese patients

(Marschall M and Schwahn-Schreiber L, 2011) and the reproducibility of the technique (Asensi V, 2006; Bazzocchi A, 2011).

According to Suehiro K (2013), lipedema shows two types of ultrasound patterns. In the first case, an increase in subcutaneous cellular tissue thickness is observed with hyperechogenicity (prevalent in regions near the ankle), without ultrasound alterations or disruptions in the dermal-hypodermal junction. In the second case, the increase in subcutaneous tissue thickness and hyperechogenicity remain, but there is a fenestrated pattern in the dermal-hypodermal region, which keeps its structure in part without showing similarities to cases of advanced lymphedema. This pattern enables to echogenically differentiate lipedema from obesity, where dermal-hypodermal disruptions are absent.

Lymphedema ultrasound signs described by Naouri M (2010), which help to distinguish it from lipedema, are: increase in dermal thickness, hypoechogenicity of the dermis and loss of definition of the dermal-hypodermal junction.

However, according to Monnin-Delhom ED (2002), the ultrasound of lipedema shows a homogeneous increase in subcutaneous fat without edema or an increase in fibrosis.

Marschall M. and Schwahn-Schreiber L. (2011) suggest classifying the severity of lipedema based on ultrasound criteria. It is the only classification based on ultrasound criteria, providing objective data about the thickness of adipose tissue at infrapatellar level. They suggest 4 degrees based on hypodermis thickness measured by ultrasound in a point located 6-8 cm above the medial malleolus, being skin thickness in healthy subjects of 2.1 mm.

This classification provides objective data that, together with anamnesis and medical history, enable to specify the seriousness of lipedema, and can be used both to follow up and assess the response to treatments.

- 12-15 mm: mild lipedema
- 15-20 mm: moderate lipedema
- >20 mm: severe lipedema
- >30 mm: serious lipedema

Ultrasounds can be considered a first-line, non-invasive diagnostic technique for edemas of extremities of non-systemic causes (Forner-Cordero I, 2010).

However, **it has the following limitations:**

- Variability of the different machines.
- Long learning curve.
- Variability to reproduce the measurements performed, especially at the level of the adipose tissue (Asensi V, 2006; Bazzocchi A, 2011).
- Limitation to diagnose lipedema in obese subjects (Marschall M and Schwahn-Schreiber L, 2011; Reich-Schupke S, 2013), although it might be avoided by determining anthropometric data.

ELASTOGRAPHY

Elastography is an ultrasound method that enables to visualize soft tissue elastic properties, and represents an extension of traditional ultrasound.

The purpose of the technique is to quantify or qualitatively prove the elastic characteristics of tissue under study, caused by deformations induced by the operator's hand (slight compression or vibration). Thus, B mode ultrasounds combined with elastography would provide more information about the existence of fibrosis associated with lymphedema, unlike lipedema *(Figure 15).*

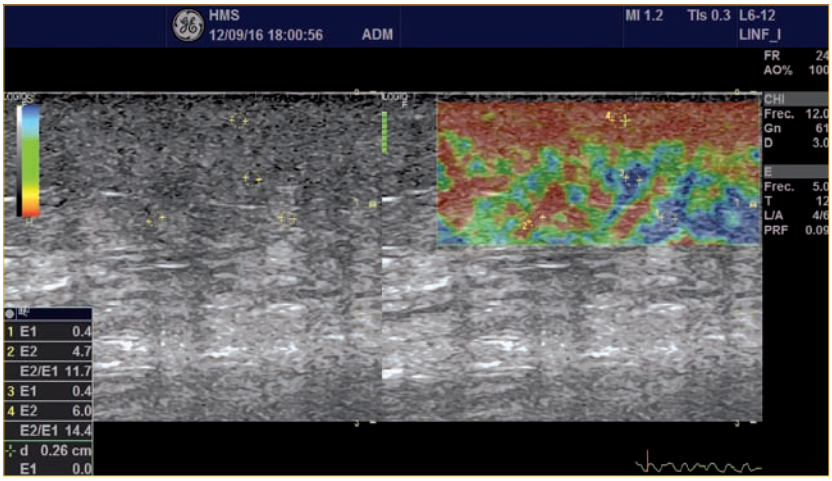


Figure 15.
EElastography of lymphedema. The scale of colors (left) indicates the tissue's degree of elasticity (H: hard [red] and S: soft [blue]), showing areas of subcutaneous fibrosis in red (right)

There are references about the use of elastography on lymphedema (Adriaenssens N, 2012; Onorato A, 2014), but there are no references on lipedema.

Being operator-and machine-dependent, this technique would show the same limitations as ultrasounds, as well as limitations to reproduce the results.

Although there are increasingly more publications about the applicability of elastography, its use as first line of study is still limited by its cost, programs variation and training requirements, although it can provide information for the differential diagnosis of lymphedema and lipedema.

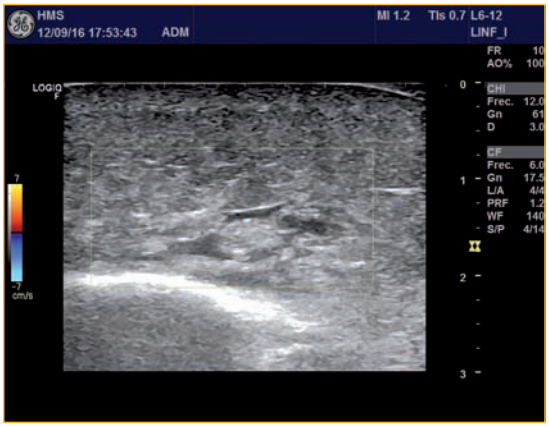
COLOR DOPPLER ULTRASOUND

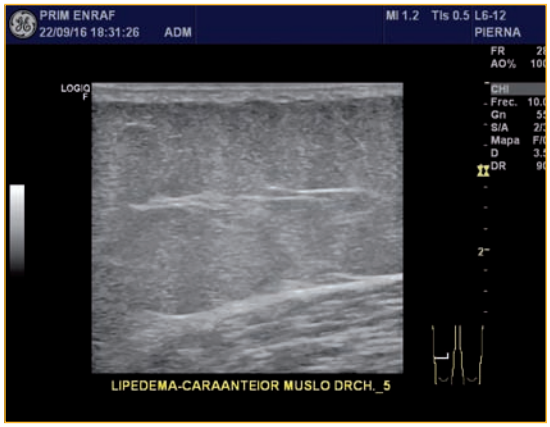
The color Doppler ultrasound is currently the diagnostic test of choice for vascular studies, since it allows to obtain anatomical and functional data about the arterial and venous systems and perivascular tissues; it also enables the study of the thrombus, differential diagnosis between extrinsic compression (cysts, tumors, etc.) and vein thrombosis, the study of edema of the extremities, location of reflux in the superficial and deep venous systems, as well as the study of vascular malformations.

It is performed with 7-12 MHz multifrequency linear probes and study programs for vascular and soft tissues; this configuration allows to study both the vascular system as well as the adipose tissue of the extremities.

Figure 16a shows a pattern of "lymphatic lakes" (hypoechoic structures without blood flow when performing a color Doppler ultrasound) and skin thickening in Grade II lymphedema, whereas *Figure 16b* shows a homogeneous increase in the adipose tissue of the lipedema.

16a





16b

Figures 16a and 16b.
16a: Color Doppler ultrasound of lymphedema "lymphatic lakes" Figure 16b: Ultrasound of lipedema

There is a great variety of machines and programs for arterial and venous vascular studies, and the learning curve is long, so the ultrasound must be performed by personnel with experience in circulatory pathologies.

The color Doppler ultrasound applied to the study of edema of the extremities enables to:

- Rule out arteriovenous vascular malformations and arteriovenous fistulas.

- Rule out deep vein thrombosis: Differentiate between extrinsic venous compression due to cysts or tumors, and vein thrombosis; study the characteristics of the vein thrombus and post-thrombotic sequelae (obstruction and/or deep reflux).

- Study the superficial and perforating venous system, and analyzing the presence and duration of spontaneous and induced reflux.

- Study the lymph nodes, since it is highly sensitive to the detection of increases in nodal size, and useful for pre-operative selection and post-operative control in nodal transposition and venous-lymphatic anastomosis (Sánchez Nevárez MI, 2014).

Together with echographies, Doppler ultrasounds are indicated for the study of edema of the extremities as first-line diagnosis when deep vein thrombosis is suspected, or as a supplementary technique in the differential diagnosis of chronic edema of the extremities when a lipedema-related venous disease is suspected, although this CG suggests to do it regularly to rule out venous reflux due to the high prevalence of this venous pathology in the general population.

COMPUTED TOMOGRAPHY (CT)

LThe evolution of multicut CTs allows to obtain a morphological pattern both of the body surface and of deeper planes, being able to quantify and qualify different areas, from the skin and adipose tissue to the musculoskeletal system. It is an objective, reproducible, operator-independent study to quantify changes at the level of superficial and visceral fat tissue.

It has the following advantages:

- It enables an objective, reproducible, operator-independent study to quantify changes at the level of superficial and visceral fat tissue.

It allows an extended diagnosis of arteriovenous malformations to learn if they affect only skin or they reach deeper planes, being able to plan for a treatment.

However, its limitations include:

- High cost.

- It irradiates the patient, limiting its use as a technique to diagnose lipedema and follow up therapeutical response.

According to Monnin-Delhom ED (2002), computed tomography has a 95% sensitivity and a 100% specificity to diagnose lipedema, where an increase of the adipose tissue with little or no edema has been observed.

Lipedema may show skin thickening, but subcutaneous fluid accumulation, beehive pattern and involvement of muscle compartments are typical of lymphedema, and are not observed in lipedema.

Changes associated with lymphedema are typical and located at skin level, as skin thickening, and in the subcutaneous fat, above the superficial fascia, with thickness increased and typical beehive-pattern images *(Figure 17)*. Muscle involvement is variable, enabling to differentiate lymphedema from other types of edema, like edema associated with vein thrombosis.
In venous edema, extra and intrafascial compartments are involved.

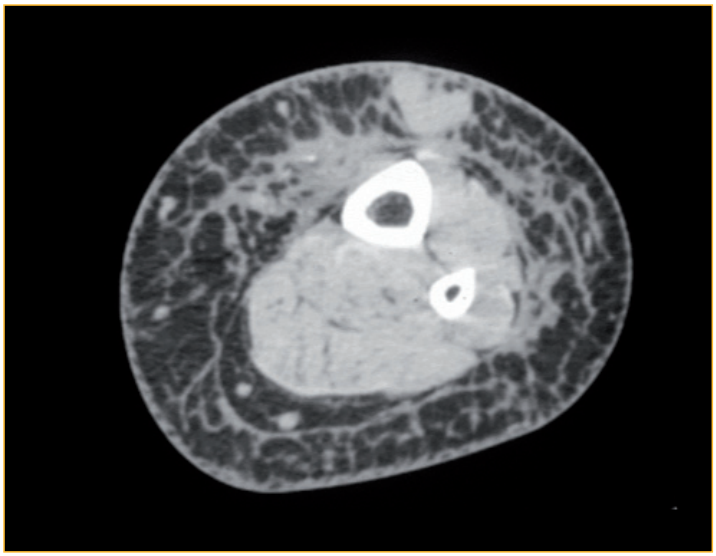


Figure 17.
Computed tomography of lymphedema: Typical "beehive" pattern.
(Image courtesy of Dr. Elisabeth Christol-Delhom. Imagerie m?dicale CHU St. Eloi. France)

CT scans in patients with edema of lower extremities are meant to rule out the presence of any obstructive mass in the abdomen and pelvis that may generate a lymphedema (Sánchez Nevárez M, 2014).

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic Resonance Imaging (MRI) or Nuclear Magnetic Resonance Imaging (NMRI) are non-invasive imaging techniques because they don't use ionizing radiation.

Advantages:

- It enables to assess fat tissue in a non-invasive way by applying a specific sequence for image analysis.

- It specifically differentiates fat from edema by application of T1- and T2-weighted images and fat saturation.

- It doesn't irradiate the patient.

Limitations:

- High cost.

- Inability to study patients with ferromagnetic implants and pacemakers.

- To study superficial adipose tissue and obtain good-quality images, 1.5- or 3-tesla MRI scanners are required, with surface coils that allow to see superficial structures in more detail, limiting its availability to follow up treatment results.

In Monnin-Delhom ED (2002)'s work, no significant differences in the signal's intensity are found between normal extremities and those with lipedema, when T1 and T2 sequences and T1 post-gadolinium are studied. In lipedema, an increase in adipose tissue thickness without evidence of edema is observed.

Findings in lipedema:

- Skin is not thickened.

- There is a homogeneous, symmetrical increase of subcutaneous tissue thickness, without fluid infiltration or muscle involvement *(Figure 18).*

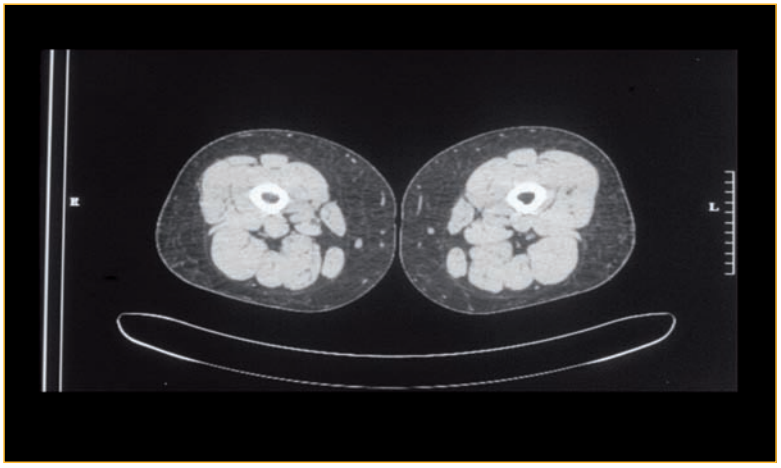


Figure 18.
Magnetic Resonance Imaging of lipedema. Homogeneous increase of adipose tissue without skin thickening (Image courtesy of Dr. Elisabeth Christol-Delhom. Imagerie médicale CHU St. Eloi. France)

Just as in CT scans, lymphedema is shown as a beehive pattern in MRI images. These, which are typical of fluids, are due to the edema, they can be modified through drainage techniques and are consistent with anechogenic findings in ultrasounds *(Figure 19).*

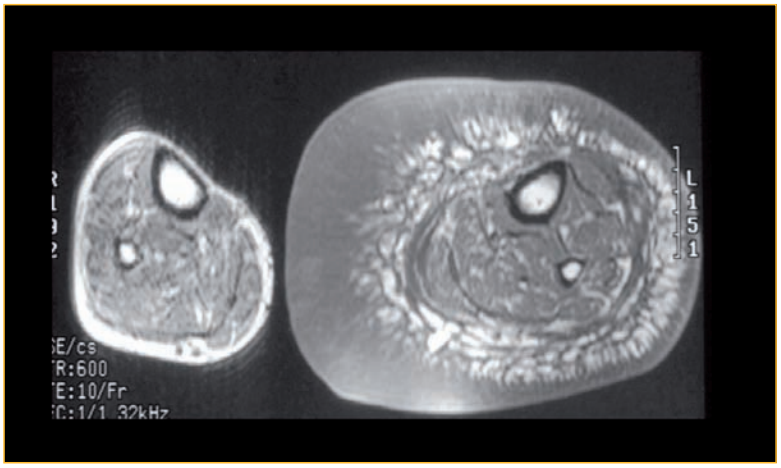


Figure 19.
Magnetic Resonance Imaging of lymphedema: Typical "beehive" pattern. (Image courtesy of Dr. Elisabeth Christol-Delhom. Imagerie médicale CHU St. Eloi. France)

MRIs also enable differential diagnoses with other edemas of the extremities, such as muscle compartment involvement, which is secondary to edema due to vein thrombosis *(Figure 20)*.

