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Unraveling lipedema: comprehensive insights and the path to future discoveries

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Lipedema is a chronic disease characterized by the symmetrical accumulation of adipose tissue in the lower body, primarily affecting women. Despite being recognized for over 85 years, the pathophysiology, diagnosis, and treatment of lipedema remain complex and not fully understood. This review consolidates current knowledge, emphasizing histological, genetic, and hormonal factors, alongside diagnostic and therapeutic approaches. Histological studies highlight changes such as adipocyte hypertrophy, increased fibrosis, and vascular alterations like angiogenesis. Genetic studies suggest a strong familial component, with multiple loci potentially influencing disease onset, yet the condition remains polygenic and influenced by environmental factors. Hormonal influences, particularly estrogen, play a significant role in disease pathogenesis. Diagnostic imaging techniques like dual-energy X-ray absorptiometry (DXA), ultrasound (US), and magnetic resonance imaging (MRI) provide valuable insights but are not definitive. Therapeutic strategies, including diet, weight loss, and Complex Decongestive Therapy, offer symptom management but are not curative, with liposuction considered for severe cases where conservative methods fail. The condition's complexity stems from genetic, hormonal, and environmental influences, necessitating further research to improve diagnostic and treatment strategies. Integrating genetic and hormonal insights into clinical practice could enhance patient outcomes and quality of life, highlighting the need for continued exploration and understanding of lipedema.

Lipedema is a chronic disease characterized by a distinctive and often painful accumulation of adipose tissue. It has long been recognized as a progressive condition[1], although some experts have recently questioned this definition[2–4], and this is currently under debate. According to some established criteria, pain is not a mandatory requirement for diagnosing lipedema[5], although it is emphasized in others[3]. The fat distribution is circumferential and symmetrical, primarily affecting the buttocks, hips, and lower limbs, but can also involve the upper limbs. Importantly, it typically spares the trunk, hands, and feet, leading to a pronounced 'pear-shaped body' (Figs. 1 and 2) that is distinct from general obesity or the usual nonpathological gynoid fat distribution.

First described by Allen and Hines in 1940[6], awareness of lipedema has grown globally only in recent years. As an example of recent progress, approximately 80% of all PubMed-indexed publications on lipedema have been published in the last decade, although many consist of case reports, small series, or hypothesis-driven reviews, with limited high-quality evidence. In 2022, lipedema was officially recognized in the 11th revision of the International Classification of Diseases (ICD-11)[7] under the codes EF02.2 (lipedema) and BD93.1Y (lipolymphedema). Lipedema fat is often described as gelatinous, with palpable nodules, and typically displays the characteristic 'cuff sign', where fat abruptly terminates at the wrists or ankles (Figs. 1c, e, 2b and c), sparing hands and feet[8]. One of the current key challenges is the widespread lack of formal training among healthcare professionals in identifying this form of pathological adipose tissue, resulting in many women self-diagnosing after searching online for phrases such as 'painful fat legs', highlighting a significant gap in medical education regarding lipedema.

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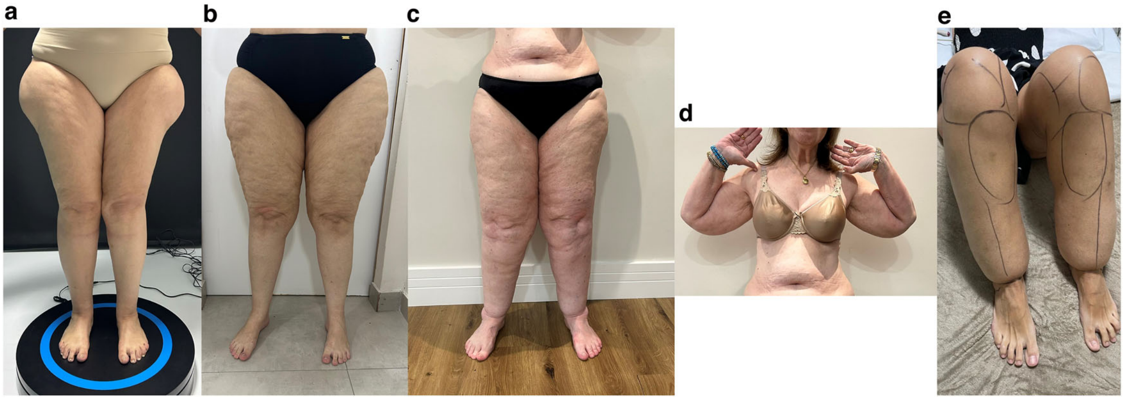

Fig. 1 | Types of lipedema. a Type 1 with fat tissue accumulation around the hips and buttocks (saddle bag phenomena). **b** Type 2 with fat accumulation from hips to knees. **c** Type 3 with hip to ankle phenotype with a typical 'cuff sign' at the ankle. **d** Type 4 with tissue hanging below the arm due to loss of elasticity and heaviness. **e** Type 5 with tissue dominating the calf region only.

Fig. 2 | Stages of lipedema. a Stage 1 with smooth and soft skin, underlying hypodermis thickened on palpation. **b** Stage 2 with skin indented over palpable pearl-sized nodules ('orange peel skin'). **c** Stage 3 with folds and divots over deforming, larger fat mass. **d** Stage 4 with concomitant lymphedema.

Epidemiology

Available studies on the prevalence of lipedema are both sparse and often yield inconsistent findings. A 2010 study reported at least 1 case in every 72,000 individuals within the general population[9]—a figure that almost certainly underrepresents the true incidence. The widespread unfamiliarity with lipedema contributes to frequent misdiagnoses, as it is commonly mistaken for other conditions such as general obesity or lymphedema. A 2006 survey among UK vascular specialists found that only 46% of surveyed professionals were able to accurately recognize the disorder[10]. More recent findings from a Turkish study of 508 medical doctors[11] revealed that while 51% of physicians were familiar with the term, only 29.9% reported having seen or referred patients with the condition, and more than half indicated 'no idea' about its clinical features (51.4%) or treatment options (50.9%). These statistics underscore the critical need for improved medical education, standardized guidelines, and increased public awareness.

Regarding its prevalence, a German report identified lipedema in 11% of postpubertal women presenting with leg swelling[12], while research from Spain found a rate of 18.8% among women with similar symptoms[13]. However, these figures reflect selected populations and should not be taken as representative of the general population. The vast majority of people affected by lipedema are women, with symptoms typically arising during puberty. Some initiatives have been undertaken to assess the disease prevalence through community screenings. A preliminary study indicated a 5% prevalence of lipedema among 813 women screened in a German general practice[14]. In Brazil, a survey-based screening tool[15] was administered to 253 women, revealing a predicted prevalence of 12.3% among women aged 18-69, but its weak methodology probably overestimates the real number. As a matter of fact, a paradox exists: as the majority of women with lipedema are underdiagnosed, with lipedema being more discussed by the lay public, many women are probably being misdiagnosed and offered non-evidence-based interventions.

Genetics

Recent studies suggest a family history of lipedema is quite common, with estimates ranging from 30% to 89%[16], indicating a strong genetic influence on the disease. Cases of lipedema in children under 10 years are nearly always associated with a positive family history of the disease[17].

It is likely that the risk of lipedema is influenced by multiple loci[18], and the onset of the disease may be triggered by a complex interplay between environmental, hormonal, and other exposures. Women's susceptibility to these triggers probably depends on their genetic background.

Despite the strong suggestion of a genetic basis, studies on the role of single allele variants in the risk of lipedema have so far not demonstrated a causal relationship with the condition. There are case reports of lipedema in families with genetic syndromes, such as Williams Syndrome (*ELN* mutation)[19], Sotos Syndrome (*NSD1* mutation)[20], and carriers of *PIT-1* mutation[21]. A multi-gene candidate approach study evaluated 305 loci and reported 17 probable deleterious lesions in 21 out of 162 participants[18], with a plausible mechanism for a causal relationship with lipedema.

A study utilizing whole-exome sequencing in a family with non-syndromic lipedema identified a missense variant in the *AKR1C1* gene, leading to partial loss of function in three affected women[22]. *AKR1C1*, which encodes an enzyme involved in steroid metabolism, particularly in the conversion of progesterone and androgens, may influence adipose tissue biology. This variant's association with lipedema suggests a potential genetic link, possibly altering lipid metabolism, adipogenesis, or hormonal regulation.

MTHFR polymorphisms have also been associated with a higher risk of lipedema in women with body composition and morphology similar to

Box 1 | Main findings of the role of estrogen in Lipedema pathogenesis (Al-Ghadban et al.[30])

Estrogen Receptor Expression:
- Estradiol treatment significantly increased the expression of estrogen receptors ERα and ERβ in healthy and lipedema ASCs in 2D culture.
- In 3D cultures, estradiol treatment decreased the expression of ERα and GPER in lipedema spheroids, but not in healthy spheroids.

Expression of Estrogen-Metabolizing Enzymes:
- Estradiol treatment increased the expression of enzymes such as 17-beta-hydroxysteroid dehydrogenase (HSD17B7, conversion of estrone to estradiol), hormone-sensitive lipase, and steroid sulfatase (conversion of estrone sulfate — inactive form — to estradiol) in lipedema ASCs.
- HSD17B7 expression was higher in hormone-deprived lipedema cells than in healthy cells, suggesting a possible increased conversion of estrone to estradiol in lipedema.
- CYP19A1 (aromatase) was more expressed in healthy ASCs.

Stem Cell Proliferation and Markers:
- Estrogen increased the proliferation and expression of mesenchymal stem cell markers (CD73, CD90, CD105) in healthy ASCs, but not in lipedema ASCs.

Adipogenesis:
- Estrogen treatment significantly increased the expression of PPAR-γ2 in differentiated lipedema adipocytes, which correlates with the increase in adipocyte size observed in lipedema tissue.

lipedema[23]. More recently, in 2022, a genome-wide association study (GWAS) with 130 lipedema carriers identified six gene regions associated with body shape, lipoma formation, adiposity, and sex hormone biology, including the genes *CPE*, *ZNF25*, and *ZNF33A*, which are related to estrogen biology[24]. A supplementary study explored an inferred phenotype of lipedema in the UK Biobank, based on a high percentage of leg fat and low waist-hip ratio in 24,450 women, identifying 18 loci associated with similar pathway involvements, replicating associations for markers near the *VEGFA* and *GRB14-COBLL1* genes[25]. To date, no study evaluating epigenetic modifications in lipedema has been published.

Associations discovered through GWAS are correlative and lack functional validation to confirm their causal role in lipedema and require replication in additional studies. There is no evident overlap between lipedema GWAS and associations reported for primary lymphedemas or lipodystrophies.

In summary, while research has identified various genes and loci associated with lipedema, no single gene has been demonstrated as the primary cause of the condition. The current view suggests that lipedema is a complex condition, polygenic in origin, influenced by genetic and environmental factors, and that identifying specific genetic alterations remains a challenge yet to be elucidated.

Hormonal influence on lipedema

The influence of hormones on the pathophysiology of lipedema is complex and not yet completely understood, but clinical and genetic studies suggest important associations. First, lipedema affects almost exclusively women, suggesting a strong link with hormonal factors. Symptoms frequently begin or worsen during periods of significant hormonal changes, predominantly at puberty (15.7–67.3%), but also during pregnancy/lactation (9.5–63.1%), menopause (1.9–21%), or with the use of exogenous hormones like oral contraceptives (1.2–3.8%)[16]. Interestingly, rare case reports of lipedema in men are linked to conditions with elevated estrogen and low testosterone, including hypogonadism and advanced liver disease[21,26–28].

Sex hormones, such as estrogen and progesterone, are believed to play a role in the pathophysiology of lipedema, although the exact mechanisms are not fully known. One hypothesis suggests that estrogen receptor alpha (ERα) and matrix metalloproteinase-14-dependent fibrotic pathways may be affected in lipedema, leading to the remodeling of fibrous septa in adipose tissue[29].