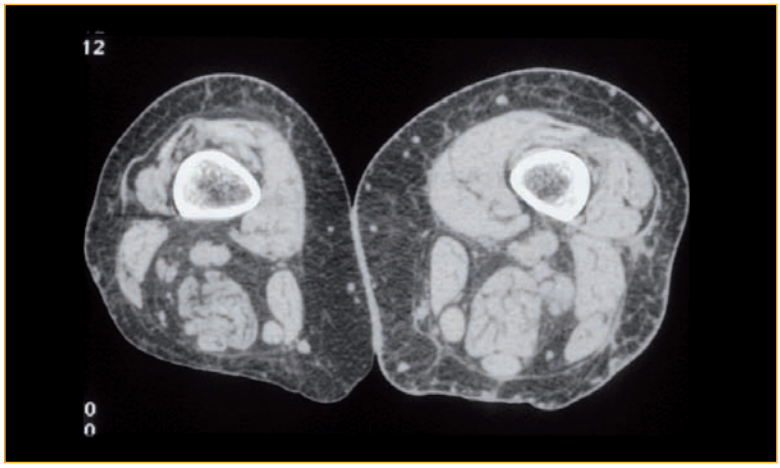


Figure 20.
MRI of deep vein thrombosis (Image courtesy of Dr. Elisabeth Christol-Delhom. Imagerie médicale CHU St. Eloi. France)

A special application of MRIs is the Magnetic Resonance Lymphangiography (MRL) that enables to study superficial lymph circulation in a non-invasive way in case of doubt about the diagnosis.

MRIs main application for the study of edema of lower extremities is to diagnose lymphedema, not being indicated for lipedema except in case of diagnostic doubt, although, as it was mentioned above, it is a non-invasive technique that differentiates well between fat tissue and edema.

OTHER SUPPLEMENTARY DIAGNOSTIC TECHNIQUES

STUDY TECHNIQUES OF LYMPHATIC MICROCIRCULATION

Direct lymphatic surgery to treat lymphedema, such as lymphatic venous anastomosis and lymph node transfer, has led to the use of little-invasive study techniques of lymphatic microcirculation that can provide data on superficial lymph circulation as well as detect abnormalities like dermal reflux (Lee BB, 2013).

One of these techniques is **Indocyanine Green Lymphography for the follow-up of surgical interventions of the lymphatic system, because it is non-invasive and does not use radiation, like in the case of conventional lymphoscintigraphy** (Yamamoto T., 2011; Chang D.W., 2013).

CONTACT THERMOGRAPHY

Microencapsulated liquid cholesterol crystal Contact Thermography enables to detect body temperature changes in the area examined in a simple, quick and convenient manner. These changes are mainly based on circulation changes in the area, so they vary between subjects and based on environmental conditions at the moment of determination. There are also heat-sensitive infrared cameras that can graphically record these findings. The procedure is susceptible to environmental variations and the subjectivity of the observer, limiting the reproducibility of this method *(Figure 21)*.

The most important problem is the environmental variation of temperature, so, to minimize these variations, it is recommended that, before the test, the patient remains at least 20 minutes at rest, preferably lying down, in a room at 22-24 ºC. Images obtained can be assessed using Curri SB (1985)'s thermographical classification of FEP in five stages:

Stage 0: Uniform image. Normal.

Stage I: Spotted image. Edema.

Stage II: Alteration of microcirculation.

Stage III: Areas with micronodules ("leopard skin").

Stage IV: Areas with macronodules ("black holes").

Although there is not a description of thermographic findings typical of lipedema, the author's findings would match the degree of hypothermia described in the clinical signs.

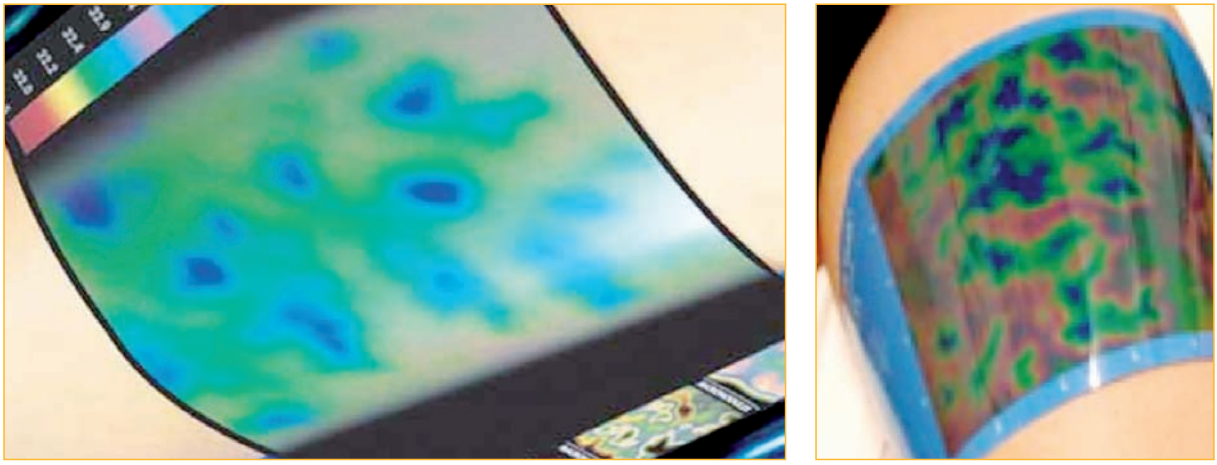


Figure 21. Contact thermography images.
(Taken from Curri SB. Rapporti vasculo-tessutali. In: Ribuffo A, Bartoletti CA, editors. La cellulite. Rome: Salus Int Ed; 1985)

(DUAL ENERGY X-RAY ABSORPTIOMETRY) DEXA

Widely used to calculate bone mass (densitometry), this technique enables to study the whole body and regional distribution (visceral and peripheral) of fat tissue. It correlates well with the anthropometric data.

In the study of obesity, it is mainly used to assess total fat mass of the patient before and after treatment.

The main advantages of this method include low doses of radiation, a study time of about 12-15 minutes for body composition, and good image resolution of the whole body, but its limitations are the cost and, although in low doses, it uses ionizing radiation.

Some authors consider that **this technique is very useful both for the follow-up and therapeutic control of lipedema and lymphedema, since it enables to study changes in the volume of the extremities and their relationship with fat and water variations** (Brorson H, 1998, 2009).

.

DETERMINING BODY COMPOSITION USING BIOIMPEDANCE

To correctly diagnose a patient with overweight/obesity, it is necessary to supplement anthropometric data with a body fat percentage determined using Bioimpedance.

The advantages of this technique include its simplicity, being non-invasive, its reproducibility, no variability between operators and easy application in clinical practice. It enables to obtain reliable values of body composition that can be reproduced (Pérez Miguelsanz MJ, 2010).

Bioimpedance devices use the body's electrical properties to measure the flow of an electric current of very low voltage through it. The technique consists of applying an electric current between two separate points of the body, and measuring its resistance. Resistance is very low in fluids (blood, urine), which means that they are good electrical conductors. Bones and fat show maximum resistance so, when body fat increases, so does resistance.

It is important to keep in mind that these devices don't measure body composition directly, but only estimate it by measuring the current and its modifications when flowing through the body. The analysis of these variations compared to reference patterns in the device's software enables to estimate total body water, fat-free or lean mass, and fat mass in association with the individual's height, weight, age, gender, and race or ethnic origin.

Bioimpedance techniques applied to the study of body composition allows for a more accurate diagnosis of overweight/obesity as well as a follow-up of treatment response.

VOLUMETRIC TECHNIQUES OF THE EXTREMITIES

These techniques are clearly indicated to follow up and quantify lymphedema, and they should be applied to follow up therapeutic responses in lipedema; however, not all are of common use, so this Consensus Group highlights the usefulness of circometry/perimetry to follow up therapeutic results in lipedema, as well as to learn about the different techniques currently available for the study of lymphedema in the extremities, including, among others:

- Volumetry by water displacement of the extremity: It is considered the reference method, but used little in clinical practice because of the "discomfort" to perform i*t (Figure 22).*

- Perimetry by Infrared: It uses infrared light to measure the extremity's outline and estimate its volume. Due to its high cost, use is limited in clinical practice.

- Circometry/perimetry: Since it is simple, harmless and valid, it is the most widely used method in clinical practice *(Figure 23).*

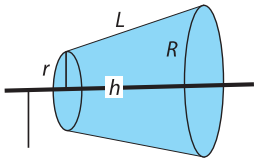
Figure 22.
Volumetric technique by water displacement

CIRCOMETRY/PERIMETRY

It involves the manual measurement of the perimeters of the extremities with a simple measuring tape at 2-4 cm regular intervals, or using anatomical references.

There isn't just one valid measuring way, but the most widely known is that described by Mortimer PS (1990), starting at the cubital styloid, every 4 centimeters, in a proximal direction towards the upper extremity. The external malleolus of the lower extremity can be taken as reference; measurements can be performed every 4-6 cm. This measurement must be taken into account because, when calculating the volume using the truncated cone formula, it will be the "h".

To indirectly measure the volume (V) of the extremities, the truncated cone formula will be used, where "h" is the height of the measured segment, and "C" the different circumferences of the cone. The total volume will be estimated by adding all the segments that are similar to truncated cones.



$$V = h(C_1^2 + C_1C_2 + C_2^2)/12\pi$$

Formula for a truncated cone

When taking measurements, it is important for reference points to always remain the same, so patients' follow-up can be performed, and the evolution of the extremities' volume can be observed.

In unilateral lymphedema, both extremities must be measured: its indicative value is usually determined by a difference of over 2 cm between both legs, or based on the difference in volume shown in milliliters or as a percentage, compared with the healthy contralateral leg.

Furthermore, it is considered lymphedema if excess volume in the extremity involved is greater than 10% compared with the contralateral leg.

Based on the seriousness of the lymphedema (percentage of excess volume of the extremity with lymphedema compared with healthy contralateral leg) the International Society of Lymphology (2003) defines three degrees:

- **Mild:** <20% excess volume of the extremity
- **Moderate:** 20-40% excess volume of the extremity
- **Severe:** >40% excess volume of the extremity

In bilateral lymphedema, these measurement techniques enable to assess volume changes in the extremities after treatment.

These techniques are validated for the diagnosis and follow-up of therapeutic responses in lymphedema, but its indications are not standardized for the diagnosis and follow-up of lipedema.

Figure 23.
Perimetry/circometry technique

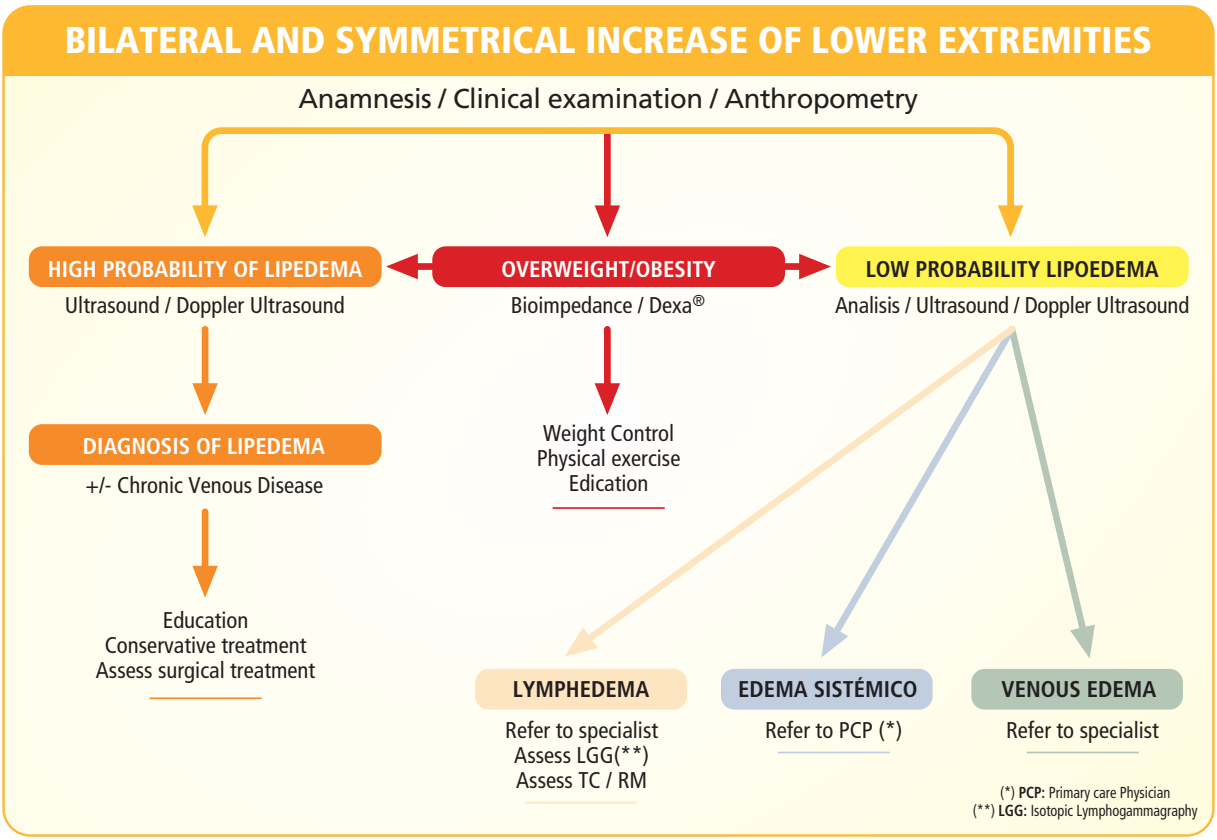


Table 2: Diagnostic algorithm

KEY POINTS

- The diagnosis of lipedema is basically clinical and, in general, no supplementary tests are necessary except when lymphedema is suspected, in which case the diagnosis of choice is by lymphoscintigraphy.
- Imaging methods are not essential, but they can be useful to follow up variations in adipose tissue thickness and in the volume of the extremities in response to treatment.
- The main limitation of supplementary techniques like lymphoscintigraphy, ultrasounds and circometry is their reproducibility.
- MRI's limitation is its high cost, although it would be the diagnostic technique of choice, since it is non-invasive and can distinguish between fat tissue and edema of the extremities using T1- and T2-weighted studies and fat saturation.
- A differential diagnosis to distinguish lipedema from overweight/obesity must be performed using anthropometry, bioimpedance and, if possible, imaging techniques like Dexa®.
- It is important to assess the cost, efficacy and reproducibility of supplementary diagnostic methods in lipedema to analyze the results of the different therapeutic procedures with scientific evidence.
- Ultrasounds and Doppler ultrasounds are first-line, diagnostic techniques for the study of edemas of extremities of non-systemic causes.
- High-resolution ultrasound enables to distinguish lipedema from lymphedema, and determines the seriousness of lipedema based on adipose tissue thickness, being a useful tool for its diagnosis and follow-up.

CHAPTER IV

BIBLIOGRAPHY.