A recent study explored how estrogen contributes to the pathogenesis of lipedema[30]. Using adipose-derived stem cells (ASCs) from women with and without lipedema, researchers examined the expression of estrogen receptors (ERα, ERβ, GPER) and estrogen-metabolizing enzymes after estradiol exposure (Box 1). The study revealed that estrogen influences adipocyte proliferation and differentiation, with distinct responses in lipedema ASCs compared to healthy controls. These alterations suggest that hormonal dysfunction may underlie lipedema, similarly to other estrogen-driven conditions such as breast cancer. The findings highlight the complex hormonal regulation of adipose tissue in lipedema and point to new therapeutic possibilities, including targeting estrogen metabolism, inflammation, and fibrosis.

Lipedema histological findings and pathophysiology

Significant changes occur in the subcutaneous adipose tissue (SAT) in lipedema, which is typically associated with a lower risk of hypertension and insulin resistance compared to excess visceral adipose tissue. Histologically, lipedema tissue is often described as fibrotic, with hypertrophic adipocytes[31,32], fluid accumulation, macrophage infiltration, and capillary hyperpermeability[33] (Box 2). In advanced stages, fibrosis and adipocyte apoptosis[34] may hinder fat mobilization, paralleling findings in obesity where fibrosis impairs post-bariatric weight loss[35,36]. Yet these observations are far from uniform, as much of the literature is based on small, heterogeneous samples, limiting broad generalization. A recent study by Michelini et al.[37] advanced this field by demonstrating distinct vascular abnormalities, calcium crystal deposition, and preserved adipocyte integrity despite macrophage infiltration, suggesting that calcium dysregulation, rather than classical inflammation, may be central to disease progression.

Whether edema is intrinsic to lipedema remains debated. Some define edema strictly as free extracellular fluid[38], while others include sodium and glycosaminoglycan-bound water[5], which may explain the gelatinous texture of affected tissue. Imaging and spectroscopy studies provide indirect evidence of altered sodium and extracellular water handling, with signals distinct from both obesity and lymphedema. Excess fluid in the extracellular matrix (ECM) can exist both as free tissue fluid, as seen in conditions like heart failure, nephrotic syndrome, and lymphedema, or as fluid bound to glycosaminoglycans (GAGs)[5]. GAGs, through their negative sulfate charge, attract sodium and water, which may contribute to the gelatinous consistency of lipedema tissue. Ultrasonographically, only free fluid is detectable (as in lymphedema), while GAG-bound fluid, typical in isolated lipedema, remains invisible[39]. Importantly, some studies have suggested that untreated lipedema, particularly in advanced stages, may be associated with secondary lymphatic insufficiency[40,41]; however, this remains under debate, and it has also been proposed that coexisting obesity, rather than lipedema itself, is a key contributor to lymphatic dysfunction.

Indirect evidence for altered fluid dynamics in lipedema arises from advanced imaging and biophysical studies. Magnetic resonance imaging (MRI) studies show elevated sodium concentrations in skin, adipose tissue, and muscle[42], while bioimpedance spectroscopy demonstrates progressively increased extracellular water with advancing disease stage[43]. Clinically,

Box 2 | Main histological findings in Lipedema adipose tissue

- **Adipocyte Hypertrophy:** Adipose tissue affected by lipedema is commonly described as having fibrotic masses composed of hypertrophic adipocytes. The expansion of the SAT is influenced by increased cell diameter, both in SAT and dermal adipose tissue[31,33,127].
- **Fibrosis:** There is an increase in fibrosis in the affected tissue, both in the dermis and SAT. This indicates an accumulation of fibrous connective tissue[32,67].
- **Calcium Deposition:** Massive calcium crystal deposition was found in hypertrophic adipocytes and, to a lesser extent, in endothelial cells of lipedema tissue[37]. This suggests altered cellular calcium metabolism, potentially linked to hormonal imbalances, contributing to adipocyte pathology and inflammation.
- **Cellular Infiltration:**
  - Adipose tissue in lipedema shows signs of infiltration by numerous capillaries, monocytes, fibroblasts, and mast cells.
  - Studies report an increased count of macrophages (CD45+/CD68+) in the tissue affected by lipedema[31,128]. There is evidence of an increase in M2 polarized macrophages (CD163+)[128,129], which is associated with anti-inflammatory processes and tissue remodeling.
  - An increased number of CD45+ hematopoietic cells has also been observed[128].
- **Vascular Alterations:**
  - Increased blood vessel density and signs of new blood vessel formation (angiogenesis).
  - Some studies describe an increase in dermal blood vessels and skin angiogenesis.
  - Reports indicate dilation of lymphatic vessels, although there is not always an increase in the number of vessels.
- **Adipocyte Tissue Remodeling and Necrosis:**
  - Lipedema might be associated with adipose tissue remodeling, including adipocyte death and concurrent regeneration, with proliferating CD34+ adipose stem/progenitor cells observed in some samples[34]. Some studies have reported necrotic adipose tissue[34].
- **Extracellular Matrix Alterations:** The ECM in lipedema adipose tissue may also be altered, with an increase in interfibrillar space potentially related to the accumulation of interstitial fluid[130], which can be linked to GAGs[5].
- **Proliferation of ASCs:** ASCs derived from lipedema patients show increased proliferation rates[131]. Additionally, these ASCs may exhibit greater adipogenic differentiation. An increase in the cell cycle regulator BUB1 in these cells suggests a contribution to pathological adipogenesis[132].

anecdotal reports of symptom flares after high-sodium meals are consistent with biochemical findings of altered sodium balance. MR lymphangiography (MRL) studies further support the presence of edema in lipedema SAT with distinct distribution patterns from morbid obesity and secondary lymphedema[44], suggesting a unique subcutaneous fluid profile. In preclinical models, sodium accumulation triggers activation of the tonicity-responsive enhancer binding protein (TonEBP) in macrophages, leading to VEGF-C secretion and lymphatic hyperplasia that help regulate interstitial volume. Although this TonEBP–VEGF-C pathway has not yet been examined in human lipedema, it may underlie the distinct sodium retention and lymphatic alterations characteristic of the disorder[45].

Recent multi-omics and metabolomics studies have begun to advance, but also add new layers of complexity to lipedema pathophysiology. Two key studies[46,47] employed complementary approaches to explore its molecular features and potential diagnostics. Kempa et al.[46] reported alterations in amino acid metabolism and elevated pyruvate, nominating pyruvic acid as a potential biomarker, while Straub and colleagues[47] identified ceramide elevations, shifts in glutamic acid and methionine sulfoxide, and broader adipokine dysregulation. These findings were not entirely concordant between the two studies, highlighting the need for replication in larger cohorts and drawing attention to methodological limitations such as modest sample sizes and lack of external validation. Straub et al.[47] also challenged the prevailing assumption of lipedema as a primarily inflammatory condition, reporting reduced local inflammation and enhanced mitochondrial function within affected adipose tissue—features that stand in contrast to the hypoxia-driven inflammation and fibrosis typical of obesity-related adipose expansion[48].

Beyond local metabolic shifts, systemic hypotheses seek to explain how vascular and hormonal environments shape disease progression. Kruglikov and Scherer[49] proposed that lipedema reflects a 'pseudopregnancy' state of gluteofemoral white adipose tissue, characterized by heightened sensitivity to lipopolysaccharides and complement dysfunction, leading to low-grade inflammation and adipose expansion. Similarly, microvascular and lymphatic abnormalities, including capillary fragility, impaired veno-arterial reflexes, elevated VEGF, and lymphatic endothelial permeability[33,50,51], are proposed to exacerbate swelling[52] and lipid accumulation. Yet, these vascular features overlap substantially with obesity-associated adipose dysfunction[53,54], complicating differentiation.

Adipose tissue expansion is closely linked to endothelial dysfunction, which contributes to hypoxia, impaired angiogenesis, increased vascular permeability, and disrupted lipid trafficking[55]. In preclinical models of obesity, hypoxia-driven endothelial dysfunction promotes systemic insulin resistance through chronic inflammation[56,57], excessive macrophage infiltration[58], immune cell polarization toward a proinflammatory phenotype[59], and ECM remodeling[60], ultimately impairing adipocyte function and exacerbating metabolic dysregulation. Adipose tissue expansion in human obesity is also associated with reduced oxygenation, creating a hypoxic microenvironment that disrupts metabolic homeostasis[48]. However, these studies have primarily focused on abdominal SAT, making it difficult to determine whether similar mechanisms apply to femoral adipose tissue. Additionally, lipedema is associated with a more favorable metabolic profile, suggesting that distinct regulatory mechanisms may govern adipose-endothelial interactions in different fat depots.

Diagnosis of Lipedema

The diagnosis of lipedema is based on clinical parameters, as proposed in 1951 by Wold et al.[61] (Box 3). Based on distribution, five types and four clinical stages of lipedema have been described (Boxes 4 and 5, Figs. 1 and 2). However, some experts argue that staging may not fully capture symptom severity and could have limited utility in disease management[2]. Keith et al.[4] recently proposed a standardized research case definition of lipedema to address the lack of consensus. Based on a narrative review, the framework defines five essential characteristics—female sex, pain/tenderness, disproportionate adipose tissue, skin/tissue changes, and lack of response to diet—and five less substantiated features (cuffing, nonpitting edema with negative Stemmer sign, hormonal association, family history, easy bruising) for optional inclusion. This approach aims to improve diagnostic sensitivity and specificity, strengthening the evidence base and facilitating meta-analyses and cross-study comparisons.

Box 3 | Clinical criteria for diagnosing lipedema[61]

- Disproportional fat distribution with bilateral and symmetrical limb enlargement and minimal or no involvement of hands and feet.
- Lack of significant influence of weight loss on fat distribution.
- Presence of pain, tenderness, and spontaneous bruising on limbs.
- Increased sensitivity to touch and a feeling of limb fatigue.
- Minimal or no pitting edema.
- No reduction of pain or discomfort with limb elevation.

Box 4 | Types of Lipedema

- Type I: fat accumulation around the hips and buttocks.
- Type II: fat accumulation in the area from the hips to the knees.
- Type III: hip to ankle phenotype with a typical 'cuff sign' at the ankle (i.e., fat deposits beginning abruptly above the malleoli).
- Type IV: fat accumulation in the arms (with or without lower limb involvement).
- Type V: fat dominating the calf region only (rarer phenotype).

Box 5 | Stages of Lipedema

- Stage I: Thickening and softening of the subcutis with small nodules; skin is smooth.
- Stage II: Thickening and softening of the subcutis with larger nodules due to increased fibrous tissue; skin texture is uneven ('mattress phenomenon').
- Stage III: Thickening and hardening of the subcutis with large nodules, disfiguring lobules of fat on the inner thighs and inner aspects of the knees/overhanging masses of tissue.
- Stage IV: Lipolymphedema.

Associated comorbidities and differential diagnosis

Lipedema shares clinical features with other conditions[8], such as obesity and lymphedema. This makes differential diagnosis essential, requiring detailed clinical examination and, when necessary, complementary tests[62] to ensure appropriate treatment. Additionally, several other diseases can coexist with lipedema[63], with some considered complications of the condition.

The relationship between obesity and lipedema is complex and multifaceted. Both conditions involve excess fat accumulation, but they differ in their underlying pathophysiological mechanisms, distribution patterns, and clinical implications. Lipedema is characterized by a symmetrical accumulation of subcutaneous fat, primarily in the lower body, which is often painful and not necessarily associated with elevated overall body mass index (BMI). Its fat distribution is distinct and less responsive to conventional weight loss methods[1]. Obesity, on the other hand, is a condition of excess body fat resulting from an imbalance between caloric intake and expenditure, affecting the entire body[64]. It is often associated with metabolic abnormalities and can be managed through diet, exercise, and medical interventions.

Obesity frequently coexists with lipedema[63] and may exacerbate its symptoms. While obesity is not a direct cause of lipedema, weight gain can worsen the symptoms of lipedema by adding stress and increasing the mechanical load on the joints, vascular and lymphatic systems, and exacerbate pain and mobility issues associated with lipedema[65]. This can lead to increased swelling, pain, and progression to lipolymphedema in some cases[66].