Adriaenssens N, Belsack D. Buyl R. Ruggiero L. Breucq C. De Mey J et al. Research article: Ultrasound elastography as an objective diagnostic measurement tool for lymphoedema of the treated breast in breast cancer patients following breast conserving surgery and radiotherapy. Radiol Oncol. 2012;46(4):284-295

Andrade M. Clinical Diagnosis. General Overview. In: Lee BB, Bergan J, Rockson SG. Editors Lymphedema. A Concise Compendium of Theory and Practice. London. Springer 2011, p.83-88

Arias-Cuadrado A, Álvarez-Vázquez MJ, Martín-Mourelle R, Villarino-Díaz Jiménez C. Clínica, clasificación y estadiaje del linfedema. Rehabilitación (Madr). 2010;44(S1):29-34

Asensi V, Martin-Roces E, Collazos J, Cartón JA, Maradona JA, Alonso A et al. Association between physical and echographic fat thickness assessments and a lipodystrophy grading scale in lipodystrophic HIV patients: practical implications. Aids Res Human Retroviruses. 2006;22(9):830-36

Bazzocchi A. Filonzi G. Ponti F. Sassi C, Salizzoni E, Battista G et al. Accuracy, reproducibility and repeatability of ultrasonography in the assessment of abdominal adiposity. Acad Radiol. 2011;18(9):113-1143

Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. Angiology. 1995;46(4):333-9

Birkballe S, Jensen MR, Noerregaard S,Gottrup F, Karlsmark T.Can tissue dieletric constant measurement aid in differentiating lymphoedema from lipoedema in women with swollen legs? Br J Dermatol. 2014;170(1):96-102

Brautigam P, Földi E, Schaiper I, Krause T, Vanscheidt W, Moser E. Analysis of lymphatic drainage in various forms of leg edema using two compartment lymphoscintigraphy. Lymphology. 1998; 31:43-55

Brorson H, Ohlin K, Olsson G, Karlsson MK. Breast cancer-related chronic arm lymphedema is associated with excess adipose and muscle tissue. Lymphat Res Biol. 2009; 7:3-10

Brorson H, Svensson H, Norrgren K, Thorsson O. Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. Lymphology. 1998;31: 156-172

Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous by pass cases for treatment of extremity lymphedema. Plast. Reconstr. Surg. 2013; 132: 1305-14

Coppel T, Cunnen J, Fetzer S, Gordon K, Hardy D, Jones K, et al. Best practice guidelines: the management of lipoedema [Internet]. London: Wounds UK; 2017. Available from: *http://www.wounds-uk.com/best-practice-statements/best-practice-guidelines-the-management-of-lipoedema*

Czerniec S, Ward L, Refshauge K, Beith J, Lee M, York S, et al. Assessment of breast cancer-related arm lymphedema-comparison of physical measurement methods and self-report. Cancer Investig. 2010;28(1):54-62

Dutch Society for Dermatology and Venerology. Lipedema guidelines in the Netherlands 2014 [Internet]. Utrecht: NVDV; 2014. Available from: https://diseasetheycallfat.tv/wp-content/uploads/2015/08/Dutch-lipoedema-guideline-2014.pdf

Forner-Cordero I., Cuello Villaverde E, Forner Cordero A. Linfedema: Diagnóstico diferencial y pruebas complementarias. Rehabilitación (Madr). 2010;44(S1),14-20

Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis, and treatment of the disproportional fatty deposition syndrome - systematic review. Clin Obes. 2012; 2:86-95

Forner Cordero I, Tortosa Soriano G, Alabajos Cea A, Ponce Garrido AB, Muñoz Langa J. Effect of Compression Alone or Combined with Exercise in Patients with Lipedema. A Pilot Study. Eur. J. Lymph., 2016: 28(74):70

Herbst KL, Rare adipose disorders (RADs) masquerading as obesity. Acta Pharmacol Sin.2012;33(2):155-72

Herpertz U. Das Lipödem. Lymphol. 19 (1995),1-7

International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema. Consensus document of the International Society of Lymphology. Lymphology 2003; 36(2): 84-91)

Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campissi C. et al. Diagnosis and treatment of Primary Lymphedema. Consensus Documento of The International Union of Phlebologu (IUP). Int. Angiol.2013;32(6).541-74

Marshall M, Schwahn-Schreiber L. Prevalence of lipoedema in professional women in Germany (Lipoedema-3-Study). Phlebologie. 2011; 40:27-134

Meier-Vollrath I, Schmeller W. Lipoedema, current status, new perspectives. J Dtsch Dermatol Ges [Internet]. 2004; 2:181-6. Available from:
http://www.lymphasystems.uk/lymphasystems-uk/medical/what-is-lypoedema

Monnin-Delhom ED, Gallix BP, Achard C, Bruel JM, Janbon C. High resolution unenhanced computed tomography in patients with swollen legs. Lymphology. 2002; 35:121-28

Mortimer PS, Investigation and management of lymphoedema. Vascular Medicine. 1990;1(1): 1-20

Naouri M, Samimi M, Atlan M, Perrodeau E, Vallin C, Zakine G, et al. High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. Br J Dermatol. 2010 Aug; 163(2): 296-301

Onorato A. La elastosonografia con tecnica ARFI (acoustic radiation force impulse) per lo studio delle modificazioni dei tessuti epifasciali nel linfedema dell'arto superiore [Tesis doctoral]. Lugar de publicación: Universitá degli Studi di Udine; Udine.2014. https://dspace-uniud.cineca.it/handle/10990/454.

Ophir J, Cepsedes EI, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging, 1991;13:111-134

Pérez Miguelsanz MJ, Cabrera Parra W, Varela Moreiras G, Garaulet M. Distribución regional de la grasa corporal. Uso de técnicas de imagen como herramienta de diagnóstico nutricional. Nutr Hosp. 2010;25(2):207-223

Piller N, Lee BB, Rankin J, Keeley V, Box R. Our interest is swelling — but what's in a name? J Lymphoedema. 2017;12(1):52-5

Reich-Schupke S, Altmeyer P. Stücke M. Thick legs – not always lipedema. J Dtsch Dermatol Ges. 2013 Mar;11(3):225-33

Sánchez Nevárez MI, Valoración médica, diagnóstico y estadificación en. Guía de Práctica Clínica. Orientación Diagnóstica y Terapéutica del linfedema. Puigdellivol C y Alonso B Edimsa. 2014, p.28-30

Suehiro K, Morikage N, Murakami M, Yamashita O, Samura M, Hamano K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. Ann Vasc Dis 2013;6(2):180-8

Williams WH, Ochart M., Bernas MJ. Witte CL. Radionuclide Lymphoscintigraphy. In: Lee BB, Bergan J, Rockson SG. Editors Lymphedema. A Concise Compendium of Theory and Practice. London. Springer 2011, p 145-154

Yamamoto T, Yamamoto N, Doi K, Oshima A, Yoshimatsu H, Todokoro T et al. Indocianine Green (ICG)-enhance lymphography for upper extremity lymphedema: a novel severity staging system using dermal backflow (DB) patterns. Plast. Reconstr. Surg. 2011; 128(4): 941-7

CHAPTER V

CONSERVATIVE TREATMENT.

DRUG TREATMENT

Except for the treatment of pain, the etiopathogeny of which is multifactorial and that will be discussed later in this chapter, no evidence that drug treatments have clinical benefits for lipedema has been found in the studies reviewed.

Although no studies supporting the use of phlebotonics or lymph drugs for lipedema have been published, drug treatments would be appropriate in those cases with associated edema to reduce it, improve its evolution and control its complications. Due to the action of these drugs (increase in venous tone, decrease in capillary permeability and increase in lymph flow), they could also help improve heat-associated heaviness and treat the symptoms of chronic venous disease (Abbad CM, 2015).

The use of diuretics would not be indicated, since there is not a real edema, but an increase in thickness of adipose tissue. The coexistence of edema may be either due to a systemic cause, or to immobility or associated venous or lymphatic insufficiency. In each case, the treatment should be customized and based on the diagnosis.

TREATMENT OF PAIN

Pain is usually triggered by small stimuli, such as pressure over the skin or simple palpation of subcutaneous adipose tissue. Patients usually describe it with mixed characteristics, both nociceptive and neuropathic, and in many cases accompanied by phenomena suggesting peripheral and/or central sensitization manifested as hyperalgesia or allodynia. Lontok E. (2017) associates it with compression of nerve endings or inflammatory phenomena.

An increase in joint pain, especially in knees and hips, has been described in association with poor joint alignment and hypermobility derived from hyperlaxity. Degenerative changes driven by greater weight overload must be taken into account as well (Hodson S, 2013).

Common analgesics are usually prescribed, although patients with clear neuropathic pain, or signs or symptoms indicating an alteration of sensitivity should be treated with specific drugs, like gabapentin.

An appropriate assessment of pain using validated scales is advisable. The questionnaire "Douleur Neuropathique-4" (DN4), validated in Spanish (Pérez R, 2007), has 10 items with descriptions and signs of pain; it is easy to score (each positive item is scored 1), and a total score of 4 or more (over 10) suggests the existence of neuropathic pain ***(SEE ANNEX 3).***

As it will be seen in the appropriate section, liposuction has also shown to be effective to decrease pain (Schmeller W, 2006; Warren AG, 2007).

In the field of aesthetic medicine, the use of mesotherapy/intradermotherapy with authorized drainage medication also temporarily improves pain and heaviness in extremities in patients with lipedema; however, more studies are required to validate this technique.

KEY POINTS

- Due to its lack of characterization, there isn't a specific protocol to treat pain in patients with lipedema.
- It is recommended to properly characterize pain using a validated scale.
- Compression therapy, manual lymphatic drainage, liposuction and specific drugs for pain with neuropathic features have proven to be useful to reduce the pain that is typical of lipedema.
- More studies are required to use scientific evidence for validating the indications of each one of these techniques in the treatment of pain associated with lipedema.

COMPRESSION THERAPY

Compression therapy has shown to be useful to reduce pain when the proper garments are used and patients use them properly (Williams A, 2016). Compression therapy used in combination with Manual Lymphatic Drainage (MLD) is particularly efficient to control pain (Todd M, 2016).

Compression is an active force exerted by external mechanical means with elasticity. Containment is passive and mechanically against an increase in volume associated with muscle contraction. Even though compression is usually mentioned alone, in practice the compression/containment action is inseparable.

Compression therapy includes different modalities::

1. COMPRESSION GARMENTS:

It should be distinguished between:

- Types of garment: Based on the patient's morphology, socks of the leotard kind, or feet-free garments of the leggings kind or knee highs can be used *(Fig. 24* and *Fig. 25)*. In turn, compression garments use different fabrics:

Figure 24.
Compression garment on lipedema: Short flat-fabric sock

Figure 25.
Compression garment on lipedema: Circular-fabric tights

- Types of fabric:

A) Circular fabric. Garments with cylindrical shape that can't be adapted to large deformities. The compression they exert on the ankle must be taken into account, since patients with lipedema are characterized by having an increased fat deposit at the malleolus level, with an abrupt change of volume between the foot and the ankle. For this reason, these garments can produce "cuts" in this area, achieving the opposite effect to the desired one.

B) Flat fabric. The fabric is knitted and sown with a flat seam, enabling its adaptation to large deformities. The fabric is thicker and less elastic than the one used in circular garments, and is visually less aesthetic.

- Degrees of compression:

There are different degrees of compression based on the country that manufactures the garments. To date, it has not been possible to unify the criteria across Europe.

Below, there is a table with pressures from different countries (Clark M, 2016) (Table 3).
The most widely used in Spain is the German standard.

	British standard BS 6612:1985	French standard ASQUAL	German standard RAL-GZ 387:2000
Evaluation method	**HARTRA**	**IFTH**	**HOYS**
Class I	14-17 mmHg	10-15 mmHg	18-21 mmHg
Class II	18-24 mmHg	15-20 mmHg	23-32 mmHg
Class III	25-35 mmHg	20-36 mmHg	34-46 mmHg
Class IV	No descrita	>36 mmHg	>49 mmHg

Table 3.
Degrees of compression in different countries (taken from Clark M, Krimmel G, 2006).

It is important to re-emphasize that treatments with compression garments won't result in a decrease of adipose tissue thickness.

The prescription of compression garments for lipedema will be personalized, since their use is not considered necessary in all cases. Not every woman with lipedema can be "locked" in a compression garment if there is no associated edema, since in this case the purpose is to contain it and prevent its progression.

It is important to take into account the difficulty to use this garments, since putting them on is not easy, less so for obese individuals with little flexibility who rely on others for their personal hygiene. In these cases, one solution may be to use velcro adjustable garments.

The use of compression garments is recommended at least when doing exercise (Hardy D, 2015; Forner-Cordero I, 2016), if taking a long trip by plane, for people with jobs requiring to be a long time on their feet, and with associated orthostatic, venous and/or lymphatic edema.

Rejecting the use of compression garments is a disadvantage for maintaining the treatment results. A high percentage of patients discontinue treatment due to apparent lack of clinical improvement or even worsening of the symptoms, or due to incorrect adaptation of the garment to their needs, because they chose the wrong size or degree of compression.

In many cases, a more flexible strategy is advisable, initially using a minor compression and, once the patient has adhered to treatment, increasing it to an effective level of compression.

Different practical recommendations concerning the use of elastic socks have been described:

- Make sure the garment is well adapted, with no folds, especially in knees and ankles. Carry out practical demonstrations about putting on the compression garment while monitoring the patient.

- Inform the patient about aiding devices to put the garment on.

- Warn the patient about clinical signs or symptoms to be aware of to remove the compression garment, such as in case of pain, paresthesia or dysesthesia, or alterations in the color of the extremity.

- Make the patient aware of the benefits of elastic support to control lipedema, such as improvement of symptoms and mobility, although decrease in volume is not achieved.

- Explain the cares that the compression garment needs per the manufacturer's recommendations.

- Evaluate time of revision and re-assessment of the type of garment, such as replacement, adaptation of the degree of compression or type of garment, among others.

There is currently no evidence that compression therapy may prevent the risk of suffering associated lymphatic insufficiency (Fonder MA, 2007; Langendoen SI, 2009; Todd M, 2010).

This Consensus Group agrees with authors such as Reich-Schupke S. (2017) and Coppel T. (2017) on the fact that compression therapy for lipedema is indicated to:

- Reduce pain.

- Improve comfort. Patients feel more comfortable when wearing the socks because of the support feeling.

- Help to slightly remodel the extremities and improve mobility.

- Contain a possible associated edema.

Compression therapy has contraindications that should be assessed prior to prescribing a compression garment. It is essential to check that no arteries are compromised, and that there is absence of acute heart failure, skin ulcerations, peripheral neuropathies or associated neurological disease and/or severe distortion of the form of the extremity, preventing the correct adjustment and adaptation of the garment.

Indications of the degrees of compression

Based on the class of compression (mmHg), and always prescribed by a doctor according to each patient, the following may be some of the indications for garments:

- Class 1 (15-23 mmHg): mild venous insufficiency (tired legs), incipient varicosis during pregnancy, prevention of orthostatic edema, prevention of lymphedema (Stage 0/1).

- Class 2 (24-33 mmHg): moderate venous insufficiency with trunk varicose veins, post-surgery of varicose veins, post-sclerotherapy, prevention of deep vein thrombosis, lymphedema (Stage 1/2), post-liposuction.

- Class 3 (34-46 mmHg): severe venous insufficiency with trophic skin changes, post-thrombotic edema and lymphedema (Stage 2/3) in lower extremities.

- Class 4 (over 49 mmHg): venous ulcer, severe lymphedema in lower extremities.

2. COMPRESSION BANDAGE:

It is not indicated for lipedema, except there is an associated lymphatic component, in which case the use of inelastic bandages associated with complex decongestive therapy (CDT) will be necessary *(Figure 26)*.

Figure 26. *Multi-layer bandaging of lymphedema*

3. VELCRO ADJUSTABLE GARMENTS

They can be used as therapy in the reduction phase, or as a maintenance measure to treat associated lymphedema.

4. INTERMITTENT PNEUMATIC PRESSOTHERAPY

This therapy, which uses pneumatic compression boots, will be discussed later.

KEY POINTS

- Compression does not decrease fat tissue.
- Compression therapy is indicated for orthostatic edema, venous insufficiency or lymphedema associated with lipedema.
- It is also used because it improves pain, supports tissues and helps to remodel the extremities.

DIET AND NUTRITION

According to estimates by the **World Health Organization (2017),** overweight and obesity have increased worldwide: in 2016, 39% of adults 18 years of age or older (39% of men and 40% of women) were overweight, and 13% were obese.

In Spain, obesity in adults has a prevalence of 18% in women and of 13% in men. In individuals over 65 years old, it affects 31% of men and 40% of women. Obesity in Spanish children and young individuals is one of the highest in Europe (16% of boys and 12% of girls).

In Spain, morbid obesity has increased from 1.8 in 1000 residents to 6.1 in 1000 residents in 2006 (Spanish Society of Cardiology). This represents 1% of the population (in the U.S., morbid obesity affects 5-6% of the population). Women are the most affected by morbid obesity (6.8 in 1000 women and 5.4 in 1000 men).

The etiology of obesity includes genetic and environmental factors, but actions will be taken mainly to control the latter, since severe hypocaloric diets prevent or reverse obesity even in individuals with genetic predisposition. The number of adipocytes is fixed during childhood and adolescence, and it is higher in obese than thin subjects. About 10% of adipocytes are renewed each year.

Overweight/obesity is defined as an increase in the body's energy reserves in the form of fat with an increase in adipose tissue.

Based on BMI, it is considered overweight when: IMC ≥25 kg/m^2, and obesity when IMC ≥30 kg/m^2.

The diagnosis will be performed by means of: interviews, physical examinations, anthropometry (determination of height, weight, Body Mass Index (BMI), waist and hip measurements), bioimpedance techniques, imaging techniques (basically ultrasounds and DEXA) and analyses.

It is important to determine body fat distribution based on the waist-to-hip ratio (WHR):

- Android or central adiposity (visceral and extra-visceral): It is associated with co-morbidities (hypertension, type II diabetes cardiovascular and oncological risks)

WHR >1.0 (male) and >0.9 (female)

- Gynoid or peripheral adiposity: It can be associated with circulation disorders (venous, lymphatic), skin alterations (contact areas) and the dynamic of walking.

WHR <1.0 (male) and <0.9 (female)

Therefore, the diagnosis and treatment of overweight/obesity is important for patients with lipedema. Both factors aggravate the condition and may lead to psychosocial problems, so they must be treated.

Patients with lipedema that maintain a normal weight and exercise regularly show fewer symptoms, better functional capacity and fewer complications than patients who don't (Coppel T, 2017).

To maintain body weight, it is essential to balance food intake and energy expenditure (represented by baseline metabolism, thermogenesis and physical activity).

It is important to consider that energy expenditure varies based on age, gender and/or body fat percentage, factors that will have to be taken into account when prescribing treatment and especially during maintenance. Physical activity, including exercise programs and daily activities (walking, climbing stairs, shopping, maintaining body posture, etc.), is highly variable between individuals.