The presence of obesity can complicate the clinical picture and make management more challenging. The progression of lipedema may involve a positive feedback loop where excess lymphatic fluid leads to adipose tissue remodeling, which further disrupts lymphatic function[66]. Mechanical forces from increased adipose tissue may also restrict lymphatic flow, contributing to disease progression. In conclusion, although obesity and lipedema are distinct conditions, they are interrelated in ways that can influence the onset and progression of symptoms. Obesity should be viewed as the major comorbidity that can exacerbate lipedema symptoms rather than a primary trigger. Understanding the nuanced relationship between these conditions is essential for accurate diagnosis, effective treatment, and improved patient outcomes.

Regarding metabolic complications, some studies suggest that early-stage lipedema may be associated with a reduced incidence of metabolic syndrome and type 2 diabetes[65]. In obesity, the accumulation of upper-body adiposity is strongly correlated with increased risks of metabolic syndrome and diabetes due to its role in insulin resistance and systemic inflammation[64]. On the other hand, lipedema, characterized by lower-body adipose tissue accumulation, is anedoctally reported to confer a protective metabolic profile, which might explain the lower prevalence of metabolic complications in this population. A recent study assessed metabolic function in women with obesity and lipedema (Obese-LIP group), who were matched for age, BMI, total body fat mass, and percentage body fat with women with obesity but without lipedema (Obese group)[67]. The study assessed plasma lipid profile, oral glucose tolerance (OGTT), and whole-body insulin sensitivity by hyperinsulinemic-euglycemic clamp procedure. The Obese and Obese-LIP groups did not differ for fasting plasma lipid profile, glucose, insulin, C-peptide concentrations, 2-hour post-OGTT, plasma glucose levels, HbA1c, or hepatic insulin sensitivity. However, whole-body (primarily skeletal muscle) insulin sensitivity was ~48% higher in the Obese-LIP group than in the Obese group. A third group of lean, healthy women was also included in the study serving as a comparison. The Obese-LIP group exhibited higher fasting plasma glucose, C-peptide, triglyceride, and 2-hour glucose concentrations assessed by OGTT, as well as elevated HbA1c compared with the Lean group. The Obese-LIP group also had lower HDL-cholesterol and reduced hepatic and whole-body insulin sensitivity compared with the Lean group.

A Swedish national cross-sectional study using an online survey with 245 women with lipedema[63] found that common comorbidities among participants included overweight and obesity (41.7% and 30.2%, respectively), hypothyroidism (20%), hypertension (25.3%), fibromyalgia (17%), and depression (13.5%). Another German online survey including 209 patients[68] identified hypothyroidism (35.9%), allergies (34.4%), depression (23%), migraine (22.5%), sleep disorders (21.5%) and hypertension (13.4%) as the main comorbidities associated with lipedema. Noteworthy, hypothyroidism and depression occurred at a frequency far beyond the average prevalence in the German population. Also of great interest, following surgical treatment with liposuction, the frequency and/or intensity of headache attacks became markedly reduced, as stated by 32 out of 47 migraine patients (68.1%).

Dercum's disease (painful adiposis) shares similar features with lipedema[69], such as the presence of pain, spontaneous bruising, and depression. However, differences lie in Dercum's disease, presenting with multiple painful lipomas progressing to circumscribed or generalized fat deposition, which is not observed in lipedema.

Eating disorders such as periodic binge eating attacks, bulimia, and anorexia nervosa can also coexist with lipedema[5,70,71]. Although eating disorders can contribute to weight gain and exacerbate lipedema symptoms, the reverse can also occur: stigma and negative emotions related to disproportionate fat accumulation or pain may trigger emotional eating in susceptible individuals[70].

Joint hypermobility occurs in up to half of the women with lipedema[69], illustrating its association with connective tissue disorders, such as Ehlers-Danlos Syndrome. This suggests a potential underlying connective tissue disorder common to both conditions. Both lipedema and joint hypermobility can cause pain and mobility issues, particularly in the lower limbs, which may further complicate management. Accordingly, Ehlers-Danlos Syndrome and lipedema may involve genetic factors affecting connective tissue integrity. Research into these genetic links could provide insights into their relationship and potential common pathways.

Lymphedema can either be a complication of lipedema or a differential diagnosis[8]. While it has been suggested that lipedema may progress to or be associated with lymphedema, this remains a matter of debate, with some evidence indicating that lymphatic insufficiency may be more closely related to coexisting obesity rather than lipedema itself. Clinically, there are distinctions between these two conditions, such as Stemmer's sign, which is considered positive in lymphedema, when the skin at the base of the second toe cannot be pinched and lifted due to skin and underlying tissue thickening. This sign has a sensitivity of 92% for predicting lymphedema presence[72], but its specificity is only 57%, demanding complementary testing for suspected lymphedema when the sign is negative.

Significant edema in a patient may indicate the coexistence of chronic venous insufficiency with lipedema[73,74] and therefore should be investigated. It affects around 25% of women with lipedema and 50% of those with lipolymphedema[5], mainly when overweight and advanced age are present. Key signs and symptoms include pitting edema (negative Stemmer's sign) around ankles and feet, pruritus, restless legs, and nocturnal cramps, which often improve with limb elevation. In advanced stages of venous insufficiency, skin changes like ochre dermatitis, white scars, and ulcers may develop[5]. Diagnosis can be confirmed with complementary tests such as venous doppler ultrasound (US). In the setting of significant edema, other systemic diseases must be ruled out, such as chronic kidney disease, heart failure, liver dysfunction, and myxedema[1].

Diagnostic imaging in lipedema

A recent systematic review of 32 studies with 1154 patients analyzed different imaging modalities for the diagnosis of lipedema[62], including US, lymphoscintigraphy, MRI, computed tomography (CT) scans, dual-energy X-ray absorptiometry (DXA), and indocyanine green lymphography. Noteworthy, only 4 out of the 32 studies included in this review presented data on the diagnostic performance for lipedema. Imaging techniques primarily focus on quantitative measurements and visual assessment of subcutaneous fat and the lymphatic system. Available imaging methods include:

- **US:** can be useful to distinguish lipedema from lymphedema. In lipedema, SAT is thickened and hypoechogenic compared to controls, while the skin remains normal. In contrast, lymphedema is characterized by SAT expansion, increased skin thickness at the ankle and calf, and dermal hypoechogenicity[39]. US can also be used to diagnose lipedema. One study suggests a cutoff value of 11.7 mm for the pretibial region as a diagnosis of lipedema (79% sensitivity, 96% specificity), followed by 17.9 mm for the thigh (67% sensitivity, 94% specificity) and 8.4 mm for lateral leg thickness (78% sensitivity, 84% specificity)[75].
- **Lymphoscintigraphy:** considered the gold standard in evaluating lymphatic pathways, it helps exclude lymphatic dysfunctions by assessing lower limb edema or enlargement. Patients with lipedema usually show normal lymphatic flow and uptake, but may be slower compared to normal individuals. A study demonstrated lymphoscintigraphic changes (delay in transport and asymmetric distribution) in 47% of patients with lipedema[76]. Asymmetry between the lower limbs is also a feature observed in lymphoscintigraphy, contrasting with the bilateral clinical presentation of the disease. However, a study showed similar lymphoscintigraphic changes in patients with lipedema and obesity[41], limiting its use for differential diagnosis between these conditions.
- **CT:** can be used to evaluate patients with enlarged limbs, showing homogeneous soft tissue enlargement without skin thickening, subcutaneous edema, or muscle hypertrophy. A single study reported excellent CT performance in diagnosing lipedema, with 100% sensitivity and 95% specificity[77]. However, diagnostic cutoff values were not presented in their study. Additionally, limitations include radiation exposure and maximum table weight, as well as the inability to visualize lymphatic vessels.
- **MRI and MRL:** MRI provides information about fluid distribution and the degree of fibrosis in subcutaneous fat[78] (Fig. 3). MRL, its modified form, is useful for evaluating lymphatic circulation when lymphatic involvement is unclear. Lipedema is characterized by an increased layer of subcutaneous fat without changes in signal intensity between T2 and T1 weighted images[78]. MRL, which uses a contrast agent in the skin of the forefoot, can identify anatomical and physiological changes in the lymphatic system, aiding in differentiation between lipedema and lymphedema[79,80]. In MRL, lipedema may show dilated lymphatic vessels up to 2 mm, indicating a subclinical lymphostasis[79]. A MRL-specific protocol without injection, using T2-weighted and fat-suppressed sequences, can also be used to evaluate subcutaneous tissue and differentiate lipedema from lymphedema, lipolymphedema, and lipophlebolymphedema, avoiding the need for contrast[81]. However, cost, acquisition time, and local reactions to gadolinium injection are obstacles to a wider implementation of these methods.
- **DXA:** can provide information on fat distribution, lean mass, and bone mass, being useful for diagnosis, staging, and follow-up of patients with lipedema (Fig. 4). A study by Buso et al. found that the leg fat mass to total fat mass ratio was found to have the highest sensitivity at 95% for a cutoff value of 0.384 and the trunk/legs fat mass ratio exhibited the highest specificity at 93% for a cutoff value of 1.276[82]. DXA is non-invasive, low-cost, and involves low radiation exposure.
- **Indocyanine Green Lymphography (ICG):** an emerging technique for visualizing superficial lymphatic vessels along the limb and assessing tissue fluid drainage. In patients with lipedema, this technique revealed changes in superficial lymph flow, such as slow flow, an increased number of abnormal lymphatic vessels, and higher fluorescent intensity in the skin[83]. ICG lymphography has greater sensitivity and specificity than lymphoscintigraphy for diagnosing lymphedema[84].

The review identifies several limitations in the studies on diagnostic imaging for lipedema, primarily highlighting biases in patient selection and reference standards. Inconsistencies in applying the internationally recognized diagnostic criteria by Wold et al.[61] and the lack of comprehensive

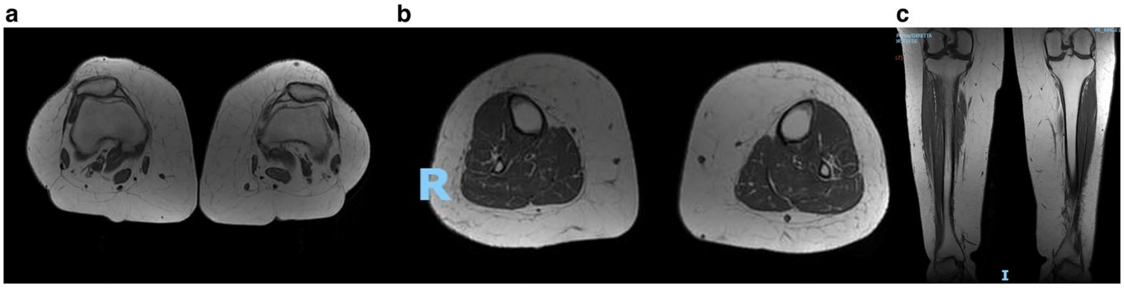

Fig. 3 | MRI features of lower-limb lipedema. Magnetic resonance T1-weighted images of the **a** knee joint line axial view **b** mid-section of the lower legs axial view and **c** lower leg coronal view showing diffuse thickening with volumetric increase of the SAT in the legs, with some areas of mild edema and fluid layers, more evident in the knee joint line.

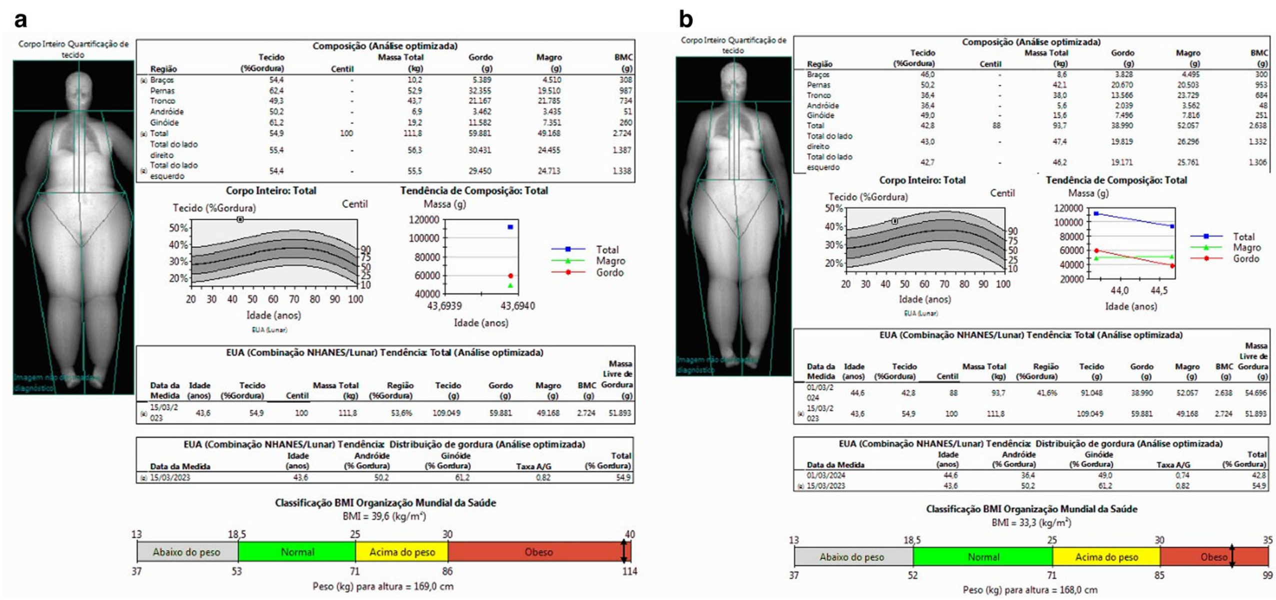

Fig. 4 | Body fat redistribution after intensive lifestyle modification in lipedema. Dual-energy X-ray Absorptiometry before (**a**) and after (**b**) 12 months of intensive lifestyle modification with diet (low-carbohydrate, avoiding alcohol, sugar, and ultra-processed foods) plus physical activity, resulting in an impressive 20.9 kg fat tissue loss (minus 11.7 kg in the legs and 1.6 kg in the arms) with massive improvement in pain and swelling sensation. This challenges the current paradigm that all patients with lipedema are highly resistant to localized fat loss.

diagnostic performance data, such as ROC curves, sensitivity, and specificity, further complicate the findings. The studies also suffer from significant heterogeneity in design, imaging techniques, and criteria, coupled with small sample sizes and inadequate healthy comparison groups. Additionally, the imaging findings often overlap with conditions like lymphedema and obesity, lacking specificity for lipedema. The absence of pathognomonic imaging patterns, limited prospective studies, and a need for standardized criteria underscore the challenges in accurately diagnosing and understanding lipedema, necessitating more robust research approaches.

Clinical treatment of lipedema

The primary goals of lipedema treatment include relieving symptoms (especially pain), improving physical function, and preventing disease progression to more advanced stages. Obesity is commonly associated with lipedema, particularly in advanced stages (3 and 4)[63]. The LIMPRINT cross-sectional study, which included 7397 lymphedema patients (57% with a BMI > 30 kg/m²), found that increased body weight negatively impacts the progression to more advanced stages of edema/lymphedema[85]. Furthermore, higher weight makes achieving effective swelling control with compression therapy significantly more challenging.

These findings underscore the importance of maintaining a healthy body weight as a key component of lipedema management. Anti-obesity treatments, including medications as recommended by the Brazilian Association for the Study of Obesity and Metabolic Syndrome (ABESO)[86], should be considered an important step in addressing lipedema in individuals with elevated overall adiposity. Recent discussions on clinical obesity highlight that the primary goals of treatment are to improve the clinical manifestations of obesity, achieve remission when possible, and prevent progression to further complications[87]. In the case of lipedema, which is often associated with overweight and obesity, signs and symptoms such as pain, heaviness, hypersensitivity, and reduced quality of life may already be evident in the early stages of the disease. These observations highlight the importance of initiating early management with anti-obesity therapy when anthropometric criteria are met, in order to prevent progression to advanced stages of lipedema, when mobility limitations commonly develop. Additionally, weight fluctuations, particularly during hormonally sensitive periods like adolescence, postpartum, or menopause, should be minimized, as they can worsen lipedema symptoms[1].

Successful treatment requires aligning patient and physician expectations. Clear explanations of the diagnosis, the underlying pathophysiology, and the limitations of conservative therapies in reducing regional fat accumulation are essential. Psychological support is often necessary to address the psychosocial distress and reduced

Box 6 | General dietary treatment guidance for lipedema[93,133]

Abolish:
- Chemicals (ultra-processed and industrialized products)
- Artificial preservatives, synthetic flavorings, colorings, and stabilizers

Consume in moderation:
- Alcohol
- Salt
- Sugars and simple carbohydrates
- Products with processed flour
- Animal proteins and fats (especially red and processed meat)

Prioritize consumption:
- Fruits and vegetables
- Whole foods
- Grains
- Healthy proteins

quality of life that can undermine long-term adherence to treatment plans[1,88].

Diet and weight loss

The dietary prescription should prioritize weight reduction through a hypocaloric diet in patients with increased overall body fat. Ideally, the diet should be low in carbohydrates, rich in fiber, vegetables, and greens, with moderate amounts of protein and poly- and monounsaturated fats, which provide antioxidant and anti-inflammatory benefits (Box 6). Avoidance of consumption of ultra-processed foods is also crucial, since its consumption is systematically associated with several adverse health outcomes[89], including obesity, and several studies suggest they drive excessive food consumption.

There are few clinical studies specifically designed for individuals with lipedema, which limits consensus on the best dietary approach. Some suggested options include the Mediterranean diet[90], ketogenic diets[91,92] (e.g., a very low-calorie ketogenic diet for 8–12 weeks followed by a maintenance phase), and time-restricted intermittent fasting, provided adequate protein intake is maintained. However, most studies lack weight-matched control groups.

The first randomized controlled trial (RCT) involving 70 women with lipedema and obesity compared a low-carbohydrate diet (LCD) to a control low-fat diet over 8 weeks, both with an intake of ~1200 kcal[93]. The LCD, with 75 g carbohydrates (25% energy) and 73 g fat (55% energy), led to greater weight (-10.2 vs. -7.4 kg) and fat mass loss (-8.6 vs. -4.3 kg) compared to the control group. It also produced more significant pain reduction (e.g., pain severity score and severest pain) and improvements in quality of life, particularly emotional well-being, energy, and social functioning. These results suggest that the pain relief observed was independent of weight loss. One hypothesis is that it may stem from a reduction in tissue water or edema, potentially alleviating nerve pressure and decreasing pain[33], along with anti-inflammatory effects mediated by elevated beta-hydroxybutyrate, such as lower levels of IL-6 and TNF-α[94]. The authors also hypothesized that LCDs, by enabling a higher intake of polyunsaturated fatty acids and improving the omega-3 to omega-6 balance, may aid in reducing inflammation[95], suggesting that the Mediterranean diet could also be beneficial for lipedema patients[90]. Furthermore, the LCD group experienced improvements in psychological well-being, which could indirectly reduce pain perception. These factors suggest that the pain reduction is likely a result of both physiological changes and enhanced psychological well-being. While the observed results are interesting, caution should be exercised when interpreting these initial findings, particularly regarding the greater weight loss observed in the LCD group and whether the better outcomes in pain and quality-of-life measures in this group are truly weight-independent. LCDs are known to induce faster weight loss in the early stages; however, studies have shown that calorie-matched LCDs and low-fat diets achieve comparable outcomes over the long term[96]. Nevertheless, the short study duration limits definitive conclusions, underscoring the need for larger, long-term trials.

Recently, a study by Cifarelli et al.[67] aimed to understand the effect of moderate (~9%) diet-induced weight loss, achieved over a period of 3 months, on body composition and metabolic function in women with obesity and lipedema. In addition, upper and lower-body adipose tissue biology was investigated before and after weight loss. The study reported that weight loss decreased total body fat mass due to reductions in both upper-body (~15% decrease in abdominal SAT and intra-abdominal adipose tissue volumes) and lower-body fat (~10-15%). However, the contribution of leg fat mass to total body fat mass and the android-to-gynoid ratio did not change after weight loss, suggesting no effect on body fat distribution. Whole-body insulin sensitivity was greater in women with obesity and lipedema than BMI-matched controls with obesity and further improved following weight loss. Specifically, hepatic insulin sensitivity increased by ~75% and whole-body insulin sensitivity assessed during the clamp procedure increased by ~15% after weight loss. Although the sample size was relatively modest ($n = 9$), the use of the hyperinsulinemic-euglycemic clamp to assess the primary outcome of metabolic function enhances the robustness of the study. This technique is considered the gold standard for quantifying insulin sensitivity and provides sufficient sensitivity and reproducibility to detect physiologically relevant differences even in smaller cohorts. In addition, all participants underwent a screening that included medical history, physical examination, standard blood tests, and a 2-h OGTT—with exclusion of individuals with diabetes, liver disease other than metabolic dysfunction–associated steatotic liver disease, excessive alcohol intake, physical activity (PA), or use of medications known to affect metabolic outcomes, including hypoglycemic agents, systemic corticosteroids, and lipid-lowering therapies. The same study[67] also assessed transcriptomic changes by bulk RNA sequencing in thigh and abdominal SAT in women with obesity and lipedema. The following results were reported: i) decreased expression of genes related to lymphatic/vascular function, namely Vascular Endothelial Growth Factor C (*Vegfc*) and its cognate receptor *Flt4* (Fms Related Receptor Tyrosine Kinase 4) encoding for VEGF receptor 3, and ii) increased expression of genes related to fibrosis and ECM remodeling in thigh SAT compared to abdominal SAT. Thigh SAT in women with lipedema also had a greater number of total and M1-like macrophages and higher expression of genes related to inflammation. Weight loss improved insulin sensitivity but did not alter adipose tissue inflammation or fibrosis at least in the short term and at this extent of fat reduction. The findings suggest that weight loss should be the first-line therapy for women with obesity and lipedema, as it improves insulin sensitivity and reduces fat mass, although it does not affect inflammation or fibrosis in adipose tissue. These results challenge the prevailing notion that lipedema fat is resistant to weight loss, demonstrating that it can decrease in response to a negative energy balance (Fig. 4, AM Faria personal data), as also reported by others[97]. However, it is important to note that current methodologies do not allow differentiation between lipedema-specific and other adipose tissue depots. Therefore, it remains uncertain whether the leg fat loss observed in these studies[67,97] reflects changes in lipedema tissue specifically.

Fig. 5 | Clinical response to complex decongestive therapy in lipedema. a Posterior view before (left) and after (right) complex decongestive therapy plus photobiomodulation and manual therapy in a lipedema type 3 stage 2 patient. **b** Anterior view before (left) and after (right) complex decongestive therapy in a lipedema type 3 stage 2 patient with associated chronic venous insufficiency.

Physical activity

PA is a paramount, non-pharmacological intervention consistently recommended for women with lipedema. Recognizing that individuals may experience pain and functional impairments, the approach to PA must be carefully adapted to each patient's specific disease stage and unique needs. Despite these challenges, consistent engagement in tailored PA should be encouraged to improve quality of life, assist in pain management, and alleviate characteristic clinical symptoms across all stages of the condition. A small randomized study investigated the effects of a 6-week supervised multimodal exercise program in patients with lipedema[98]. Participants in the exercise group ($n = 11$) engaged in aerobic and strengthening exercises twice weekly, while controls ($n = 11$) received general PA guidance. The exercise program led to significant improvements, including reductions in pain (at rest, during activity, and at night), decreased limb edema, and enhancements in exercise capacity, lower extremity muscle strength, endurance, and function, although between-group differences were not statistically significant. A few other studies suggest that PA may have beneficial effects when combined with physiotherapy[99–103]. However, existing research does not isolate the effects of PA alone and often lacks control groups. The current evidence base does not support definitive conclusions regarding the therapeutic effects of PA on lipedema symptoms. Thus, RCTs are needed to establish its efficacy in this context.

The Italian Society of Motor and Sports Sciences and the Italian Society of Phlebology have issued a consensus statement regarding the role of exercise as a non-pharmacological approach in the management of lipedema[104], with multiple potential beneficial effects on lipedema SAT, including the modulation of inflammation and lipolysis[105]. Endurance training can improve mitochondrial function and lipid metabolism in SAT, helping prevent abnormal fat accumulation[105]. Regular exercise may also reduce inflammation in lipedema SAT by enhancing catecholamine release and promoting a shift from pro-inflammatory M1 to anti-inflammatory M2 macrophages[106]. Exercise promotes lymphatic drainage, reducing fluid accumulation and swelling, with water-based activities particularly effective due to hydrostatic pressure. PA also supports adipocyte health via myokine and exosome release, and stimulates angiogenesis, improving blood flow and oxygenation to counteract hypoxia in advanced lipedema[104].