The goals of overweight/obesity treatments are:

- **Medical:** Avoid co-morbidities and their deleterious effects on health.
- **Social:** Improve quality of life and self-esteem.

The treatment of overweight/obesity is well systematized and includes:

• **Diet:** Energy intake must be reduced based on each individual (age, gender, fat mass percentage) until reaching a negative energy balance, so the body can get the energy it needs to function from fat deposits. This is accomplished with a hypocaloric diet or special, customized diets, such as a high-protein diet or Very Low-Calorie Diet (VLCD).
Obesity is a chronic process, so diets will be planned for the long term.

Even though dieting mainly reduces abdominal fat deposits, there is a reduction effect in total body volume and fat mass, including the extremities with lipedema, although this decrease in volume is less than in the lower half of the body so, to normalize the volume of the lower extremities, supplementary treatments may be required once normal weight has been reached and maintained.

• **Exercise:** The benefits of exercising in general will be analyzed in detail, supplementing the practice of physical exercise programs with an increase in physical daily activities.

• **Drug treatment:** Drug treatments are indicated with moderate hypocaloric diets in patients with obesity (BMI ≥30) or overweight (BMI ≥27-30), showing at least one weight-related co-morbidity. Orally-administered Orlistat is a specific inhibitor of gastrointestinal lipases preventing fat hydrolysis. Liraglutide is an injectable glucagon-like peptide-1 analogue —GLP-1— that binds with, and activates, the receptor, powering glucose-dependent insulin secretion in pancreatic ß cells, indicated for type II diabetes and the treatment of obesity. Naltrexone 16 mg/Bupropion 360 mg (Mysimba®): Naltrexone is an opioid receptor antagonist, and bupropion is a weak inhibitor of dopamine and norepinephrine neuronal reuptake with central action. FDA-approved, but not available in Spain at the moment: 7.5 mg Phentermine/46 mg Topiramate (oral); 10 mg Lorcaserin.

• **Surgical techniques:** For the treatment of morbid obesity, where patients' psychological stability and long-term commitment are essential. It includes techniques such as bariatric surgery (gastric bypass) and restrictive (adjustable gastric banding, tubular gastrectomy) or endoscopic techniques such as intragastric balloon.

KEY POINTS

- Overweight and obesity are frequently associated with lipedema and constitute aggravating factors that worsen mobility, favor osteoarticular complications and affect patients' quality of life and self-esteem.
- It is essential to rule out overweight/obesity in patients with lipedema through anamnesis, physical examinations, anthropometry techniques (determination of height, weight, Body Mass Index (BMI), waist and hip measurements) and blood tests (to rule out co-morbidities).
- Patients with lipedema should always be treated for overweight/obesity to reduce associated complications.
- It is suggested to perform bioimpedance techniques because they provide data on body water and fat percentages, and their changes after treatment.
- Imaging techniques (Dexa®, ultrasounds, etc.) provide additional data about the location of fat (visceral and superficial) and enable to follow up and objectify the results of the treatment.
- Patients with lipedema that maintain a normal weight and exercise regularly show fewer symptoms, better functional capacity and fewer complications than patients who don't.

REHABILITATION THERAPY: PHYSICAL THERAPY AND EXERCISE

The goals of the conservative treatment must be focused on reducing pain, improving mobility, managing obesity, preventing secondary joint issues, minimizing the impact on the ability to perform daily activities, improving the appearance of the extremities and promoting self-care (Coppel T, 2017).

The terms used worldwide to talk about conservative therapies in the context of lipedema are: "Complex Physical Therapy" (CPT), "Complex Decongestive Therapy" (CDT; most used) or "Complex Decongestive Physical Therapy". When applied to patients with lymphedema, it is also called "Lymphedema Decongestive Therapy" (LDT).

CDT consists of a group of therapies indicated for the treatment of edema. It includes manual lymphatic drainage (MLD), compression therapy and containment with garments, bandages or intermittent pneumatic pressotherapy, posture cares and specific exercises, as well as skin cares to prevent infections.

CDT has been considered for many years as the treatment of choice for lipedema. However, when this therapy is applied to reduce leg volume in patients that show no edema-associated components, it usually fails, being also inefficient even in some patients with edema, caused by a combination of mechanical and dynamic insufficiency without involvement of the lymphatic system (Langendoen SI, 2009; Dutch Guides, 2014).

Patients with lipedema-associated obesity need to know that, to obtain good results from treatment, they should lose weight, increase physical activity and begin the Decongestive Therapy all at the same time.

If there were walking and arch support alterations, these should also be corrected to improve the walking dynamic.

MLD is a very specific type of massage that must be performed by specialized physical therapists, and which is designed to improve physiological drainage by stimulating the activity of the lymphatic vessels and eliminating excess fluid and macromolecules of tissues (Torres M, 2006).

Other effects that can be attributed to MLD are reduction of inflammation and relief of symptoms such as pain. Its analgesic effect can be explained by the soft pressure of the drainage maneuvers (normally below 70 mmHg), and the repetition and slowness of the movements that stimulate skin's mechanical-receptors and activate the pain-inhibitory neurons through a "Control Gate".

Furthermore, it has a regulating effect of the autonomous nervous system, decreasing the activity of the sympathetic nervous system and therefore increasing that of the parasympathetic nervous system. This effect creates a feeling of wellbeing in the patient because he/she relaxes, reducing stress, anxiety, and heart and breathing rates (Johansson K,1999, Williams AF,2002, Williams A, 2010).

Because of the effects described above, MLD, combined with compression therapy, is useful to treat pain in lipedema, and when associated with other pathologies, such as lymphedema, orthostatic edema or venous insufficiency.

Some patients even feel psychological benefits produced by relaxation, and mention an improvement of their quality of life (Ekici G, 2009; Hammer JB, 2007; Kim SJ, 2009; Szolnoky G, 2008; Todd M, 2016; Weiss JM, 2002). There is evidence of pain reduction (Level 1c) and improvement of physical function (Level 4c) (Haesler E, 2016).

MLD is not the best treatment for a "pure" lipedema, since its application will never reduce fat nor modify the volume or shape of the lower extremities.

Many times this therapy is offered with false expectations; however, the benefits that patients with associated pathologies get are important, specially to reduce pain, as it is reflected in the articles mentioned above.

MLD contraindications: Acute infections, failure or decompensation signs of congestive heart failure, suspicion of concomitant malignant disease or tumor relapse. This last one is not completely consensual, although more recent studies seem to rule out that it increases the possibility of disease spread (Godette K, 2006).

The treatment of obesity, as well as the correction of other factors, such as osteoarticular disorders and poor arch support, should be approached simultaneously to CDT.

KEY POINTS

- CDT and MLD are not indicated to reduce the volume of the extremities in lipedema when this is associated with edema.
- Compression therapy-related MLD can improve capillary fragility, and reduce pain and discomfort in patients.
- CDT is useful when lipedema shows a lymphatic component.
- The treatment of obesity, as well as the correction of other factors, such as osteoarticular disorders and poor arch support, should be approached prior or simultaneously to CDT.

PHYSICAL ACTIVITY, EXERCISE AND SPORTS

One of the most important recommendations to have good health is physical activity, but patients with lipedema require a precise indication about how to plan and regulate physical exercise, or practice some sports, whether for fun or to compete.

The areas affected by lipedema do not decrease in volume with physical exercise, although it can help to maintain weight and improve patients' quality of life (Salmon P, 2001; Penedo, FJ, 2005; Todd M, 2016; International Society of Lymphology, 2013; Fetzer A, 2015).

There is controversy about the indication and benefits of exercising in lipedema. Current evidence is in many cases clinical, criteria are not unanimous, and therefore more scientific studies are needed in this field.

It would be desirable for patients to achieve the following goals:

- Improve their general health, self-esteem and quality of life.
- Maintain their weight. If they are overweight/obese, they should be treated with a diet. It is important to re-emphasize that, without a proper diet, the patient won't lose weight or fat just by exercising.
- Gain strength and muscle resistance, mainly in lower extremities, and favor mobility.
- Prevent circulatory, joint and muscle problems.

To reach these goals, it is recommended to:

- Gradually do low- or moderate-impact aerobic exercise. High-intensity or high-impact exercise and contact sports are not usually the most beneficial; they can worsen the signs and symptoms of articular degeneration and pain.

- Practice sports with moderation.

- Don't do sports that increase pain or hematomas (like contact sports).

- Do any type of cardiovascular fitness training.

- Try to activate large muscle groups. It is more advisable than working isolated groups. That is, do exercises that involve contracting all muscles possible, e.g. do squats instead of just knee bends.

- Train with other people (Irwin BC, 2012). It has been proven that individuals who exercise with others perform better and increase adherence, thus increasing their confidence to solve problems related with self-image and other psychological aspects.

There is currently controversy about the need to wear compression garments during exercise. More studies are required to confirm the advantage of using them, since some patients say that they restrict their movements or are uncomfortable for exercising (Cormie P, 2013); furthermore, there is little evidence of its benefits.

Despite this, most experts still consider it advisable to wear them, especially if there is an associated edema: patients can remove them if they make exercising difficult, but they need to put them back on after exercising and during the rest of the day.

Some practical recommendations to follow:

- Walking or Nordic walking. Several scientific studies support the greater benefits of Nordic walking over walking, since speed is increased, therefore raising cardiovascular fitness, accelerating metabolism, improving motion, flexibility, strength and resistance (Church SC, 2002; Porcari JP, 1997; Schiffer T, 2006; Takeshima MM, 2013; Tschentscher M, 2013).

In obese women, Nordic walking elevates the intensity of the exercise and adherence to the training program without increasing the perception of effort (Figard-Fabre H, 2011). Therefore, it can be stated that it is more effective to walk with canes by properly using the technique. There are increasingly more studies supporting the benefits of Nordic walking for different pathologies, such as intermittent claudication, cardiac diseases, fibromyalgia, Parkinson, sport injuries and/or chronic back pain.

- Functional exercises. They improve muscle tone and strengthen the trunk and extremities in untrained individuals. Some examples are: hypopressive abdominal gymnastics, Pilates and body consciousness exercises, proprioception circuits on stable and unstable planes, functional workout using external or your own weight for resistance. It is preferable to have a 3/5 muscle balance (based on Daniels scale, Grade 3 means full range of articular motion against gravity), and they are appropriate to prepare for other sports.

- Water exercise. Activities like aquagym, walking in a pool, swimming, using resistance materials or movement aids with fins. Water physical properties reduce stress on joints and pain, increase cardiovascular fitness and strength, and favor mobility (Baum G, 1998; Tsourlou T, 2006; Grosse SJ, 2009; Petrick M, 2001; Sevimli D, 2015; Volaklis K, 2007).

In patients with associated circulatory problems (lymphedema, venous insufficiency), water exercises and immersion itself make them feel light and free due to stimulation of the venous and lymphatic circulation by hydrostatic pressure (Di Prampero PE, 1986). Furthermore, if practiced regularly, they can decrease pain, as mentioned in the consensus document of the International Society of Lymphology (2013).

- Bicycle (stationary, touring or mountain). The sitting position frees the lower extremities from weight and the joints from stress, making movements easy. It increases cardiovascular fitness, helps build muscles in trunk and legs, and increases balance, resistance and bone density (Oja P, 2011).

- Sports like yoga, Pilates and others combining different ways of muscle fitness, which is led, controlled

and coordinated by breathing (Hagner-Derengowska M, 2015). These disciplines share muscle strength and stretching principles, as well as focus and a body-mind connection. Thus, besides the physical benefit, they also affect the psychological aspect by generating a feeling of wellbeing.

All exercises are performed following different breathing types/patterns, which make the exercise easy, protect structures, prevent injuries and increase focus. Deep, isolated breathing is also advisable, since it increases the concentration of oxygen reaching the tissues, and increases lymph flow, contributing to potential volume loss in the extremities when there is lymphostasis (Mortimer PS, 1990; Todd M, 2016).

There is controversy about the results from exercise revisions concerning the decrease in BMI, but these are consistent with positive results in studies performed on sedentary women. Mazzarino M (2015) shows that the Pilates method can reduce pain, and improve quality of life and resistance of the lower extremities.

Regarding yoga, although some publications mention its benefits for patients with overweight and abdominal adiposity (Cramer H, 2016), in a systematic review by Lauche R (2016), no positive effects on weight loss, body mass index, body fat percentage or waist circumference were found.

KEY POINTS

- More scientific studies are required about the practice of physical exercise because, although there is clinical evidence of its benefit, criteria are not unanimous.
- Physical activity improve the quality of life and self-esteem of patients with lipedema.
- It enables to gain strength and muscle resistance, and favors mobility.
- It helps to prevent circulation, joint and muscle alterations.
- Exercising without following a proper diet is not enough to lose weight or fat.
- Physical exercise does not reduce on its own the volume of lower extremities with lipedema.

NON-SURGICAL TECHNIQUES FOR BODY CONTOURING TREATMENTS

These techniques are commonly used in aesthetic medicine and can be applied in patients with pure lipedema, or when it occurs in association with overweight/obesity, FEP, localized adiposities, symptoms of leg heaviness, orthostatic edema or chronic venous edema.

They include the use of physical therapies or infiltration techniques.

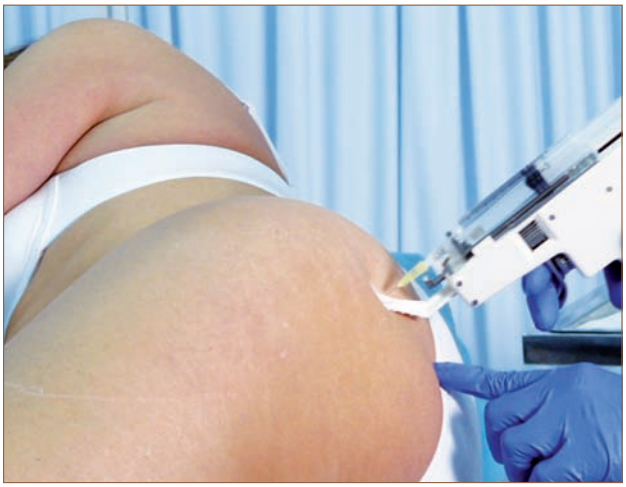
MESOTHERAPY / INTRADERMOTHERAPY

As a medical technique, mesotherapy was developed in Europe in 1952 by a French doctor called Michel Pistor. At first it was indicated for the treatment of pain and circulation disorders by infiltration of locoregional procaine. From the 70s, several studies are carried out establishing a specific pharmacokinetics of the intradermal route (Herreros FO, 2011; Ordiz García I, 2016).

Ordiz Garc?a (2012) defines the term 'mesotherapy' as: "The therapeutic action obtained when applied on the superficial papillary dermis (derived from the mesoderm), causing a double effect: pharmacological (drug-dependent) and mechanical-reflex (dependent on the action of the needle)."

More recently, the Italian Society of Mesotherapy has proposed a consensus to establish a series of recommendations for what they call "intradermal therapy" or "intradermotherapy", mentioning that, despite its therapeutic benefits, more studies should be carried out (Mammucari M, 2011). The term "intradermotherapy" is currently considered more appropriate. It can be performed manually or with the use of electronic devices (mesotherapy aids or "mesotherapy guns") *(Figure 27).*

27a



27b

Figures 27a and 27b. *Infiltration technique (mesotherapy/intradermotherapy). Manual (27a) and assisted (27b) technique.*

It is a widely used medical procedure in aesthetic medicine, as well as in other medical areas such as traumatology, rehabilitation, rheumatology, sports medicine or dermatology, although there are no scientific studies validating the technique and its indication for clinical cases as different as alopecia or the treatment of pain.

Mesotherapy/intradermotherapy is indicated for the treatment of the following aesthetic pathologies of the lower extremities: all stages of FEP when associated with weight-loss treatments; localized adiposities; supplementary treatment of idiopathic or chronic venous edema, and tired legs.

In lipedema, it causes temporary improvement of the symptoms of pain and leg heaviness, but without reducing the volume. It is evident that more studies are required to validate this technique.

INFILTRATION TECHNIQUES FOR SUPERFICIAL ADIPOSE TISSUE

(sodium deoxycholate, hypo-osmolar hydrolipoclasia):

Other infiltration techniques for the treatment of localized fat use solutions, such as sodium deoxycholate or hypo-osmolar substances (hypo-osmolar hydrolipoclasia). These are indicated to treat localized adiposities when adipose tissue has a thickness of 1.5 cm or more. Sodium deoxycholate causes panniculitis and fat necrosis, while hydrolipoclasia produces lipolysis. Unlike mesotherapy/intradermotherapy techniques, these must be infiltrated to a depth greater than 6 mm.