For optimal effectiveness, recommended modalities emphasize low-impact activities that support lymphatic drainage and build muscle strength[104]:

- **Water-Based Exercises:** Swimming, aqua jogging, and water aerobics are highly advised. The buoyancy reduces joint stress, while the hydrostatic pressure aids lymphatic flow, making them ideal for managing lower-limb edema exacerbated by gravity or heat.
- **Endurance Training:** Cyclical activities such as walking and running are valuable for improving mitochondrial function and overall lipid metabolism.
- **Strength and Flexibility Training:** Crucially, these practices focus on strengthening lower-body muscles, especially the legs and calves. Stronger muscles more efficiently propel lymph fluid, directly contributing to reduced edema, swelling, and discomfort, while also improving overall muscle tone, endurance, mobility, and physical function.

Ultimately, the development of tailored exercise programs is essential. By customizing activities to individual preferences and capabilities, adherence to the treatment plan is significantly enhanced, leading to more sustainable and effective long-term outcomes for individuals living with lipedema.

Supplements use in lipedema

Although evidence is limited, antioxidant supplements like flavonoids have been reported to alleviate lipedema symptoms similar to chronic venous insufficiency[5]. Diosmin has the potential to reduce oxidative stress, improve venous elasticity, lymphatic drainage, and pain[5]. While the U.S. Standards of Care for lipedema provide a low-grade recommendation for its use[5], clinical experience suggests partial symptom relief in some patients, and its excellent safety profile supports an empirical trial in selected cases.

Other supplements, including Omega-3 fatty acids, Vitamin C, curcumin, magnesium, selenium, serratiopeptidase, bromelain, and butcher's broom, have been proposed based on their mechanisms of action[107]. However, none have been rigorously studied in RCTs specifically for lipedema, so their routine use is not recommended.

Aspects of associated medications to be considered

Considering the distinct clinical attributes of lipedema, it is important to highlight that certain medication classes should generally be avoided in these patients[5]. These include glucocorticoids and thiazolidinediones, as they can exacerbate edema and fluid retention, as well as contribute to additional weight gain. Thiazide and loop diuretics might lead to lymphatic fluid depletion and increased local protein concentration, potentially causing local fibrosclerosis. While oral contraceptives for birth control and hormone replacement therapy for menopause are not contraindicated, their use should be prudent, with careful monitoring for any indications of disease progression.

Physiotherapy

One of the cornerstones of conservative lipedema treatment is Complex Decongestive Therapy (CDT)[106,108,109]. This composite treatment, adapted from the gold standard for lymphedema, aims to address the various clinical manifestations of lipedema[99,100]. It includes:

- **Manual Lymph Drainage:** Gentle, rhythmic massage techniques designed to stimulate lymphatic flow and reduce fluid accumulation, which can alleviate pain and hypersensitivity in affected areas.
- **Compression Therapy:** This is vital for managing interstitial edema and optimizing venous and lymphatic return[5,110]. Compression is applied using bandages, elastic stockings, or specialized garments. The recommended pressure varies with disease stage, from 10 to 20 mmHg for Stage 1 lipedema to 20 to 40 mmHg for Stages 2 and 3[5]. This therapy

Box 7 | Other potential physiotherapy approaches in lipedema

- **Musculoskeletal Motor Physiotherapy:**
  - Addresses orthopedic dysfunctions and joint biomechanics affected by lipedema (e.g., knee osteoarthritis)[134].
  - **Muscle Strengthening:** Improves lower body strength, lymphatic drainage, mobility, and physical function[98].
  - **Fascial and Orthopedic Management:** Targets fascia-muscle changes[135] and lower quadriceps weakness observed in lipedema[136].
  - **Photobiomodulation:** Low-level laser/led-light emitting diode therapy may reduce fibrosis, pain, and tissue volume in lymphedema[138] (investigational for lipedema).
  - **Vibration Therapy:** Low-frequency vibration tables can reduce lower limb circumference when combined with lymphatic drainage[139].
  - **Manual Therapy:** Connective tissue manipulation may decrease fat, fibrosis, and limb volume[135,140].
- **Electrophysical and Other Therapeutic Agents:**
  - Use with caution, as some may worsen inflammation or adipose deposition in lipedema-affected areas[137].
  - **Extracorporeal Shock Wave Therapy:** Enhances ECM, angiogenesis, and lymphangiogenesis; reduces oxidative stress and pain. When combined with CDT, it has shown improvements in skin appearance, further pain reduction, and additional decreases in limb volume[51].
- **Intermittent Pneumatic Compression Therapy:**
  - Pneumatic devices cyclically inflate and deflate to promote lymph flow and interstitial fluid absorption.
  - **Objective Benefits:** Reduces leg volume, total body water, and SAT thickness[141].
  - **Subjective Benefits:** Improves pain, swelling, heaviness, and lower limb function; enhances quality of life[100,142].

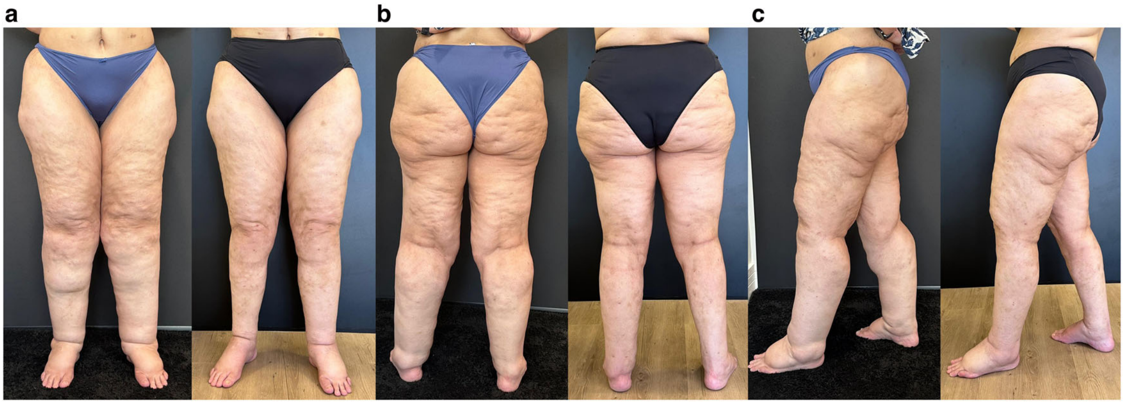

Fig. 6 | Outcomes of tumescent liposuction in advanced lipedema. **a** Anterior, **b** Posterior and **c** Lateral views of a lipedema patient type 3 stage 3 before (left) and after (right) tumescent liposuction procedure. Image courtesy of Dr. Juliana Reis (Instituto Lipedema Brasil).

also reduces inflammation and provides proprioceptive stimuli, which can help modulate pain perception.
- **Miolymphokinetic Exercise Prescriptions:** Tailored exercises designed to activate muscles, which in turn pump lymph fluid, aiding drainage and improving circulation.
- **Skin Care:** Essential for maintaining skin health and preventing complications in areas prone to swelling and fluid retention.

A growing body of evidence demonstrates that CDT significantly reduces limb volume and pain, while also improving quality of life in patients with lipedema[99,100] (Fig. 5).

Box 7 summarizes additional physiotherapy approaches currently under investigation in lipedema. Overall, physiotherapy provides a comprehensive framework to manage pain, fibrosis, edema, and lymphatic dysfunction, aiming to improve patients' quality of life. Continued research remains essential to further refine and optimize these therapeutic strategies.

Surgical treatment of lipedema

Lipedema has historically been managed with conservative therapies. However, in recent years, surgical options, particularly liposuction and reconstructive procedures, have gained traction, especially for severe cases[111]. Modern techniques using lymphatic-sparing cannulas are now the standard for surgical treatment[112].

Given that lipedema often occurs alongside obesity, bariatric surgery may be considered based on the same criteria used for individuals without lipedema—patients with a BMI ≥ 40 kg/m² or 35–40 kg/m² with obesity related diseases when clinical treatment has failed[113]. However, data on the effects of bariatric surgery on lipedema remain limited and largely anecdotal[114]. A retrospective case series of 13 patients showed that, despite an average weight loss exceeding 50 kg, pain and other lipedema-related symptoms often persisted, providing minimal relief[115]. Similarly, a recent scoping review analyzed 49 reported cases of women diagnosed with lipedema in the context of bariatric surgery[116]. Most underwent sleeve gastrectomy (51%) or Roux-en-Y gastric bypass (45%), with a mean BMI of ~50 kg/m². Lipedema was often diagnosed only after surgery, indicating that bariatric surgery alone does not significantly improve symptoms and highlighting the need for preoperative recognition and tailored management.

Liposuction has emerged as the primary surgical treatment, removing diseased SAT and improving symptoms, mobility, and quality of life[117] (Figs. 6 and 7). While younger patients with a BMI < 35 kg/m² and elastic skin tend to benefit the most, those with higher BMIs can also undergo the procedure, ideally after their lowest possible weight[118]. The tumescent liposuction technique is commonly employed, involving a saline solution mixed with adrenaline and anesthetics to facilitate fat removal with minimal trauma[112]. Brazilian guidelines suggest aspirated volumes should not exceed 7% of body weight, often requiring multiple sessions[112]. Technologies like

Fig. 7 | Combined surgical management in severe lipedema. **a** Anterior, **b** Posterior and **c** Lateral views of a lipedema patient (type 3 stage 4 – more severe disease above knees) before (left), after first procedure (middle), and second procedure (right) of tumescent liposuction plus dermolipectomy. Image courtesy of Dr Fabio Kamamoto (Instituto Lipedema Brasil).

Box 8 | Main research gaps in current lipedema knowledge

Genetic and Molecular Basis

- **Identification of Genetic Markers**: While genetic predispositions for lipedema exist, no single gene has been identified. Larger studies with lipedema patients and appropriate controls are needed to pinpoint specific genetic markers.
- **Epigenetic Factors**: The role of epigenetic modifications in lipedema has not been explored. Understanding how environmental factors influence genetic expression could provide insights into disease progression and management.

Hormonal Influences

- **Role of Estrogen and Other Hormones**: The exact mechanisms by which hormones like estrogen influence lipedema are not fully understood. Research into hormonal pathways and their impact on adipose tissue expansion and remodeling could lead to targeted therapies.
- **Hormonal Modulation**: Investigating how hormonal treatments or interventions might alter the course of the disease could offer new therapeutic avenues.

Pathophysiology

- **Understanding Adipose Tissue Remodeling**: More research is needed to understand the histological changes in lipedema adipose tissue, such as inflammation, fibrosis, and vascular alterations, and how these changes affect disease progression.
- **Inflammatory and Immune Mechanisms**: The role of inflammation and immune responses in lipedema is unclear. While macrophages are involved, further investigation into other immune cells, such as mast cells or neutrophils, is needed.

Epidemiology

- **Prevalence and Incidence:** Comprehensive epidemiological data on the prevalence and incidence of lipedema across different populations are lacking.

Diagnostic Criteria, Serum Biomarkers and Imaging

- **Standardization of Diagnostic Criteria**: There is a lack of consensus on diagnostic criteria, leading to misdiagnosis. Developing standardized criteria could improve early detection and treatment.
- **Diagnostic and Prognostic Biomarkers:** There is a need for research to identify serum biomarkers that can aid in the early diagnosis and differentiation of lipedema from other conditions. Biomarkers that predict disease progression or response to treatment could also help tailor individual management plans
- **Advanced Imaging Techniques**: While various imaging modalities have been studied, none are definitive. Research into more precise imaging techniques could aid in distinguishing lipedema from similar conditions.

Therapeutic Approaches

- **Effectiveness of Conservative Treatments**: There is a need for more systematic studies to evaluate the effectiveness of conservative treatments like diet, exercise, weight loss, anti-obesity medications, supplements and physiotherapy procedures. It is crucial to identify molecular and biological factors that may predispose specific patient subgroups to resistance to localized fat loss.
- **Long-term Outcomes of Surgical Interventions**: While liposuction is used for symptom relief, its long-term effects and optimal patient selection criteria require further investigation.

Psychosocial Impact

- **Quality of Life Assessments**: More research is needed to assess the psychosocial impact of lipedema and develop interventions that address mental health and quality of life.
- **Patient Education and Awareness**: Understanding the best methods for educating patients and healthcare providers about lipedema could improve management and reduce stigma.

Comorbidities and Differential Diagnosis

- **Association with Other Conditions**: Research into the relationship between lipedema and other conditions, such as obesity and lymphedema, could help clarify differential diagnoses and treatment strategies.
- **Impact of Comorbidities on Disease Progression**: Understanding how comorbid conditions affect lipedema could lead to more personalized treatment plans.

lasers and radiofrequency for enhanced skin tightening lack sufficient evidence. Additionally, treating varicose veins pre-surgery and incorporating physiotherapy postoperatively can optimize safety and recovery[5,112].

Combined therapies, including liposuction with dermolipectomy, have shown promising esthetic and functional results[119] (Fig. 7), though larger studies are needed to confirm these findings. A systematic review of liposuction as a tool for managing lipedema has demonstrated a significant reduction in thigh circumference, ranging from 6 to 8 cm, and an average decrease of 6.9% in leg volume following the procedure[120]. Furthermore, another study evaluating the outcomes of liposuction in 860 lipedema patients demonstrated a significant reduction in pain, with scores dropping from 6.99 to 2.24, highlighting the effectiveness of liposuction in alleviating pain perception irrespective of the disease stage or onset of lipedema[121].

Despite its benefits, liposuction carries risks. A meta-analysis of seven studies assessing 451 lipedema patients[122] highlighted temporary complications such as methemoglobinemia (100%), caused by prilocaine in the anesthetic and effectively treated with toluidine blue[123]. Additionally, 82% experienced temporary burning sensations that resolved spontaneously[123]. Less common complications included mild arm-vein phlebitis (1.8%), epileptic seizures during methemoglobinemia (0.9%), microscopic pulmonary fat embolism (0.9%), and acute pulmonary edema (0.9%)[123]. Schmeller et al. reported postoperative wound infections in 1.4% of cases and severe bleeding in 0.3%[124], while Rapprich et al. identified a single case of deep vein thrombosis (4%)[125].

In conclusion, the current evidence on the utilization of liposuction for the management of lipedema is limited, primarily due to the observational nature of most studies and the absence of standardized surgical protocols. RCTs are needed to thoroughly assess the long-term efficacy and safety of the procedure. The impact of liposuction on metabolic function remains unclear. Given that lipedema is linked to improved insulin sensitivity, it is unknown whether tissue removal could negatively affect metabolism, as suggested in other contexts[126]. It is important to note that liposuction and other surgical interventions are not definitive cures for lipedema, as patients typically require ongoing maintenance of conservative treatment pillars throughout their lives. Aligning patient expectations with realistic surgical outcomes is crucial, and surgical treatments should be reserved for women with more severe symptoms.

Concluding remarks

This review delves into the pathophysiology of lipedema, characterized by unique fat distribution and its potential association with pain and edema. Histological findings indicate adipocyte hypertrophy, fibrosis, and vascular changes, suggesting systemic implications that extend beyond the condition's disfiguring appearance. GWAS studies point to a polygenic basis, with environmental and hormonal factors, particularly estrogen, playing crucial roles in adipose tissue remodeling and disease progression, meriting further investigation.

A crucial aspect of managing lipedema lies in the emphasis on clinical conservative treatments. These include dietary modifications, weight management, regular exercise, and physiotherapy. Such interventions can play a significant role in alleviating symptoms, improving mobility, and enhancing the quality of life for patients. Diet and weight loss strategies should not be underemphasized since they are essential in managing the overall health of individuals with lipedema and concomitant overweight or obesity. The recent relevant article on adipose tissue biology and weight loss challenges the preconception that lipedema fat is entirely resistant to weight loss[67]. This perspective suggests that while lipedema fat may be more resistant to traditional weight loss methods compared to other types of adipose tissue, it is not entirely immune to reduction (Fig. 4). This insight encourages a reevaluation of treatment strategies and supports the potential for integrated approaches that combine lifestyle modifications with targeted therapies to achieve better outcomes in fat reduction and symptom management. Exercise and physiotherapy, including manual lymphatic drainage and CDT, can help manage symptoms and prevent further complications. These conservative approaches should be integrated into a comprehensive treatment plan, tailored to the individual needs of patients, and considered alongside other therapeutic options.

In cases where conservative management does not sufficiently alleviate symptoms or when the disease progresses to more severe stages, surgical interventions may be indicated. Tumescent liposuction is often considered for its ability to directly remove lipedema adipose tissue, potentially reducing pain and improving function. Surgical intervention is typically recommended for patients who experience significant physical limitations or psychological distress due to the disproportionate fat distribution. However, it is crucial that surgical options are considered carefully, with a comprehensive understanding of the potential risks and benefits, and in conjunction with ongoing conservative management to maintain results and manage overall health.

Lipedema has received much more attention in the last few years, and although this is crucial for disease awareness and better diagnosis rates, it also possesses important challenges, as with the paucity of data on ideal management, non-validated claims and therapies are being widely offered. Here we highlight some research gaps that should be bridged in order to offer the best possible care to those living with the disease (Box 8).

Data availability

No datasets were generated or analysed during the current study.

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References

1. Buso, G. et al. Lipedema: A Call to Action!. *Obesity* **27**, 1567–1576 (2019).
2. Forner-Cordero, I. & Muñoz-Langa, J. Is lipedema a progressive disease? *Vasc. Med.* https://doi.org/10.1177/1358863x241306415 (2025).
3. Faerber, G. et al. S2k guideline lipedema. *J. Dtsch Dermatol Ges.* **22**, 1303–1315 (2024).
4. Keith, L. et al. Proposed Framework for Research Case Definitions of Lipedema. *Lymphat Res Biol.* **22**, 93–105 (2024).
5. Herbst, K. L. et al. Standard of care for lipedema in the United States. *Phlebology* **36**, 779–796 (2021).
6. Allen, E. & Hines, E. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema. *Proc. Staff Meet. Mayo Clin.* **15**, 184–187 (1940).
7. *International Classification of Diseases, Eleventh Revision (ICD-11)*, https://icd.who.int/browse11 (2019/2021).
8. Lomeli, L. D., Makin, V., Bartholomew, J. R. & Burguera, B. Lymphedema vs lipedema: Similar but different. *Cleve Clin. J. Med* **91**, 425–436 (2024).
9. Child, A. H. et al. Lipedema: an inherited condition. *Am. J. Med Genet. A* **152A**, 970–976 (2010).
10. Tiwari, A., Myint, F. & Hamilton, G. Management of lower limb lymphoedema in the United Kingdom. *Eur. J. Vasc. Endovasc. Surg.* **31**, 311–315 (2006).
11. Bagatir, N. et al. Lipedema awareness and knowledge level among medical doctors in Turkey: A cross-sectional study highlighting the diagnosis and treatment gap. *Phlebology*, https://doi.org/10.1177/02683555251332998 (2025).
12. Földi M. F. E. & Kubik S. *Textbook of Lymphology*. (Elsevier, 2005).
13. Forner-Cordero, I., Szolnoky, G., Forner-Cordero, A. & Kemeny, L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome - systematic review. *Clin. Obes.* **2**, 86–95 (2012).
14. Podda, M., Kottmann, T., Kaak, I., Baum, S. & Rapprich, S. Treatment of lipoedema using liposuction. *Phlebologie* **44**, 121–132 (2018).
15. Amato, A. C. M., Amato, F. C. M., Benitti, D. A. & Amato, L. G. L. Development of a questionnaire and screening model for lipedema. *J. Vasc. Bras.* **19**, e20200114 (2020).
16. Eakin, G. & Peterson, S. *Lipedema: A Current Understanding of its Pathology and Natural History*, https://static1.squarespace.com/static/5775899ac534a5e813c050db/t/651595ab6fc6510c8a69185f/1695913388209/Lipedema%E2%80%93A+Current+Understanding+Pathology+%26+Natural+History_May2023.pdf (2023).
17. *Learning By Listening: Early Findings from the Lipedema Foundation Registry Survey*, https://lipedema.org/lfr-report (2022).
18. Michelini, S. et al. A Multi-Gene Panel to Identify Lipedema-Predisposing Genetic Variants by a Next-Generation Sequencing