Although these are commonly used techniques in the field of aesthetic medicine to treat localized adiposities in abdomen, flanks, hips and knees, no studies have been published about their indication and safety for the treatment of lipedema.

CARBOXYTHERAPY

Carboxytherapy involves the subcutaneous or intradermal administration of carbon dioxide (CO2). Its most well-known effects are: capillary vasodilation, decrease in the affinity of hemoglobin to oxygen, which is transferred more easily to tissues, and activation of ß-adrenergic receptors of the adipocyte with lipolytic action.

Carboxytherapy is a commonly used technique in aesthetic medicine to treat body contouring alterations, such as skin flaccidity in thighs, arms and abdomen, localized adiposities, and all stages of FEP. There are no references to its application for the treatment of lipedema, although in FEP it reduces localized fat, especially in the area of the thighs and hips, and improves "orange peel" (Georgia SK, 2010).

Adverse effects, inherent to the treatment itself, include pain or burning sensation, subcutaneous emphysema and ecchymosis. CO2 has not toxicities and metabolizes through the lungs and kidney. Its safety profile is very high because, due to its high solubility, it has a low embolizing risk.

Commonly used doses in aesthetic medicine (30-50 ml/minute/session) are easily compensated by slight hyperventilation, and there is no hypercapnoea or acidosis in normal subjects.

ULTRASOUNDS (US). SHOCK WAVES

The 20th century brought about the application of several techniques from physical medicine (use of electric currents or electrotherapy, iontophoresis, ultrasounds) that remained, and even increased, in the 21st century, with the development of new applications and extending the use of others (ultrasounds, radiofrequency) to the medical field. Most of these techniques are used in physical therapy and rehabilitation.

While thermal effects prevail in high-frequency US (1-3 MHz), which are frequently used in physical therapy, low-frequency US (30-50 Hz), also known as cavitation, usually have a dominant mechanical effect and act at a larger depth. Experimental studies show that low- and high-frequency ultrasounds have a lipolytic action (Silva Gon?alves WL, 2009; Miwa H, 2002; Insua Nipoti E, 2013) on the adipose tissue, but also compact the stroma (Insua Nipoti E, 2013).

There are no specific studies on lipedema, but a reduction in the thickness of adipose tissue and improvement of "orange peel" at the bitrochanteric and abdominal levels of localized fat have been observed (Insua Nipoti E, 2013).

Shock waves are sound waves (ultrasounds), characterized by high-pressure amplitude in relation to environmental pressure; these waves move through the medium, producing extrem

pressure differences and an increase in temperature. To be used with medical purposes, sound waves are generated outside the body and introduced in it without affecting the skin, since acoustic waves travel following acoustic-optic laws.

The use of shock waves is indicated for the treatment of kidney stones and several bone and soft-tissue pathologies of the musculoskeletal system. They are contraindicated in skin infections, bone tumors, metastasis, pacemakers, pregnancy, children in growth phase and coagulopathies.
Since 2005, they began to be used in aesthetic medicine with effects on flaccidity, FEP and localized adiposities (Russe-Wilflingseder K, 2013).

Shock waves cause hyperemization through vasodilator effects, favor the formation of ATP (adenosine) at the level of the muscle, stimulating the neoformation of muscle fibers, and reinforces muscles, reducing muscle flaccidity. They have also been attributed with a stimulating effect on lipolysis, although it has not been proven yet.

In his work, Siems W (2005) shows that the use of shock waves would decrease oxidative stress, measured by blood tests, in patients with lipedema and/or FEP. However, there are no later works available or protocols validating their use in lipedema, so more studies are necessary to assess their efficacy.

ELECTROMAGNETIC RADIATION (EM): LASER, RADIOFREQUENCY, INFRARED

Radiation is a source of energy transmitted through space, without the need of direct contact between the emission source and the area applied. Radiation produces an electromagnetic field that can penetrate tissues, causing a thermal effect. Electromagnetic radiation for aesthetic purposes includes: radiofrequency, infrared (with a superficial thermal effect that causes vasodilation and increases microcirculation) and lasers.
These techniques are used in aesthetic medicine for the treatment of body contouring alterations, such as FEP, flaccidity, localized adiposities or adiposities related to weight-loss treatments.

Low laser level therapy (LLLT) has been recently introduced for the treatment of localized adiposities (Gold MH, 2011; Jackson RF, 2013) but no protocols are available for lipedema. However, being a "cold" laser, LLLT therapy might be indicated in lipedema, intended for biostimulation and biomodulation of tissues, although more studies are required to support it.

It should be noted that, within percutaneous laser therapy (not associated with liposuction techniques), an FDA-approved laser that creates localized heat at the level of superficial fat has been recently developed to treat localized adiposities (Decorato JW, 2017). Due to its characteristics, this technique would be contraindicated in lipedema when there is concomitant venous and/or lymphatic insufficiency.

The same happens with radiofrequency or infrared, since they cause local heating effects. However, this type of technique is indicated for the treatment of localized adiposities, especially in the gluteal-femoral area, and improves the appearance of "orange peel" (Goldberg DJ, 2008; Van Der Lugt C, 2009; de la Casa Almeida M, 2014).

PRESSOTHERAPY

Negative-pressure devices have an accessory (suction pad or rollers) that is plugged-in in a vacuum-producer mechanism. They are effective in every stage of FEP, where an improvement of "orange peel", skin smoothing and reduction in the thickness of localized fat, especially at the bitrochanteric level, are observed.

Positive-pressure devices (intermittent pneumatic pressotherapy) use compressors that insert air at a certain pressure in compartments that are specially designed to fit the extremities. The most widely used are pneumatic boots with several compartments that allow the pressure to advance in a distal to proximal direction, in a cyclical way *(Figure 28).*

28a   28b

Figuras 28a and 28b.
Sequential pneumatic pressotherapy device (pressotherapy boots)

Positive pressotherapy acts on the veins and the interstitial compartment, making venous return and fluid drainage easy. It doesn't drain the proteins accumulated in the interstitial space, and no effect on fat tissue has been proven either, therefore it's not indicated for lipedema, except if associated with venous and/or lymphatic edema.

It is mainly indicated for chronic venous edema and post-operative edema. It has been suggested that it favors the reabsorption of edemas and hematomas after liposuction (Zaleska M, 2015; Chardonneau JM, 2007).

It is contraindicated in the presence of neoplastic lesions, infections, skin trophic lesions, acute deep vein thrombosis and systemic edema, and it must be used with caution in uncontrolled hypertensive patients.

THERMAL THERAPY/CRYOTHERAPY TECHNIQUES

They involve applying cold and/or heat to treat body contouring alterations.

Thermal therapy or application of heat: Local application of heat is used in the supplementary treatment of overweight, fibrous FEP and localized adiposities.

In aesthetics, applying heat includes: using heating creams, saunas, sweat blankets, paraffin, ultrasounds, infrared, electrotherapy and thermal hydrotherapy.

Due to its heating effect, these therapies are contraindicated in venous and/or lymphatic alterations as well as in lipedema, since heat can worsen the symptoms.

Cryotherapy or application of cold: This technique is used to treat chronic venous edema, tired legs, FEP and flaccidity; it uses substances that lower skin temperature by contact (gels, cold bandages, cold baths, etc.), and must be differentiated from other techniques that use cold, such as cryolipolysis, intended for the treatment of localized adiposities.

Cryolipolysis uses equipment made by a suction system that keeps the temperature below 0 ?C during the entire application. After the FDA's approval for the treatment of localized adiposities in the flanks (Manstein D, 2008; Coleman SR, 2009), new applications for localized fat in abdomen and double chin have been introduced, but their use in lipedema is not known.

KEY POINTS

- There are no prospective studies comparing the results from different non-surgical techniques to reduce the thickness of adipose tissue and improve "orange peel".
- Most publications refer to the treatment of FEP and localized adiposities in the abdomen, flanks and gluteal-femoral area with improvement of volume and "orange peel", although without support from scientific evidence.
- There are no publications on the use of mesotherapy/intradermotherapy to treat lipedema. Although clinical practice points at pain relief without changes in volume, scientific studies are required to validate this technique.
- The application of non-invasive techniques with lipolytic purposes and to improve the stroma might have a place in the therapeutic protocols of lipedema, although the experiences of the members of this Group are consistent with the fact that most of these techniques relieve the pain of the extremities, but barely reduce their volume.
- The purpose of non-surgical treatments is to improve body contouring and, although they don't offer final results, they are a good complement of thinning techniques.

CHAPTER V

BIBLIOGRAPHY.

Abbad CM, Rial Horcajo R, Ballesteros Ortega MD, García Madrid C. Guías de Práctica Clínica en Enfermedad Venosa Crónica. ID Médica Ed., 2015

Baum G: Aquarobics: The Training Manual New York: WB Saunders; 1998

Clark M, Krimmel G. Lymphoedema and the construction and classification of compression hosiery. In: Lymphoedema Framework. Template for Practice: compression hosiery in lymphoedema. London: MEP Ltd; 2006

Coleman SR, Sachdeva K, Egbert BM, Preciado J, Allison J. Clinical efficacy of noninvasivecryolipolysis and its effects on peripheral nerves. Aesthetic Plast Surg. 2009 jul; 33(4):482-8

Coppel T, Cunnen J, Fetzer S, Gordon K, Hardy D, Jones K, et al. Best practice guidelines: the management of lipoedema [Internet]. London: Wounds UK; 2017. Available from: *http://www.wounds-uk.com/best-practice-statements/best-practice-guidelines-the-management-of-lipoedema*

Cormie P, Pumpa K, Galvao DA, Turner E, Spry N, Saunders C et al. Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: A randomised controlled trial [with consumer summary]. J Cancer Survivorship [Internet]. 2013;7:413-24. Available from: *https://www.ons.org/content/cormie2-lymphedema-weight-2013*

Cramer H, Thoms MS, Anheyer D, Lauche R, Dobos G. Yoga in Women With Abdominal Obesity. A randomized controlled trial. Dtsch Arztebl Int 2016; 113(39): 645-52; DOI: 10.3238/arztebl.2016.0645. Available from: *https://www.aerzteblatt.de/int/archive/article?id=182667*

Chardonneau JM. La compression pneumatique intermittente: un atout pour les lourdeurs de jambe. Phlebologie 2007; 60:139–42

Church SC, Earnest CP, Morss GM. Field testing of physiological responses associated with Nordic Walking. Res Q Exerc Sport [Internet]. 2002; 73:296-300

Decorato JW, Chen B, Sierra R. Subcutaneous adipose tissue response to a non-invasive hyperthermic treatment using a 1060 nm laser. Lasers in Surgery and Medicine,2017, 49(5), 480-9

de la Casa Almeida M, Suarez Serrano C, Medrano Sanchez EM, Diaz Mohedo E, Chamorro Moriana G, Rebollo Salas M. The efficacy of capacitive radio-frequency diathermy in reducing buttock and posterior thigh cellulite measured through the cellulite severity scale. J Cosmet Laser Ther. England; 2014 Oct;16(5):214–24

Di Prampero PE. The energy cost of human locomotion on land and in water. Int J Sports Med [Internet]. 1986;7(2):55–72

Dutch Society for Dermatology and Venerology. Lipedema guidelines in the Netherlands 2014 [Internet]. Utrecht: NVDV; 2014. Available from: https://diseasetheycallfat.tv/wp-content/uploads/2015/08/Dutch-lipoedema-guideline-2014.pdf

Ekici G, Akbayrak T, Yuksel I. Comparison of manual lymph drainage therapy and connective tissue massage in women with fibromyalgia: a randomized controlled trial. J Manipulative. Physiol Ther. 2009;32(2):127-33.

EzureT, Amano S. Increased subcutaneous adipose tissue impairs dermal function in diet-induced obese mice. ExpDermatol. 2010;19(10):878.-82

Fetzer A, Wise C. Living with lipoedema: reviewing different self-management techniques. Br J Community Nurs. 2015; Suppl Chronic: S14, S16-9

Figard-Fabre H, Fabre N, Leonardi A, Schena F. Efficacy of Nordic walking in obesity management. Int J Sports Med [Internet]. 2011; 32:407-17

Fonder MA, Loveless JW, Lazarus GS Lipedema, a frecuently unrecognized problem. J Am Acad Dermatol.2007;57(2):S1-S3

Forner-Cordero I, Tortosa Soriano G, Alabajos Cea A, Ponce Garrido AB, Muñoz Langa J. Effect of Compression Alone or Combined with Exercise in Patients with Lipedema. A Pilot Study. Eur. J. Lymph., 2016: 28(74):70

Georgia S K Lee. Carbon dioxide therapy in the treatment of cellulite: an audit of clinical practice. Aesthetic PlastSurg 2010; 34: 239-243

Godette K, Mondry TE, Johnstone PA. Can manual treatment of lymphedema promote metástasis?. J SocIntegr Oncol. 2006;4(1):8-12.

Gold MH, Khatri KA, Hails K, Weiss RA, Fournier N. Reduction in thigh circumference and improvement in the appearance of cellulite with dual-wavelength, low-level Láser energy and massage. J CosmetLáserTher 2011; 13: 13—20

Goldberg D J, Fazeli A, Berlin AL. Clinical, laboratory, and MRI analysis of cellulite treatment with a unipolar radiofrequency device. Dermatol Surg 2008; 34: 204—209

Grosse SJ. Aquatics for individuals with disabilities: research implications.Int J Aquatic Res Edu [Internet]. 2009;12(3):422. Available from:
http://www.humankinetics.com/acucustom/sitename/Documents/DocumentItem/17511.pdf

Güleç AT. Treatment of cellulite with LPG endermologie. Int J Dermatol 2009; 48: 265-270

Haesler E. Evidence Summary: Single modality treatment of lymphoedema: Manual lymphatic drainage.Wound Practice and Research. 2015;14(2):116-118

Hagner-Derengowska M, Kaluzny K. Kochanski, B. Hagner W. Borkowska A. Czamara, A. et al. Effects of Nordic Walking and Pilates exercise programs on blood glucose and lipid profile in overweight and obese postmenopausal women in an experimental, nonrandomized, open-label, prospective controlled trial.Menopause [Internet]. 2015;22(11):1215-23. Available from: *https://insights.ovid.com/pubmed?pmid=25803666*

Hamner JB, Fleming MD. Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer. Ann SurgOncol. 2007;14(6):1904-8

Hardy D. Compression Garments, friend or foe? Presentation at Lipoedema UK Conference & AGM, Reading, UK, 26 June 2015.

Hardy D, Williams A. Best practice guideline for the management of lipoedema. Br J Community Nurs. 2017 Oct 1;22(Sup10): S44-S48. doi: 10.12968/bjcn.

Harvie M, Howell A. The 2-Day Diet: The Quick & Easy Edition: The. Original, Bestselling 5:2 Diet. Vermilion, Reading. BMJ Case Rep 2014, pii: bcr2013009538. doi:10.1136/bcr-. 2013-009538.

Herreros FO, Moraes AM, Velho PE. Mesotherapy: a bibliographical review. An Bras Dermatol [Internet]. 2011; 86(1):96-101

Hodson S, Eaton S. Lipoedema management: gaps in our knowledge. J Lymphoedema. 2013; 8(1): 30-4

Insua Nipoti EM. Técnicas de lipoclasia y sus aplicaciones en el tratamiento del panículo adiposo superficial. Resultados a nivel clínico y experimental". [Tesis doctoral] [Internet]. Madrid: Universidad Autónoma de Madrid; 2013. Available from:
https://www.educacion.gob.es/teseo/mostrarRef.do?ref=1074768

International Society of Lymphology (ISL). The diagnosis and treatment of peripheral lymphedema: Consensus Document of the International Society of Lymphology. Lymphology [Internet]. 2013;46(1):1-11. Available from: *https://www.ncbi.nlm.nih.gov/pubmed/23930436*

Irwin BC, Scorniaenchi J, Kerr NL, Eisenmann JC, Feltz DL. Aerobic exercise is promoted when individual performance affects the group: a test of the Kohler motivation gain effect. Ann Behav Med [Internet]. 2012; 44(2):151–9. doi:10.1007/ s12160-012-9367-4

Jackson RF, Roche GC, Shanks SC. A double-blind, placebo-controlled randomized trial evaluating the ability of low-level laser therapy to improve the appearance of cellulite. Lasers Surg Med. United States; 2013 Mar;45(3):141–7.

Johansson K, Albertsson M, Ingvar C, Ekdahl C. Effects of compression bandagingwith or without manual lymph drainage treatment in patientswithpost-operative arm lymphedema. Lymphology 1999; 32(3): 103–10. Available from: *https://journals.uair.arizona.edu/index.php/lymph/article/viewFile/17363/17142*

Kim SJ, Kwon OY, Yi CH. Effects of manual lymph drainage on cardiac autonomic tone in healthy subjects.Int J Neurosci. 2009; 119(8):1105-17

Langendoen SI, Habbema L, Nijsten TEC, Neumann HAM Lipoedema: from clinical presentation to therapy. A review of the literature. Br J Dermatol. 2009;161(5): 980-86

Lauche R, Langhorst J, Lee MS, Dobos G, Cramer,H. A systematic review and meta-analysis on the effects of yoga on weight-related outcomes. Prev Med [Internet]. 2016; 87:213-232

Lontok E, Briggs L, Donlan M, Kim Y, Mosley E, Riley EAU, et al. Lipoedema: a giving smarter guide. Milken Institute; 2017 Santa Monica (CA), USA

Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson RR. Selective cryolysis: a novel method of non- invasive fat removal. Lasers Surg Med. 2008; 40:595–604.

Mammucari M, Gatti A, Maggiori S, Bartoletti CA, Sabato F. Mesotherapy, definition, rationale and clinical role: a consensus report from the Italian Society of Mesotherapy. Eur Rev Med Pharmacol Sci. 2011; 15(6): 682-694.

Mazzarino M, Kerr D, Wajswelner H, Morris ME. Pilates method for women's health: Systematic review of randomized controlled trials. Arch Phys Med Rehabil [Internet]. 2015;96(12):2231-42

Miwa H, Kino M, Han LK, Takaoka K, Tsujita T, Furuhata H. Effect of ultrasound application on fat mobilization. Pathophysiology [Internet]. 2002;9(1):13

Mortimer PS. Investigation and management of lymphoedema. Vascular Medicine. 1990;1(1): 1-20

Oja P, Titze S, Bauman A, de Geus B, Krenn P, Reger-Nash et al. . Health benefits of cycling: a systematic review. Scand J Med Sci Sports [Internet]. 2011;21(4):496-509

Ordiz García I. Mesoterapia en las alteraciones estéticas del entorno corporal. En: Fernández-Tresguerres JA. Madrid: Panamericana; 2012. p. 507-14

Ordiz García I. Vías transdérmicas de administración de fármacos. [Tesis doctoral]. [Internet]. Universidad de Oviedo; Oviedo. 2016. Available from: *https://www.educacion.gob.es/teseo/mostrarRef.do?ref=1276689*

Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current opinion in psychiatry 2005; 18(2), 189-193

Perez R, Galvez S, Huelbes J, Insausti D, Bouhassira S, Diaz S, Rejas J. Validity and reliability of the Spanish version of the DN4 (DouleurNeuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component Health QualLife Outcomes [Internet]2007; 5:66. Available from: *http://doi.org/10.1186/1477-7525-5-66*

Petrick M, Paulsen T, George J. Comparison between quadriceps muscle strengthening on land and in water. Physiotherapy [Internet]. 2001; 87:310–317

Porcari JP, Hendrikson, TL, Walter PR, Terry L, Walsko, G. The physiological responses to walking with and without Power Poles on treadmill exercise. Res Q Exerc Sport [Internet]. 1997; 68:161-66

Reich-Schupke S, Altmeyer P, Stücke M. Thick legs – not always lipedema. J DtschDermatolGes. 2013 Mar;11(3):225-33

Russe-Wilflingseder K, Russe E, Vester JC, Haller G, Novak P, Krotz A. Placebo controlled, prospectively randomized, double-blinded study for the investigation of the effectiveness and safety of the acoustic wave therapy (AWT(R) for cellulite treatment. J Cosmet Laser Ther. England; 2013 Jun;15(3):155–62

Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. Clinical psychology review 2001; 21(1), 33-61.

Schiffer T, Knicker A, Hoffman U, Harwig B, Hollmann W, Struder, HK. Physiological responses to Nordic walking,walking and jogging. Eur J ApplPhysiol [Internet]. 2006; 98:56-61.

Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. J Cutan Med Surg. 2006; 10:7-10

Sevimli D, Kozanoglu E, Guzel R, Doganay A. (The effects of aquatic, isometric strength-stretching and aerobic exercise on physical and psychological parameters of female patients with fibromyalgia syndrome. J PhysTherSci [Internet]. 2015;27(6):1781-6

Siems W, Grune T, Voss P, Brenke R. Anti- fibroesclerotic effects of shock wave therapy in lipedema and cellulite. Biofactors [Internet]. 2005; 24(1-4):275-82.

Silva Gonçalves WL. Bernardes Graceli J. Lyrio Santos R. Cicilini MA, Bissoli NS, Abreu GR. Ultrasound lipoclasia on subcutaneous adipose tissue to produce acute hyperglycemia and enhanced acute inflammatory response in healthy female rats. Dermatol. Surg [Internet]. 2009; 35(11):1741-1745

Szolnoky G, Nagy N, Kovács RK, Dósa-Rácz E. A. Szabó, K. Bársony, et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. Lymphology. 2008; 41:161-166

Takeshima N, Islam MM, Rogers ME, Rogers NL, Sengoku N, Koizumi D et al. Effects of nordic walking compared to conventional walking and band-based resistance exercise on fitness in older adults. J Sport Sci Med [Internet]. 2013;12(3):422

Todd M. Diagnosis and management of lipoedema in the community. Br J Community Nurs. 2016; 21(Suppl 10): S6-S12

Torres M. Drenaje linfático manual. En: Torres M, Salvat I, editores. Guía de maspterapiaparafisioterapeutas. Madrid: MédicaPanamericana; 2006. p. 239-67

Tschentscher M, Niederseer D, Niebauer J. Health benefits of Nordic walking: a systematic review. Am J Prev Med [Internet]. 2013; 44:76-84

Tsourlou T, Benik A, Dipla K, Zafeiridis A, Kellis S. The effects of a twenty-four weeks aquatic training progam on muscular strength performance in healthy elderly women. J Strength Cond Res [Internet]. 2006; 20(4):811–18

Van Der Lugt C, Romero C, Ancona D, Al-Zarouni M, Perera J, Trelles MA. A multicenter study of cellulite treatment with a variable emission radio frequency system. Dermatol Ther 2009; 22:74—84

Volaklis K, Spassis AT, Tokmakidis SP. Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness. Am Heart J [Internet]. 2007; 154(3): 560.e1-560.e6. Available from: *http://dx.doi.org/10.1016/j.ahj.2007.06.029*

Warren AG, Janz BA, Borud LJ, Slavin SA. Evaluation and management of the fat leg syndrome. PlastReconstrSurg 2007;119: 9e-15e

Weiss JM, Spray BJ. The effect of complete decongestive therapy on the quality of life of patients with peripheral lymphedema.Lymphology [Internet]. 2002;35(2):46-58.

Williams A. Manual lymphatic drainage: exploring the history and evidence base.Br J Community Nurs 2010;15: Sup3, S18-S24 Available from:
https://www.magonlinelibrary.com/doi/pdfplus/10.12968/bjcn.2010.15.Sup3.47365

Williams A, MacEwan I. Accurate diagnosis and self-care support for women with lipoedema. Pract Nurs 2016; 27(7):325-32

Williams AF, Vadgama A, Franks P, Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. Eur J Cancer Care 2002; 11(2): 254–61

Zaleska M, Olszewski WL, Kazmarek M. The effects of three-years pneumatic compression of postinflammatory and posttraumatic edema of lower limbs. Eur J Lymphol 2015; 26:39

CHAPTER VI

SURGICAL TREATMENT.

In the last decade, the surgical treatment of lipedema has become the only **definitive option for these patients;** it is described in clinical guidelines and protocols and must be performed by a plastic surgeon. The main objective is to reduce the fat compartment by decreasing the circumference and volume of the extremities.

The surgical treatment of lipedema can be performed at any time, and it is particularly indicated in those patients who do not respond properly to conservative treatment (Schmeller W, 2014).

LIPOSUCTION

It is the least invasive method to eliminate subcutaneous fat tissue, and the treatment of choice for those patients without co-morbidities who do not respond to conservative treatment (Schmeller W, 2014, Dadras M, 2017) *(Figure 29).*

Results obtained in the longitudinal study carried out by Dadras M (2017) corroborate the results from authors like Rapprich S, (2011), Schmeller W, (2012) and the recent long-term study by Baumgartner A (2016), which show that liposuction is a safe, effective treatment for lipedema, with good long-term results and few complications.

Figure 29. *Removal of liposuction fat*

Prior to undergoing surgery, **weight must be normalized,** and it is important that patients adhere to the conservative treatment because it is not appropriate to suggest a liposuction if the patient is not willing to **follow a proper pre- and post-operative treatment.**

Prior to surgical treatment, associated aggravating factors such as edema, obesity, unhealthy lifestyle or lack of physical activity must be corrected.

TYPES OF LIPOSUCTION

1. Tumescent: A solution containing saline, anesthetics and adrenaline is injected in the subcutaneous space to turn the area tumescent. Saline produces hydrodissection, which separates fat cells from the septa of the connective tissue. Adrenaline reduces the bleeding. *(Figure 30).*

2. Super Tumescent: A larger amount of solution is injected in the subcutaneous space.

3. Water-Assisted Liposuction (WAL): The amount of solution injected is lower, and a modified cannula is used, allowing to inject the solution and simultaneously aspirate fat cells, directly removing them from the connective tissue (Stutz J, 2009).

4. Vibroliposuction: This power-assisted technique is a type of liposuction that uses a vibration cannula. Invented by Malak, it was called vibroliposuction (Rebelo, A., 2006). The use of this technique combined with super tumescent infiltration is a safe and efficient method to treat lipedema. (Schmeller W, 2006; Klein JA, 1987; Illouz, YG, 1989; Sattler G, 2002, Habbema L, 2009; Fife CE, 2010; Forner-Cordero I, 2012; Rapprich S, 2011).

Any one of the types mentioned above can be used to treat lipedema (Hoffmann JN, 2004).

Laser or ultrasonic liposuction produces heat, so it must be avoided because there is a bigger risk of concomitant lymphatic damage.

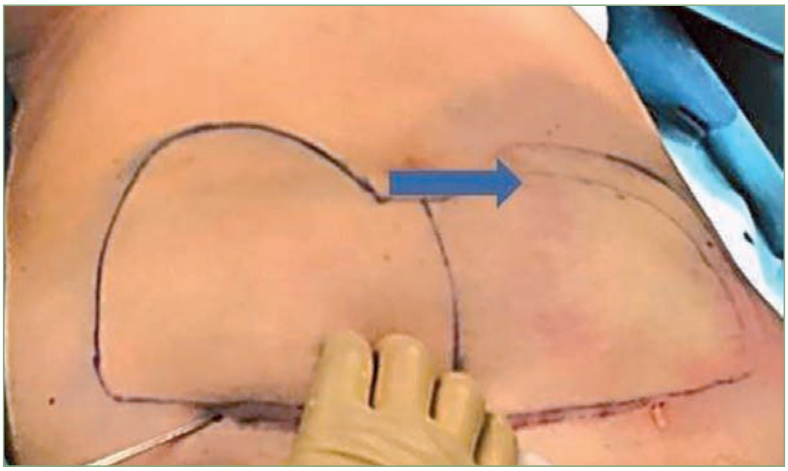


Figure 30. *Tumescent infiltration*

LIPOSUCTION TECHNIQUES

In lipoaspiration, small incisions are performed in the skin to insert the cannula. These incisions measure 2-4 mm and are made in the most appropriate locations for fat removal.

In lipedema, the liposuction technique is different from conventional techniques. Thinner, more blunt cannulas are used, and lipoaspiration must follow an axial or longitudinal pattern, not transversal like it's common in traditional liposuction. The goal is to minimize potential lesions of the superficial lymphatic system (Mladick R, 1990).

A perfect anatomical knowledge and right execution of the technique are essential to reduce the possibility of complications in areas as specific as ankles and knees (Frick A, 1999).

It is a sequential treatment because, to obtain satisfactory results and meet the safety criteria, an average of 2-3 interventions must be performed, with a variable range of 1-6.

RESULTS

In lipedema, not only liposuction reduces the volume of fat in the affected areas (Rapprich S, 2011), but it also reduces pain, spontaneous hematomas and edema, decreases pressure sensitivity and improves mobility, which translates into a better quality of life.

These changes remain stable throughout the parameters in the long term, like some studies have shown (Schmeller W, 2012, 2014; Peled AW, 2012, Dadras M, 2017). However, it is necessary to carry out post-operative cares and long-term controls, like maintain the weight, exercise and follow healthy habits. Authors like Schmeller W (2006 y 2012) also recommend to keep the conservative treatment.

It has been proven that liposuction using the tumescent technique is a safe and appropriate procedure to treat lipedema (Habbema L, 2009).

It is important that these results can be objectively quantified. Pre- and post-operative digital pictures can help to do this. Methods such as ultrasounds or MRIs allow to obtain measurable values. High-resolution ultrasounds are particularly useful as precise diagnostic, measuring and follow-up techniques. It is an efficient, low-cost method that enables to assess changes in subcutaneous tissue thickness after surgery (Whittle P, 2004).

Hormone variations, weight modifications or discontinuation of the maintenance treatment may cause new accumulations of fat in areas that were subjected to liposuction.

DERMOLIPECTOMY

This surgical treatment involves the removal of large localized deposits of lipedematous tissue. These deposits cause serious mechanical difficulties, or even complete inability to walk.

Despite liposuction's less invasive approach, there are cases of important mechanical limitations, where removal by longitudinal excision may be the only treatment (Miller TA, 1998, Wollina U, 2014).

In excisional dermolipectomy, incisions are longer, significantly less cosmetic, and more likely to cause complications.

PREOPERATIVE ASSESSMENT AND TREATMENT

It is important to properly select the patients with lipedema before performing any surgery, to minimize the risks and get the best functional and aesthetic results.

In general, patients must follow a conservative treatment for 6-8 months before undergoing surgery (Dadras M, 2017), based on the clinical guidelines established, for example, by Lontok E (2017), although these cares must be indicated based on each case.

Prior to surgical treatment, it is necessary to:

- Rule out co-morbidities increasing anesthetic and surgical risks.

- Control weight, including when bariatric surgery has been prescribed for morbid obese individuals prior to liposuction and/or dermolipectomy (Coppel T, 2017)

• Have a good emotional control. It is essential to enjoy a balanced psychological and mental state prior to a surgical treatment, since this is a long process often requiring several surgical interventions.

• Analyze skin characteristics to explain the possible need of post-liposuction surgeries to remove excess skin tissue.

• Get the patient to commit to use compression garments in a post-operative setting.

• Create realistic expectations about the possible results.

It is suggested to do the following tests prior to surgery:

• Measuring of the extremities involved (perimetry, **ANNEX 2**).

• Ultrasound

• Visual analog scale for pain (**ANNEX 4**).

• Body Mass Index (BMI).

• Record of the activity (METS, **ANNEX 6**).

• Quality of Life Scale SF36 (**ANNEX 5**).

• Lymphogammagraphy (LGG)

• Indocyanine Green Lymphography to visualize the superficial lymphatic system. For this, 0.2 ml of indocyanine green contrast agent is intradermally injected between the toes. The pattern of lymphatic distribution is visualized with a camera. This is the most sensitive test for the premature detection of lymphatic alterations (Burnier P, 2017). Contrast dermal extravasation is a sign of alteration of the superficial lymphatic system *(Figure 31).*

It is important to confirm the presence or absence of lymphedematous components (Buck DW, 2016; Warren Peled A, 2016) because the results obtained may vary, especially if a specific post-operative treatment guideline is discontinued in case of concomitant lymphedema. The presence of lymphedema is not a contraindication to perform a liposuction, but long-term results are more uncertain. In this group of patients, post-operative CDT is of special importance.

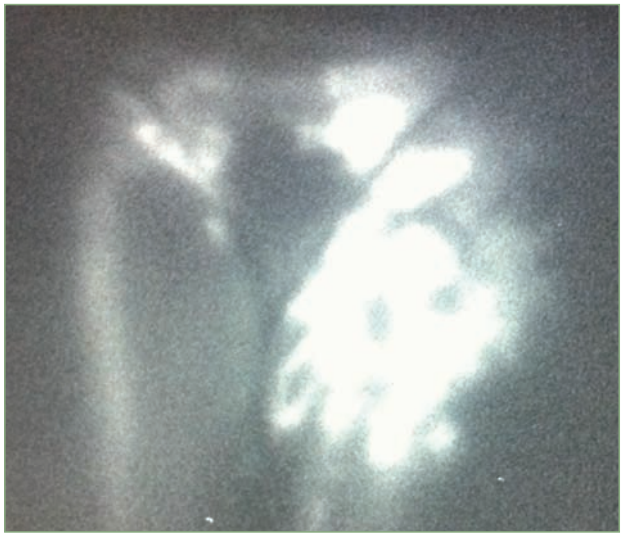


Figure 31.
Indocyanine green dermal extravasation as a sign of alteration of the superficial lymphatic system

POST-OPERATIVE CARE

During the first 4 or 5 days after the intervention, patients often need crutches to walk.