Strategy. *J. Pers. Med.* **12**, https://doi.org/10.3390/jpm12020268 (2022).
19. Waxler, J. L. et al. Altered body composition, lipedema, and decreased bone density in individuals with Williams syndrome: A preliminary report. *Eur. J. Med. Genet.* **60**, 250–256 (2017).
20. Zechner, U. et al. Familial Sotos syndrome caused by a novel missense mutation, C2175S, in NSD1 and associated with normal intelligence, insulin dependent diabetes, bronchial asthma, and lipedema. *Eur. J. Med. Genet.* **52**, 306–310 (2009).
21. Bano, G. et al. Pit-1 mutation and lipoedema in a family. *Exp. Clin. Endocrinol. Diab.* **118**, 377–380 (2010).
22. Michelini, S. et al. Aldo-Keto Reductase 1C1 (AKR1C1) as the First Mutated Gene in a Family with Nonsyndromic Primary Lipedema. *Int. J. Mol. Sci.* **21**, https://doi.org/10.3390/ijms21176264 (2020).
23. Gualtieri, P. et al. The role of MTHFR polymorphisms in the risk of lipedema. *Eur. Rev. Med. Pharm. Sci.* **27**, 1625–1632 (2023).
24. Grigoriadis, D. et al. Investigation of clinical characteristics and genome associations in the 'UK Lipoedema' cohort. *PLoS One* **17**, e0274867 (2022).
25. Klimentidis, Y. C. et al. Genome-wide association study of a lipedema phenotype among women in the UK Biobank identifies multiple genetic risk factors. *Eur. J. Hum. Genet.* **31**, 338–344 (2023).
26. Bertlich, M., Jakob, M., Bertlich, I., Schift, R. & Bertlich, R. Lipedema in a male patient: report of a rare case - management and review of the literature. *GMS Interdiscip. Plast. Reconstr. Surg. DGPW* **10**, Doc11 (2021).
27. Cadart, O. et al. Lipedema and Klinefelter Syndrome in Two Morbidly Obese Patients. *Androgens: Clin. Res. Ther.* **2**, 134–140 (2021).
28. Amato, A. C., Amato, J. S., Benitti, D. & Santos, K. D. Lipedema in men: a retrospective case series of five patients from a Brazilian Referral Center. *Cureus* **17**, e87332 (2025).
29. Kruglikov, I. L., Joffin, N. & Scherer, P. E. The MMP14-caveolin axis and its potential relevance for lipoedema. *Nat. Rev. Endocrinol.* **16**, 669–674 (2020).
30. Al-Ghadban, S., Isern, S. U., Herbst, K. L. & Bunnell, B. A. The expression of adipogenic marker is significantly increased in estrogen-treated lipedema adipocytes differentiated from adipose stem cells in vitro. *Biomedicines* **12**, https://doi.org/10.3390/biomedicines12051042 (2024).
31. Felmerer, G. et al. Adipose tissue hypertrophy, an aberrant biochemical profile and distinct gene expression in lipedema. *J. Surg. Res* **253**, 294–303 (2020).
32. Kruppa, P. et al. Lipedema stage affects adipocyte hypertrophy, subcutaneous adipose tissue inflammation and interstitial fibrosis. *Front. Immunol.* **14**, 1223264 (2023).
33. Al-Ghadban, S. et al. Dilated blood and lymphatic microvessels, angiogenesis, increased macrophages, and adipocyte hypertrophy in lipedema thigh skin and fat tissue. *J. Obes.* **2019**, 8747461 (2019).
34. Suga, H. et al. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. *J. Cutan. Pathol.* **36**, 1293–1298 (2009).
35. Bel Lassen, P. et al. The FAT Score, a fibrosis score of adipose tissue: predicting weight-loss outcome after gastric bypass. *J. Clin. Endocrinol. Metab.* **102**, 2443–2453 (2017).
36. Divoux, A. et al. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. *Diabetes* **59**, 2817–2825 (2010).
37. Michelini, S. et al. Endothelial cell alterations in capillaries of adipose tissue from patients affected by lipedema. *Obesity* **33**, 695–708 (2025).
38. Bertsch, T., Erbacher, G. & Elwell, R. Lipoedema: a paradigm shift and consensus. *J. Wound Care* **29**, 1–51 (2020).
39. Iker, E., Mayfield, C. K., Gould, D. J. & Patel, K. M. Characterizing lower extremity lymphedema and lipedema with cutaneous ultrasonography and an objective computer-assisted measurement of dermal echogenicity. *Lymphat Res Biol.* **17**, 525–530 (2019).
40. Greene, A. K. & Sudduth, C. L. Lower extremity lymphatic function predicted by body mass index: a lymphoscintigraphic study of obesity and lipedema. *Int J. Obes.* **45**, 369–373 (2021).
41. Chachaj, A. et al. Lymphoscintigraphic alterations in lower limbs in women with lipedema in comparison to women with overweight/obesity. *Front. Physiol.* **14**, 1099555 (2023).
42. Crescenzi, R. et al. Tissue sodium content is elevated in the skin and subcutaneous adipose tissue in women with lipedema. *Obesity* **26**, 310–317 (2017).
43. Crescenzi, R. et al. Lipedema and Dercum's disease: a new application of bioimpedance. *Lymphat Res. Biol.* **17**, 671–679 (2019).
44. Crescenzi, R. et al. Subcutaneous adipose tissue edema in lipedema revealed by noninvasive 3T MR Lymphangiography. *J. Magn. Reson. Imaging* **57**, 598–608 (2023).
45. Machnik, A. et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C–dependent buffering mechanism. *Nat. Med.* **15**, 545–552 (2009).
46. Kempa, S. et al. Serum metabolomic profiling of patients with lipedema. *Int. J. Mol. Sci*. **24**, https://doi.org/10.3390/ijms242417437 (2023).
47. Straub, L. G. et al. Defining lipedema's molecular hallmarks by multi-omics approach for disease prediction in women. *Metabolism* **168**, https://doi.org/10.1016/j.metabol.2025.156191 (2025).
48. Cifarelli, V. et al. Decreased adipose tissue oxygenation associates with insulin resistance in individuals with obesity. *J. Clin. Invest.* **130**, 6688–6699 (2020).
49. Kruglikov, I. L. & Scherer, P. E. Is the endotoxin-complement cascade the major driver in lipedema?. *Trends Endocrinol. Metab.* **35**, 769–780 (2024).
50. Buck, D. W. 2nd & Herbst, K. L. Lipedema: a relatively common disease with extremely common misconceptions. *Plast. Reconstr. Surg. Glob. Open* **4**, e1043 (2016).
51. Siems, W., Grune, T., Voss, P. & Brenke, R. Anti-fibrosclerotic effects of shock wave therapy in lipedema and cellulite. *Biofactors* **24**, 275–282 (2005).
52. Escobedo, N. & Oliver, G. The lymphatic vasculature: its role in adipose metabolism and obesity. *Cell Metab.* **26**, 598–609 (2017).
53. Scallan, J. P., Hill, M. A. & Davis, M. J. Lymphatic vascular integrity is disrupted in type 2 diabetes due to impaired nitric oxide signalling. *Cardiovasc Res.* **107**, 89–97 (2015).
54. Cifarelli, V. et al. Visceral obesity and insulin resistance associate with CD36 deletion in lymphatic endothelial cells. *Nat. Commun.* **12**, 3350 (2021).
55. AlZaim, I., de Rooij, L., Sheikh, B. N., Borgeson, E. & Kalucka, J. The evolving functions of the vasculature in regulating adipose tissue biology in health and obesity. *Nat. Rev. Endocrinol.* **19**, 691–707 (2023).
56. Seo, J. B. et al. Knockdown of Ant2 Reduces Adipocyte Hypoxia And Improves Insulin Resistance in Obesity. *Nat. Metab.* **1**, 86–97 (2019).
57. Halberg, N. et al. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. *Mol. Cell Biol.* **29**, 4467–4483 (2009).
58. Sun, K., Halberg, N., Khan, M., Magalang, U. J. & Scherer, P. E. Selective inhibition of hypoxia-inducible factor 1alpha ameliorates adipose tissue dysfunction. *Mol. Cell Biol.* **33**, 904–917 (2013).
59. Escribese, M. M., Casas, M. & Corbi, A. L. Influence of low oxygen tensions on macrophage polarization. *Immunobiology* **217**, 1233–1240 (2012).
60. Sun, K. et al. Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction. *Nat. Commun.* **5**, 3485 (2014).

61. Wold, L. E., Hines, E. A. Jr. & Allen, E. V. Lipedema of the legs; a syndrome characterized by fat legs and edema. *Ann. Intern Med.* **34**, 1243–1250 (1951).
62. van la Parra, R. F. D., Deconinck, C. & Krug, B. Diagnostic imaging in lipedema: A systematic review. *Obes. Rev.* **25**, e13648 (2024).
63. Falck, J., Rolander, B., Nygardh, A., Jonasson, L. L. & Martensson, J. Women with lipoedema: a national survey on their health, health-related quality of life, and sense of coherence. *BMC Women's. Health* **22**, 457 (2022).
64. Schwartz, M. W. et al. Obesity pathogenesis: an endocrine society scientific statement. *Endocr. Rev.* **38**, 267–296 (2017).
65. Torre, Y. S., Wadeea, R., Rosas, V. & Herbst, K. L. Lipedema: friend and foe. *Horm. Mol. Biol. Clin. Investig.* **33**, https://doi.org/10.1515/hmbci-2017-0076 (2018).
66. Duhon, B. H., Phan, T. T., Taylor, S. L., Crescenzi, R. L. & Rutkowski, J. M. Current mechanistic understandings of lymphedema and lipedema: tales of fluid, fat, and fibrosis. *Int. J. Mol. Sci*. **23**, https://doi.org/10.3390/ijms23126621 (2022).
67. Cifarelli, V. et al. Adipose tissue biology and effect of weight loss in women with lipedema. *Diabetes*, https://doi.org/10.2337/db24-0890 (2024).
68. Bauer, A. T. et al. New insights on lipedema: the enigmatic disease of the peripheral fat. *Plast. Reconstr. Surg.* **144**, 1475–1484 (2019).
69. Beltran, K. & Herbst, K. L. Differentiating lipedema and Dercum's disease. *Int J. Obes.* **41**, 240–245 (2017).
70. Erbacher, G. & Bertsch, T. Lipoedema and Pain: What is the role of the psyche? – Results of a pilot study with 150 patients with Lipoedema. *Phlebologie* **49**, 305–316 (2020).
71. Clarke, C., Kirby, J. N., Smidt, T. & Best, T. Stages of lipoedema: experiences of physical and mental health and health care. *Qual. Life Res.* **32**, 127–137 (2023).
72. Goss, J. A. & Greene, A. K. Sensitivity and specificity of the stemmer sign for lymphedema: a clinical lymphoscintigraphic study. *Plast. Reconstr. Surg. Glob. Open* **7**, e2295 (2019).
73. Rockson, S. G. et al. Exploring disease interrelationships in patients with lymphatic disorders: A single center retrospective experience. *Clin. Transl. Med.* **12**, e760 (2022).
74. Forner-Cordero, I., Perez-Pomares, M. V., Forner, A., Ponce-Garrido, A. B. & Munoz-Langa, J. Prevalence of clinical manifestations and orthopedic alterations in patients with lipedema: A prospective cohort study. *Lymphology* **54**, 170–181 (2021).
75. Amato, A. C. M., Saucedo, D. Z., Santos, K. D. S. & Benitti, D. A. Ultrasound criteria for lipedema diagnosis. *Phlebology* **36**, 651–658 (2021).
76. Forner-Cordero, I., Olivan-Sasot, P., Ruiz-Llorca, C. & Munoz-Langa, J. Lymphoscintigraphic findings in patients with lipedema. *Rev. Esp. Med Nucl. Imagen Mol. (Engl. Ed.)* **37**, 341–348 (2018).
77. Monnin-Delhom, E. D., Gallix, B. P., Achard, C., Bruel, J. M. & Janbon, C. High resolution unenhanced computed tomography in patients with swollen legs. *Lymphology* **35**, 121–128 (2002).
78. Dimakakos, P. B. et al. MRI and ultrasonographic findings in the investigation of lymphedema and lipedema. *Int Surg.* **82**, 411–416 (1997).
79. Lohrmann, C., Foeldi, E. & Langer, M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvasc. Res.* **77**, 335–339 (2009).
80. Lohrmann, C., Foeldi, E., Speck, O. & Langer, M. High-resolution MR lymphangiography in patients with primary and secondary lymphedema. *AJR Am. J. Roentgenol.* **187**, 556–561 (2006).
81. Guerrini, S. et al. Magnetic resonance lymphangiography: with or without contrast?. *Diagn. Inter. Radio.* **26**, 587–595 (2020).
82. Buso, G. et al. Body composition assessment by dual-energy X-Ray Absorptiometry: a useful tool for the diagnosis of lipedema. *Obes. Facts* **15**, 762–773 (2022).
83. Zaleska, M. T., Olszewski, W. L. & Krzesniak, N. E. Lower limb lipedema-superficial lymph flow, skin water concentration, skin and subcutaneous tissue elasticity. *Lymphat Res Biol.* **21**, 60–69 (2023).
84. Mihara, M. et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One* **7**, e38182 (2012).
85. Burian, E. A. et al. The impact of obesity on chronic oedema/lymphoedema of the leg - an international multicenter cross-sectional study (LIMPRINT). *Int J. Obes.* **48**, 1238–1247 (2024).
86. Moreira, R. O. et al. Pharmacologic Treatment of Obesity in adults and its impact on comorbidities: 2024 Update and Position Statement of Specialists from the Brazilian Association for the Study of Obesity and Metabolic Syndrome (Abeso) and the Brazilian Society of Endocrinology and Metabolism (SBEM). *Arch. Endocrinol. Metab.* **68**, e240422 (2024).
87. Rubino, F. et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* https://doi.org/10.1016/S2213-8587(24)00316-4 (2025).
88. Kruppa, P. et al. Lipedema-pathogenesis, diagnosis, and treatment options. *Dtsch Arztebl Int.* **117**, 396–403 (2020).
89. Lane, M. M. et al. Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. *BMJ* **384**, e077310 (2024).
90. Di Renzo, L. et al. Potential effects of a modified mediterranean diet on body composition in lipoedema. *Nutrients* **13**, https://doi.org/10.3390/nu13020358 (2021).
91. Sorlie, V. et al. Effect of a ketogenic diet on pain and quality of life in patients with lipedema: The LIPODIET pilot study. *Obes. Sci. Pr.* **8**, 483–493 (2022).
92. Verde, L. et al. Ketogenic diet: a nutritional therapeutic tool for lipedema?. *Curr. Obes. Rep.* **12**, 529–543 (2023).
93. Lundanes, J. et al. Effect of a low-carbohydrate diet on pain and quality of life in female patients with lipedema: a randomized controlled trial. *Obesity* **32**, 1071–1082 (2024).
94. Puchalska, P. & Crawford, P. A. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab.* **25**, 262–284 (2017).
95. DiNicolantonio, J. J. & O'Keefe, J. The importance of maintaining a low Omega-6/Omega-3 ratio for reducing the risk of autoimmune diseases, asthma, and allergies. *Mo Med.* **118**, 453–459 (2021).
96. Shai, I. et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N. Engl. J. Med* **359**, 229–241 (2008).
97. Jeziorek, M., Szuba, A., Kujawa, K. & Regulska-Ilow, B. The effect of a low-carbohydrate, high-fat diet versus moderate-carbohydrate and fat diet on body composition in patients with lipedema. *Diab. Metab. Syndr. Obes.* **15**, 2545–2561 (2022).
98. Sakizli Erdal, E., Ergin, C., Haspolat, M., Erturk, B. & Keser, I. Effects of multimodal exercise program on edema, pain, exercise capacity, lower extremity muscle strength and function in patients with lipedema. *Phlebology*, 2683555251343148, https://doi.org/10.1177/02683555251343148 (2025).
99. Donahue, P. M. C. et al. Physical therapy in women with early stage lipedema: potential impact of multimodal manual therapy, compression, exercise, and education interventions. *Lymphat Res. Biol.* **20**, 382–390 (2022).
100. Atan, T. & Bahar-Ozdemir, Y. The effects of complete decongestive therapy or intermittent pneumatic compression therapy or exercise only in the treatment of severe lipedema: a randomized controlled trial. *Lymphat Res Biol.* **19**, 86–95 (2021).
101. Mortimer, P. S. et al. LymphActiv: a digital physical activity behavior intervention for the treatment of lymphedema and lipedema. *Lymphat Res Biol.* **22**, 112–119 (2024).
102. Czerwinska, M., Gruszecki, M., Ruminski, J. & Hansdorfer-Korzon, R. Evaluation of the effectiveness of compression therapy combined with exercises versus exercises only among lipedema patients using