For at least 6 weeks, they must wear a circular compression garment. Later, the most appropriate compression socks for each patient will be prescribed. Compression socks must be changed every 6 months (Halk AB, 2017; Reich-Schupke S, 2017).

One week after surgery, rehabilitation treatment can begin, taking into account that premature movements of the skin can cause seromas, undesirable adherence to underlying structures, skin folds and flaccidity. This treatment must be planned based on each patient and according to the experience of each specific working group.

This CG could not reach a consensus about the systematic indication of post-operative MLD for surgical treatment of lipedema, since no studies have been found validating post-operative protocols in lipedema, and comparing results from groups with and without post-operative treatments.

The amount and frequency of MLD sessions have not been defined, but this CG considers that they must be determined based on each patient.

After the intervention, it is recommended to wear the socks 24-7 for three weeks. Later, the most appropriate compression garments for each patient will be prescribed.

Post-operative swelling and pain may take several months to resolve (Coppel T, 2017).

During the immediate post-operative setting, patients must do simple exercises: isometric exercises of the lower extremities to maintain muscle tone and improve venous return.

PUNTOS CLAVE

- The surgical treatment of lipedema is indicated in all cases, especially if the patient does not improve with the conservative treatment.
- It must be preceded by 6-8 months of conservative treatment, weight control and emotional balance.
- Liposuction in lipedema requires a specific technique and must be performed in a specialized unit.
- Techniques such as tumescent or super tumescent liposuction or WAL (Water-Assisted Liposuction) can be used while laser- or ultrasound-assisted liposuction must be avoided.
- Post-operative care must be planned individually by the surgeon and the team of specialists.

CAPÍTULO VI

BIBLIOGRAFÍA.

Allen E.V., Hines EA Jr. Lipedema of the legs: A syndrome characterized by fat legs and orthostatic edema. Proc. Staff Meet. Mayo Clin. 15: 184-7, 1940.

Baumgartner A, Hueppe M, Schmeller W. Long-term benefit of liposuction in patients with lipoedema: a follow-up study after an average of 4 and 8 years. Br J Dermatol 2016; 174:1061-7

Buck DW II, Herbst KL. Lipedema: A Relatively Common Disease with Extremely Common Misconceptions. Plast Reconstr Surg Glob Open [Internet]. 2016 Sep 28;4(9):e1043

Burnier P, Niddam J, Bosc R.et al.. Indocyanine green applications in plastic surgery: a review of the literature. Plast Reconstr Aesthet Surg 2017; 70: 814-827

Coppel T, Cunnen J, Fetzer S, Gordon K, Hardy D, Jones K, et al. Best practice guidelines: the management of lipoedema [Internet]. London: Wounds UK; 2017. Available from: *http://www.wounds-uk.com/best-practice-statements/best-practice-guidelines-the-management-of-lipoedema*

Dadras M, Mallinger PJ, Corterier CC, Theodosiadi S, Ghods M. Liposuction in the Treatment of Lipedema: A Longitudinal Study. Arch Plast Surg [Internet]. 2017 jul;44(4):324-331

Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. Adv Skin Wound Care. 2010;23(2)81-92

Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis, and treatment of the disproportional fatty deposition syndrome - systematic review. Clin Obes. 2012; 2:86-95

Frick A, Hoffmann JN, Baumeister RGH., Putz R. Liposuction technique and lymphatic lesions in lower legs: Anatomic study to reduce risks. Plast. Reconstr. Surg. 1999;103: 1868-73

Habbema L. Safety of liposuction using exclusively tumescent local anesthesia in 3,240 consecutive cases. Dermatol Surg 2009;35:1728-35

Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. Phlebology [Internet]. 2017 Apr;32(3):152-15.

Hoffmann JN, Fertmann JP, Baumeister RG, et al. Tumescent and dry liposuction of lower extremities: differences in lymph vessel injury. Plast Reconstr Surg. 2004;113:718–24

Hunstad JP, MD, Liposuction and tumescent surgery. Clin Plast Surg 2006; 33 (1):39-46.

Illouz YG, de Villers YT. General technique. In E. Dankowski (Ed.), Body Sculpturing by Lipoplasty,1st Ed. Edinburgh: Churchill Livingstone, 1989.

Klein JA. The tumescent technique for liposuction surgery, Am J Cosmetic Surg. 1987;4:1124-32

Lontok E, Briggs L, Donlan M, Kim Y, MosleyE, Riley EAU, et al. Lipoedema: a giving smarter guide. Milken Institute; 2017 Santa Monica (CA), USA).

Miller TA, Wyatt LE, Rudkin GH. Staged skin and subcutaneous excision for lymphedema: a favorable report of long-term results. Plast Reconstr Surg [Internet]. 1998 Oct;102(5):1486-98; discussion 1499-501

Mladick, R.A. Liposuction of the calves and ankles. Plast. Reconstr. Surg. 1990; 86(1):84-93.

Peled AW, Slavin SA, Brorson H. Long-term Outcome After Surgical Treatment of Lipedema. Ann Plast Surg [Internet]. 2012 Mar;68(3):303-7

Rank, B.K., and Wong, G. S. Lipoedema. Aust. N. Z. J. Surg.1966; 35: 166

Rapprich S, Dingler A, Podda M. Liposuction is an effective treatment for lipedema-results of a study with 25 patients. J Dtsch Dermatol Ges [Internet]. 2011 Jan;9(1):33-40

Rebelo, A. Power-assisted liposuction. Clin. Plast Surg.2006; 33(1):91-105.

Reich-Schupke S, Schmeller W, Brauer WJ, Cornely ME, Faerber G, Ludwig M. S1 guidelines: Lipedema. J Dtsch Dermatol Ges [Interne]. 2017 Jul;15(7):758-67

Rudkin GH, and Miller TA. Lipedema: A clinical entity distinct from lymphedema. Plast. Reconstr. Surg. 1994; 94: 841-47.

Sattler G. Liposuction in lipoedema. Ann Dermatol Venereol [Internet]. 2002; 129:1S103

Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. J Cutan Med Surg [Internet]. 2006 Jan-Feb;10(1):7-10

Schmeller W, Hueppe M, Meier-Vollrath I. Tumescent liposuction in lipoedema yields good longterm results. Br J Dermatol [Internet]. 2012;166(1):161–168

Schmeller W, Baumgartner A. Aspekte bei Liposucción de Lipödems: Zwölf Fragen - zwölf Antworten. LymphForsch [Internet]. 2014; 18:6-12

Stutz J, Krahl D. Water Jet-Assisted Liposuction for Patients with Lipoedema: Histologic and Immunohistologic Analysis of the Aspirates of 30 Lipoedema Patients. Aesth Plast Surg. 2009; 33:153–162

Warren AG, Janz, BA, Borud, LJ, Slavin, SA. Evaluation and Management of the Fat Leg Syndrome. Plast. Reconstr. Surg. 119(1), January 2007: 9e-15e

Warren Peled A, Kappos EA. Lipedema: diagnostic and management challenges. Int J Womens Health [Internet]. 2016 Aug 11 8:389-95

Whittle P, Baldassare G, Gina. Ultrasonografia de piel y anexos. Revista chilena de radiología,2004 10(2), 81-88. *https://dx.doi.org/10.4067/S0717-93082004000200007*

Wollina U, Heinig B, Schönlebe J, Nowak A Debulking surgery for elephantiasis nostras with large ectatic podoplanin-negative lymphatic vessels in patients with lipo-lymphedema. Eplasty [Internet]. 2014;14: e11

CONCLUSIONES.

Lipedema is a chronic, poorly known, underdiagnosed clinical entity, almost exclusive of the female sex, specially involving the lower extremities and often confused with lymphedema, lipodystrophies or obesity. It was originally described in 1940, but it has regained popularity probably in relation to determinants of fashion from the 21st century that demand most women to have slender bodies.

Most of the bibliography available on lipedema comes from vascular specialists, rehabilitators, lymphologists, physical therapists or lymphedema treatment units, causing a bias when it comes to knowing the real incidence of lipedema in the general population; therefore, the epidemiological data available are insufficient and of little use to help determine its exact incidence.

The etiology and physiopathology of lipedema are not clarified enough.

The diagnosis is basically clinical, since there are no specific diagnostic tests or enough scientific evidence to support it. However, its clinical practice may imply deterioration in patients' quality of life due to the physical, psychological and social impact it entails.

When this Consensus Document is published, lipedema will not be considered a disease by the WHO yet, although ICD 10 is under review (and will be followed by ICD 11), with the final version being released in May of 2018. This will include, among others, a suggestion to consider "lipoedema" and "cellulite" (FEP) under fat tissue pathologies. *https://icd.who.int/dev11/f/en*

In this context, there are also publications from the last decade in the field of plastic surgery, suggesting the surgical treatment of lipedema as an alternative to conservative therapies. More recent studies show that the technique is safe and can be indicated in certain patients, but to date there are no consensual protocols available on pre- and post-operative requirements and cares, nor controlled studies that validate the different liposuction techniques proposed (tumescent, super tumescent, WAL (Water Assisted Liposuction), vibroliposuction).

For all this, the Consensus Group wishes to convey how complex is the subject of lipedema, as well as the difficulty to obtain a unanimous consensus in every section, despite that it was possible to include many opinions in most Chapters, which are reflected in the Key Points; however, new studies leading to a Clinical Practice Guideline will be required.

The following conclusions are highlighted:

- **The need to establish whether it is a disease or an aesthetic alteration.**

When this Consensus Document is published, lipedema will not be yet considered a disease by the World Health Organization (WHO), although the review proposal of ICD 11 Beta Draft is known, according to which lipedema would be included in EE82 group (Non-inflammatory disorders of subcutaneous fat, EE82.2: Lipoedema) together with cases like subcutaneous lipomatosis (EE82.3) or cellulite (EE82.3), among others.

This group of experts believe that lipedema, when it is not associated with diseases or aggravating circumstances (obesity, venous or lymphatic insufficiency, osteoarticular disorders, immobility, etc.), may not meet all the requirements to be considered a disease. Since there are currently no consensual and accepted diagnostic criteria by the scientific community to confirm the presence of lipedema, more studies and lines of investigation are required to determine if this entity meets the criteria to be a disease, or it's an aesthetic alteration causing psychological and social discomfort to its sufferers.

- **Definition**

The term "lipedema" itself is not very accurate and can be confusing, since there is not a real edema in all cases, being a pathology of fat tissue as it has been confirmed by imaging techniques.

- **Epidemiology**

Current epidemiological data are insufficient and heterogeneous. Since diagnostic criteria are not standardized or consensual, prevalence data (most coming from hospitals or lymphedema units) vary between publications; therefore, the exact incidence of lipedema in the population in general, and in the Spanish population in particular, is unknown. However, it has been found that patients with lipedema have been demanding more treatments in recent years, which has awoken an increasing interest in this clinical entity described in 1940.

- **Aesthetic demands**

The 20th century fashion demands slender bodies, which may influence on the rejection and/isolation that patients with lipedema suffer.

- **Etiopathogenesis and physiopathology**

They are not well known, and some of the theories proposed lack enough scientific evidence. It is necessary to open new lines of investigation to study adipose tissue, to help clarify whether the lymphatic and blood circulation mechanisms described in the bibliography are involved in the etiopathogenesis of lipedema or they coexist with them.

- **Screening criteria**

It is necessary to reach a national and international consensus concerning the diagnostic criteria of lipedema and its aggravating factors. A high percentage of patients with lipedema show overweight/obesity or associated venous diseases that worsen the condition and aggravate the prognosis, so they must be duly identified and properly treated.

- **Classification**

In the analyzed bibliography, it has been found that lipedema is confused with morbid obesity, lipodystrophies, FEP, localized adiposities and rare syndromes of the adipose tissue, and that said confusion is present in current classifications, complicating patients' diagnosis and follow-up. For this reason, this Consensus Group believes it is necessary to create a new classification of lipedema that allows to validate the therapeutic results with scientific evidence.

- **Request for assistance. Treatment**

Patients with lipedema visit different professionals due to the disparity of signs and symptoms they present, like pain and volume increase of lower extremities. Since there is not currently a consensus about the most effective treatment for lipedema, this type of patients should be treated in multidisciplinary units, where an appropriate diagnosis and treatment of lipedema and aggravating factors can be made.

Because of all these reasons, this Group thinks it is necessary to perform new studies and open new lines of investigation to clarify these subjects. However, it has been unanimously agreed that patients with lipedema must be treated by a multidisciplinary team that can establish:

- The real prevalence of lipedema in the Spanish general population, for which the possibility to carry out an interview is suggested, which can be made to include large groups of patients recruited from different specializations and with the combined support of the scientific societies involved *(SEE ANNEX 1).*

- The correct diagnosis of lipedema based on consensual criteria.

- The diagnosis of overweight/obesity, which must always be treated, at the same time stimulating exercise at the expense of a sedentary lifestyle. Normal-weight patients with lipedema who exercise regularly see their symptoms improved, indicating the importance of prevention.

- Therapeutic protocols for pain, using proper assessment scales to measure the results from the different treatments (SEE ANNEXES 3 and 4).

- The analysis of the results from the different treatments, properly defining their indication and degree of scientific evidence.

- The assessment of the repercussions of lipedema on patients quality of life and psychosocially speaking, determining the need for specific therapies (SEE ANNEX 5).

- The requirements for the selection of patients that will undergo surgery, with validation of the most suitable surgical techniques and pre- and post-operative protocols.

- The promotion of multidisciplinary units for a diagnostic and therapeutic approach to lipedema.

At this point, some of the questions presented in the introduction can be tackled:

- Is the currently described physiopathology correct to explain the disease?

This Group agrees that the etiopathogenesis and physiopathology of lipedema are not well known, and some of the theories proposed lack enough scientific evidence.

- Is it a progressive alteration? Does it always get worse?

Lipedema's clinical evolution is not properly described. This group considers that elements like obesity, immobility, and lymphatic and venous insufficiency are aggravating —not etiopathogenic— factors of lipedema. The term "lipolymphedema" is used in the literature to define the connection between lipedema and lymphedema. However, it is not clear if this association is a clinical entity or an evolution of lipedema.

- Is it possible to lose weight?

Overweight/obesity are frequently associated with lipedema and constitute aggravating factors that worsen mobility, favor osteoarticular complications and affect patients' quality of life and self-esteem. Although the fat from the lower half of the body does not respond to diet or exercise, it is essential that patients with lipedema are diagnosed with overweight/obesity, and that they follow a suitable diet treatment. Patients with lipedema that maintain a normal weight and exercise regularly show fewer symptoms, better functional capacity and fewer complications than patients who don't. (Coppel T, 2017)

- When you have lipedema, is the progressive increase in body fat percentage normal?

Lipedema is an alteration increasing fat deposits in the lower half of the body, with obvious disproportion compared to the upper half. Involvement of the lower extremities is bilateral and symmetrical, except the feet, creating the so-called legs shaped as "stove pipes" or "baggy pants."

Normal-weight, low-weight, and even anorexic patients can show lipedema, although it coexists with overweight or obesity in over 50% of cases. Since this disease affects almost exclusively women, it must be remembered that, at puberty, body fat represents about 25% in women and 15% in men. In young women, fat distribution predominates in the hips (gynoid distribution), while, with age, fat tissue decreases from the extremities as it increases in the central region; this change is more obvious in post-menopausal women. However, if excess fat is consistent with abnormal BMI, overweight/obesity associated with lipedema must be considered.

- If the edema is not the main symptom: Is manual lymphatic drainage (MLD) an essential tool for the treatment?

Just as this Group has agreed, and based on a critical reading of the published bibliography, the volume increase of the extremities in lipedema answers to the symmetrical accumulation of adipose tissue and may or may not be associated with edema. The most common form is orthostatic edema, although there is no fovea. It can also be associated with systemic, venous or lymphatic edema. In case of associated lymphedema, it is not clear if it is primary or secondary to obesity present in most patients, or the causal relationship between both pathologies. The use of supplementary functional and imaging techniques (lymphogammagraphy, ultrasounds, MRI) allows to determine whether it is a "pure" lipedema or associated with edema, in which case specific treatments will be applied based on the edema etiopathogenesis.

In agreement with other authors, this working group believes that MLD is not the treatment of choice for an asymptomatic lipedema when only a decrease in the volume of the extremities is sought, since its application will never reduce fat; therefore, this treatment is offered many times with false expectations. However, it has been seen that it improves the symptoms, mainly in relation to pain (degree of evidence 1c (Haesler E, 2016), psychological benefits, and patients quality of life (Weiss JM, 2002; Kim SJ, 2009; Todd M, 2016; Szolnoky G, 2008; Hamner JB, 2007; Ekici G, 2009).

MLD would be indicated when there is associated lymphedema as part of the Complex Decongestive Therapy.

- Is it right to prescribe compression garments in all cases?

Not always. This group would like to highlight that compression therapy is indicated for orthostatic edema/venous insufficiency associated with edema and/or lymphedema associated with lipedema. It can also be used for its pain-relieving effects, as well as for the support it gives to tissues and its contribution to the remodeling of the extremities. Its prescription must always be based on each patient.

- What are the most effective treatments?

Since the etiopathogenesis of lipedema is currently unknown, there is not an etiological treatment available.

The different treatments analyzed are mainly for managing symptoms, reducing the edema (if any) and remodeling and reducing the volume of the extremities. In case of associated edema, compression therapy is an essential element.

To be able to analyze and compare the results of the different treatments using scientific criteria, it is necessary to have an appropriate clinical classification, as well as assessment tools to measure changes obtained with the different procedures.

In the field of aesthetic medicine, satisfactory results have been observed through hygienic-dietary cares and non-surgical techniques for the treatment of body contouring, especially in localized adiposities and FEP associated with lipedema; however, more studies are required in the future to determine said indications.

Achieving a normal weight and exercising regularly efficiently affect the improvement of symptoms and functional capacity, and at the same time reduce the associated complications.

In the last decade, the surgical treatment of lipedema has become an alternative option to the conservative treatment, with its main goal being to reduce subcutaneous fat, thus decreasing the circumference and volume of the extremities. The surgical treatment of lipedema can be performed at any time, and it is particularly indicated in those patients who do not respond properly to conservative treatment (Schmeller W, 2014).

It is important to point out that any therapeutic approach to lipedema must always be multidisciplinary.

ANNEXES.

ANNEX 1:

QUESTIONNAIRE ON THE PREVALENCE OF LIPEDEMA

Lipedema is a little-known alteration in the distribution of body fat, which only affects women and primarily involves the lower extremities.

Due to its clinical presentation and symptoms, patients are often misdiagnosed with circulation disorders, obesity, or rare diseases of the adipose tissue, and therefore they are not correctly and effectively treated.

A correct diagnosis will enable the establishment of the right treatment measures.

Please, answer the questionnaire on the following page.

Age:		
Sexo:	Male ☐	Female ☐
Edad de aparición:		

HISTORY

Family history (the mother or other women in the family suffer it)	YES ☐	NO ☐
Have you had liposuction or aesthetic treatments in your legs?	YES ☐	NO ☐
Have you followed a diet alone or under your doctor's supervision?	YES ☐	NO ☐
Do you take the pill or a replacement hormone therapy?	YES ☐	NO ☐
Have you had surgery or radiotherapy for an oncological disease?	YES ☐	NO ☐
Do you regularly exercise?	YES ☐	NO ☐

SYMPTOMS Do your legs currently show any of these symptoms?

Heavy legs	YES ☐	NO ☐
Pain in legs	YES ☐	NO ☐
Bloating	YES ☐	NO ☐
Easy hematomas	YES ☐	NO ☐
Cold skin sensatiom	YES ☐	NO ☐

AGGRAVATING FACTORS

Overweight/obesity	YES ☐	NO ☐
Venous disease (varicose veins)	YES ☐	NO ☐
Lymphatic disease (lymphedema)	YES ☐	NO ☐
Some heart or kidney disease	YES ☐	NO ☐

CLINICAL EXAMINATION

Involvement of lower extremities		UNILATERAL ☐	BILATERAL ☐
Weight:	Height:	BMI:	
Wais-to-hp ratio < 1,0 (men) / < 0,9 (women)			
Presence of fovea		YES ☐	NO ☐
Stemmer's sign		YES ☐	NO ☐
Signs of chronic venous disease (CEAP)		YES ☐	NO ☐
Osteoarticular disorders		YES ☐	NO ☐

ULTRASOUND/DOPPLER ECHOGRAPHY

Thickness of adipose tissue (6 cm above the internal malleolus)

12 - 15 mm: ☐	15 - 20 mm: ☐	> 20 mm: ☐	> 30 mm: ☐

Presence of venous reflux	YES ☐	NO ☐

ANNEX 2: DATA COLLECTION SHEET/CIRCOMETRY

DATE:

Waist Circumference:

Hips Circumference

RIGHT LOWER EXTREMITY. CIRCOMETRY: starting at external malleolus, every 4 cm.

C1

C2

C3

C4

C5

C6

C...

LEFT LOWER EXTREMITY. CIRCOMETRY: starting at external malleolus, every 4 cm.

C1

C2

C3

C4

C5

C6

C...

WEIGHT:

BMI:

ANNEX3: EVA PAIN SCALE/DN4 QUESTIONNAIRE
(English version of the Douleur Neuropathique questionnaire)

Answer these 4 questions by checking the boxes below with a Yes or No.

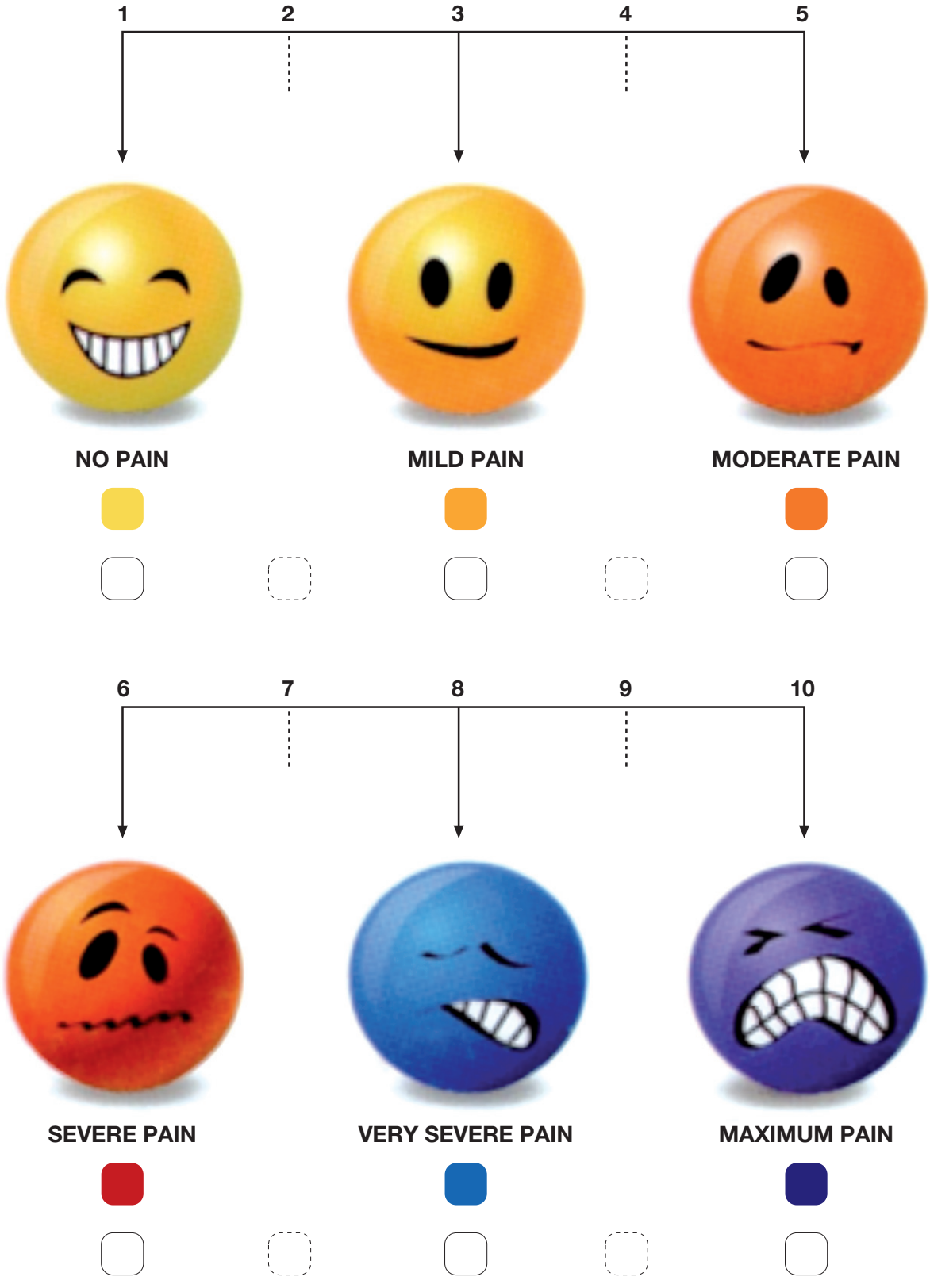
INTERVIEW WITH THE PATIENT		
Question 1. Does your pain present any of these characteristics?		
1. Burning sensation	YES ☐	NO ☐
2. Painful cold sensation	YES ☐	NO ☐
3. Electrical shocks	YES ☐	NO ☐
Question 2. Does the area where it hurts show any of these symptoms?		
1. Tingling	YES ☐	NO ☐
2. Pinching	YES ☐	NO ☐
3. Numbness	YES ☐	NO ☐
4. Stinging	YES ☐	NO ☐

EXPLORATION OF THE PATIENT		
Question 3. Has any of these signs been observed in the painful area during the exploration?		
1. Hypoaesthesia to touch	YES ☐	NO ☐
2. Hypoaesthesia after injection	YES ☐	NO ☐
Question 4. Is the pain caused or intensified by...?		
1. Friction	YES ☐	NO ☐

[1]French version (France): Bouhassira D, et al. Pain 2005; 114: 29-36.
Spanish version (Spain): Pérez C, et al. EFIC 2006.

ANNEX 4: VISUAL ANALOG SCALE FOR PAIN

SCALE 1-10 *(check the boxes below with an X)*



ANNEX 5: QUALITY OF LIFE QUESTIONNAIRE: SF-36 Health Questionnaire (version 2)

Spanish version of SF-36v2™ Health Survey © 1996, 2000 adapted by J. Alonso et al. 2003.

1. In general, would you say your health is:

❑ Excellent ❑ Very good ❑ Good

❑ Fair ❑ Por

2. Compared to one year ago, how would you rate your health in general now?

❑ Much better ❑ Somewhat better ❑ About the same

❑ Somewhat worse ❑ Much worse

THE FOLLOWING QUESTIONS ARE ABOUT ACTIVITIES YOU MIGHT DO DURING A TYPICAL DAY.

3. Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

4. Does your health now limit you in doing moderate activities, such as moving a table, using a vacuum cleaner, bowling, or playing golf?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

5. Does your health now limit you in lifting or carrying groceries?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

6. Does your health now limit you in climbing several flights of stairs?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

7. Does your health now limit you in climbing one flight of stairs?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

8. Does your health now limit you in bending, or kneeling?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

9. Does your health now limit you in walking one kilometer or more?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

10. Does your health now limit you in walking several blocks (several hundreds of meters)?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

11. Does your health now limit you in walking one block (about 100 meters)?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

12. Does your health now limit you in bathing or dressing yourself?

❑ Yes, limited a lot ❑ Yes, limited a little ❑ not limited at all

THE FOLLOWING QUESTIONS ARE ABOUT PROBLEMS WITH YOUR WORK OR DAILY ACTIVITIES.S.

13. During the past 4 weeks, did you have to cut down on the amount of time spent on work or daily activities as a result of your physical health?

❑ YES ❑ No

14. During the past 4 weeks, did you accomplish less than you would have liked as a result of your physical health?

❑ YES ❑ No

15. During the past 4 weeks, were you limited in the kind of work or daily activities as a result of your physical health?

❑ YES ❑ No

16. During the past 4 weeks, did you have difficulties doing your work or daily activities (for example, it took extra effort) as a result of your physical health?

❑ YES ❑ No

17. During the past 4 weeks, did you have to cut down on the amount of time spent on work or daily activities as a result of any emotional problems (such as feeling sad, depressed or nervous)?

❑ YES ❑ No

18. During the past 4 weeks, did you accomplish less than you would have liked as a result of any emotional problems (such as feeling sad, depressed or nervous)?

❑ YES ❑ No

19. During the past 4 weeks, did you do your work or daily activities less carefully than usual as a result of any emotional problems (such as feeling sad, depressed or nervous)?

❑ YES ❑ No

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups??

❑ Not at all ❑ Slightly ❑ Moderately
❑ Quite a bit ❑ Extremely

21. Have you had bodily pain during the past 4 weeks?

❑ None ❑ YES, very mild ❑ YES, mild
❑ YES, moderate ❑ YES, severe ❑ YES, very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

❑ Not at all ❑ Slightly ❑ Moderately
❑ Quite a bit ❑ Extremely

THESE QUESTIONS ARE ABOUT HOW YOU FEEL AND HOW THINGS HAVE BEEN WIT
H YOU DURING THE PAST 4 WEEKS.
FOR EACH QUESTION, PLEASE GIVE THE ANSWER THAT COMES CLOSEST TO THE WAY YOU HAVE FELT..

23. During the past 4 weeks, how much of the time did you feel full of life?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

24. During the past 4 weeks, how much of the time have you been very nervous?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

25. During the past 4 weeks, how much of the time have you felt so down in the dumps that nothing could cheer you up?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

26. During the past 4 weeks, how much of the time have you felt calm and peaceful?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

27. During the past 4 weeks, how much of the time did you have a lot of energy?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

28. During the past 4 weeks, how much of the time have you felt downhearted and depressed?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

29. During the past 4 weeks, how much of the time did you feel worn out?

❑ All the time ❑ Most of the time ❑ Many times
❑ Some of the time ❑ A little of the time ❑ None of the time

30. During the past 4 weeks, how much of the time have you been happy?

❑ All the time ❑ Most of the time ❑ Some of the time
❑ A little of the time ❑ None of the time

31. During the past 4 weeks, how much of the time did you feel tired?

❑ All the time ❑ Most of the time ❑ Some of the time
❑ A little of the time

32. During the past 4 weeks, how often has your physical health or emotional problems interfered with your social activities (like visiting with friends or relatives)?

❑ All the time ❑ Most of the time ❑ Some of the time
❑ A little of the time ❑ None of the time

PLEASE SAY HOW TRUE OR FALSE IS EACH OF THE FOLLOWING STATEMENTS FOR YOU

33. I seem to get sick a little easier than other people.

❑ Definitely true ❑ Mostly true ❑ I don't know
❑ Mostly false ❑ Definitely false

34. I am as healthy as anybody.

❑ Definitely true ❑ Mostly true ❑ I don't know
❑ Mostly false ❑ Definitely false

35. I expect my health to get worse.

❑ Definitely true ❑ Mostly true ❑ I don't know
❑ Mostly false ❑ Definitely false

36. My health is excellent.

❑ Definitely true ❑ Mostly true ❑ I don't know
❑ Mostly false ❑ Definitely false

ANNEX 6: RECORD OF THE PHYSICAL ACTIVITY

To prescribe a physical activity, it is advisable to provide guidance about the levels of energy consumed, and the indication must be personalized, since it depends on weight, age, and characteristics of each individual. Physical activity is measured in METs, which is the measuring unit of metabolic rate; it starts at 1, which is equivalent to the energy cost of sitting quietly. The indication of exercise of moderate intensity would be of 5-8 MET for young individuals (less than 18 years old), 4-6.5 MET for adults, and 3-5 MET for individuals over 55 years old. (Taken from the Dutch Society for Dermatology and Venereology. Lipedema guidelines in the Netherlands 2014 [Internet]. Utrecht: NVDV; 2014. Available from: *https://diseasetheycallfat.tv/wp-content/uploads/2015/08/Dutch-lipoedema-guideline-2014.pdf*

ACTIVITY	MET Value
Still (lying down, seated, standing still, eating, talking)	1.0
Driving, playing the piano, at the computer	2.0
Walking 4 km/h	3.0
Walking 5 km/h	4.0
Cycling 10-12 km/hour	5.0
Cycling 16 km/hour	6.5
Swimming (crawl) 1 km/hour	5.0
Swimming (crawl) 3 km/hour	20.0
Running/Jogging	8.0