various outcome measures. *Life* **14**, https://doi.org/10.3390/life14111346 (2024).
103. Ricolfi, L. et al. Micromassage compression leggings associated with physical exercise: pilot study and example of evaluation of the clinical and instrumental effectiveness of conservative treatment in lipedema. *Life* **14**, https://doi.org/10.3390/life14070854 (2024).
104. Annunziata, G. et al. The role of physical exercise as a therapeutic tool to improve lipedema: A Consensus Statement from the Italian Society of Motor and Sports Sciences (Societa Italiana di Scienze Motorie e Sportive, SISMeS) and the Italian Society of Phlebology (Societa Italiana di Flebologia, SIF). *Curr. Obes. Rep.* **13**, 667–679 (2024).
105. Laurens, C., de Glisezinski, I., Larrouy, D., Harant, I. & Moro, C. Influence of acute and chronic exercise on abdominal fat lipolysis: an update. *Front Physiol.* **11**, 575363 (2020).
106. Esmer, M., Schingale, F. J., Unal, D., Yazici, M. V. & Guzel, N. A. Physiotherapy and rehabilitation applications in lipedema management: A literature review. *Lymphology* **53**, 88–95 (2020).
107. Cannataro, R. & Cione, E. Nutritional supplements and lipedema: scientific and rational use. *Nutraceuticals* **2**, 270–277 (2022).
108. Szolnoky, G. et al. Lymphedema treatment decreases pain intensity in lipedema. *Lymphology* **44**, 178–182 (2011).
109. Szolnoky, G. et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. *Lymphology* **41**, 161–166 (2008).
110. Czerwinska, M., Teodorczyk, J., Spychala, D. & Hansdorfer-Korzon, R. The Usefulness of the Application of Compression Therapy among Lipedema Patients-Pilot Study. *Int. J. Environ. Res. Public Health* **20**, https://doi.org/10.3390/ijerph20020914 (2023).
111. Dadras, M., Mallinger, P. J., Corterier, C. C., Theodosiadi, S. & Ghods, M. Liposuction in the Treatment of Lipedema: A Longitudinal Study. *Arch. Plast. Surg.* **44**, 324–331 (2017).
112. Kamamoto, F. et al. Lipedema: exploring pathophysiology and treatment strategies - state of the art. *J. Vasc. Bras.* **23**, e20240025 (2024).
113. Wounds, U. Best practice guidelines: the management of lipoedema. *London: wounds UK* (2017).
114. Bast, J. H., Ahmed, L. & Engdahl, R. Lipedema in patients after bariatric surgery. *Surg. Obes. Relat. Dis.* **12**, 1131–1132 (2016).
115. Cornely, M. E. et al. Persistent lipedema pain in patients after bariatric surgery: a case series of 13 patients. *Surg. Obes. Relat. Dis.* **18**, 628–633 (2022).
116. Zevallos, A., Schmidt, J., Thaher, O., Bausch, D. & Pouwels, S. Lipedema after Bariatric and Metabolic Surgery: A Scoping Review. *Obes. Surg.* **35**, 3241–3245 (2025).
117. Georgiou, I., Kruppa, P., Schmidt, J. & Ghods, M. Liposuction for lipedema: functional therapy or aesthetic procedure?. *Aesthet. Plast. Surg.* **45**, 212–213 (2021).
118. Sudduth, C. L. & Greene, A. K. Current overview of obesity-induced lymphedema. *Adv. Wound Care* **11**, 392–398 (2022).
119. Warren, A. G., Janz, B. A., Borud, L. J. & Slavin, S. A. Evaluation and management of the fat leg syndrome. *Plast. Reconstr. Surg.* **119**, 9e–15e (2007).
120. Peprah, K. & MacDougall, D. In *Liposuction for the Treatment of Lipedema: A Review of Clinical Effectiveness and Guidelines CADTH Rapid Response Reports* (2019).
121. Seefeldt, T. et al. Breaking the circle-effectiveness of liposuction in lipedema. *J. Dtsch Dermatol Ges.* **21**, 601–609 (2023).
122. Amato, A. C., Amato, J. L. & Benitti, D. Efficacy of liposuction in the treatment of lipedema: a meta-analysis. *Cureus* **16**, e55260 (2024).
123. Wollina, U. & Heinig, B. Treatment of lipedema by low-volume micro-cannular liposuction in tumescent anesthesia: Results in 111 patients. *Dermatol Ther.* **32**, e12820 (2019).
124. Schmeller, W., Hueppe, M. & Meier-Vollrath, I. Tumescent liposuction in lipoedema yields good long-term results. *Br. J. Dermatol* **166**, 161–168 (2012).
125. Rapprich, S., Dingler, A. & Podda, M. Liposuction is an effective treatment for lipedema–results of a study with 25 patients. *JDDG: J. der Dtsch. Dermatol. Ges.* **9**, 33–40 (2010).
126. Benatti, F. et al. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: a randomized trial. *J. Clin. Endocrinol. Metab.* **97**, 2388–2395 (2012).
127. Wolf, S. et al. A distinct Cytokine profile and stromal vascular fraction metabolic status without significant changes in the lipid composition characterizes lipedema. *Int. J. Mol. Sci.* **22**, https://doi.org/10.3390/ijms22073313 (2021).
128. von Atzigen, J. et al. A comparative analysis to dissect the histological and molecular differences among lipedema, lipohypertrophy and secondary lymphedema. *Int. J. Mol. Sci.* **24**, https://doi.org/10.3390/ijms24087591 (2023).
129. Felmerer, G. et al. Increased levels of VEGF-C and macrophage infiltration in lipedema patients without changes in lymphatic vascular morphology. *Sci. Rep.* **10**, https://doi.org/10.1038/s41598-020-67987-3 (2020).
130. Allen, M., Schwartz, M. & Herbst, K. L. Interstitial fluid in lipedema and control skin. *Women's. Health Rep.* **1**, 480–487 (2020).
131. Al-Ghadban, S., Diaz, Z. T., Singer, H. J., Mert, K. B. & Bunnell, B. A. Increase in Leptin and PPAR-γ gene expression in lipedema adipocytes differentiated in vitro from adipose-derived stem cells. *Cells* **9**, https://doi.org/10.3390/cells9020430 (2020).
132. Ishaq, M. et al. Key signaling networks are dysregulated in patients with the adipose tissue disorder, lipedema. *Int. J. Obes.* **46**, 502–514 (2021).
133. de Oliveira, J., de Paula, A. C. P. & Guimaraes, V. H. D. Clinical or cultural? Dietary interventions for lipedema: a systematic review. *Maturitas* **202**, 108716 (2025).
134. Ekti, H., Toktas, H., Yesil, H. & Kaya, F. Assessment of lower extremity venous insufficiency and lipedema and their association with knee symptoms, functions, and quality of life in patients with knee osteoarthritis. *Phlebology* **39**, 251–258 (2024).
135. Ibarra, M. et al. Subcutaneous adipose tissue therapy reduces fat by dual X-ray absorptiometry scan and improves tissue structure by ultrasound in women with lipoedema and Dercum disease. *Clin. Obes.* **8**, 398–406 (2018).
136. van Esch-Smeenge, J., Damstra, R. J. & Hendrickx, A. A. Muscle strength and functional exercise capacity in patients with lipoedema and obesity: a comparative study. *J. Lymphoedema* **12** (2017).
137. Guidi, R. M., Soares, C. D., Cazzo, E. & Chaim, E. A. Electromagnetic shock wave therapy in dermatology: Microscopic analysis of its interaction with the possible reduction of adipose tissue in obese individuals. *Surg. Cosmet. Dermatol.* **12**, 352–358 (2020).
138. Smoot, B., Chiavola-Larson, L., Lee, J., Manibusan, H. & Allen, D. D. Effect of low-level laser therapy on pain and swelling in women with breast cancer-related lymphedema: a systematic review and meta-analysis. *J. Cancer Surviv* **9**, 287–304 (2015).
139. Schneider, R. Low-frequency vibrotherapy considerably improves the effectiveness of manual lymphatic drainage (MLD) in patients with lipedema: A two-armed, randomized, controlled pragmatic trial. *Physiother. Theory Pr.* **36**, 63–70 (2020).
140. Herbst, K. L., Ussery, C. & Eekema, A. Pilot study: whole body manual subcutaneous adipose tissue (SAT) therapy improved pain and SAT structure in women with lipedema. *Horm. Mol. Biol. Clin. Investig.* **33**, https://doi.org/10.1515/hmbci-2017-0035 (2017).
141. Herbst, K. L., Zelaya, C., Sommerville, M., Zimmerman, T. & McHutchison, L. An advanced pneumatic compression therapy system improves leg volume and fluid, adipose tissue thickness, symptoms, and quality of life and reduces risk of lymphedema in women with lipedema. *Life* **15**, https://doi.org/10.3390/life15050725 (2025).
142. Wright, T., Scarfino, C. D. & O'Malley, E. M. Effect of pneumatic compression device and stocking use on symptoms and quality of life in women with lipedema: A proof-in-principle randomized trial. *Phlebology* **38**, 51–61 (2023).

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Author contributions
A.M.F., C.M.V., C.R.B., R.A.O., F.R.T., and B.H. conceptualized the review, defined its scope, conducted the comprehensive literature search, performed the writing, and organized the relevant references. A.M.F., C.M.V., V.C., and B.H. contributed to the critical evaluation and synthesis of the selected literature. V.C. and P.E.S. provided additional expert insights and assisted in drafting specific sections of the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Competing interests
André M. Faria has declared no competing interests. Cynthia M. Valerio has served as a consultant for Eli-Lilly, Novo Nordisk, Merck, Boehringer Ingelheim, Chiesi and PTC. Cristiano R. Barcellos has served as a consultant for Novo Nordisk, Astra Zeneca, Merck, Eli-Lilly, Boehringer Ingelheim and Libbs. Ricardo A. Oliveira has served as a consultant for AstraZeneca, Besins, Boehringer Ingelheim, Eli-Lilly, Eurofarma, Merck, Novo Nordisk and Libbs. Jaqueline M. T. Baiocchi is a Coordinator at Instituto Lipedema Brasil, a private practice clinic located in São Paulo, Brazil. Fábio R. Trujilho has served as a consultant for Aché, AstraZeneca, BracePharma, Boehringer Ingelheim, Eli Lilly, EMS, Eurofarma, Johnson & Johnson, Myrallis, Merck, Novo Nordisk, Servier, Scitech Medical and Takeda. He is also the current president of the Latin American Obesity Federation (FLASO), President of the Brazilian Association for the Study of Obesity and Metabolic Syndrome (ABESO) and President of the Obesity Department of the Brazilian Society of Endocrinology and Metabolism (SBEM). Vincenza Cifarelli has declared no competing interests. Philipp E. Scherer has declared no competing interests. Bruno Halpern has served as a consultant for Novo Nordisk, Astra Zeneca, Merck, Eli-Lilly, Boehringer Ingelheim and Currax. He is also President-Elect of the World Obesity Federation.

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