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Review

Lipedema: What we don't know

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Summary *Background:* Lipedema is a loose connective tissue disease characterized by a disproportionate accumulation of adipose tissue in the limbs of women. Despite its incidence of 10–20%, lipedema is often underdiagnosed and misdiagnosed.
Objectives: This review aims to outline current, available evidence regarding this enigmatic syndrome and gives a synopsis of the subjects that are still unknown.
Materials and methods: PubMed and Embase searches were conducted to identify relevant articles on lipedema pathophysiology, clinical presentation, diagnosis, and treatment.
Results: Lipedema can be considered a disease of the adipocytes or a circulatory disorder of the lymphatics. The relationship between lymphatics and adipose tissue remains controversial. The clinical distinction between lipedema, lymphedema, phlebolymphedema, and lipolymphedema can be difficult. Diagnoses often coexist, further complicating the diagnosis of lipedema, which is currently made on clinical grounds alone. The value of diagnostic imaging studies is unclear. Liposuction appears to be an effective treatment and significantly improves symptoms.
Conclusion: Diagnosing lipedema remains a challenge due to its heterogeneous presentation, co-existing diseases, and lack of objective diagnostic imaging. Further directions for research include the effect of excess skin resection surgery on lymphatic drainage.

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Contents

Lipedema is a loose connective tissue (LCT) disease characterized by the disproportionate accumulation of fibrotic subcutaneous adipose tissue and extracellular fluid in the limbs of women due to microvascular inflammation.[1] There is bilateral symmetric enlargement of the subcutaneous adipose tissue in the limbs, sparing the hands, feet, and trunk. It is found almost exclusively in women and is most often isolated to the lower extremities.

There is a disproportionate increase in leg circumference in relation to a slender torso that cannot be reversed by physical exercise or diet.[2,3]

Allen and Hines first described this disease in 1940 as a clinical syndrome, characterized by the combination of subcutaneous deposition of fat in the buttocks and lower extremities and the accumulation of fluid in the legs.[4]

The reported incidence from specialized edema clinics varies between 10% and 20%.[5,6] The prevalence in the general population has been estimated to be as high as 39% in the German lipedema-3 trial.[7] Despite this high prevalence, lipedema is often underdiagnosed and misdiagnosed with other similarly presenting diseases. Lipedema, lymphedema, lipolymphedema, veno-lipolymphedema/ phlebedema, lipohypertrophy, gynecoid obesity, and Dercum's disease are all part of a spectrum of pathologies that are not well defined. There are multiple factors, which are likely interconnected, that influence this spectrum of diseases. Diagnoses also often coexist, further complicating the diagnosis of lipedema.

Progression of lipedema could lead to venous disease (veno-lipedema) and lymphatic abnormalities (lympho-lipedema) and vice versa, which further complicates its diagnosis and treatment.[8]

The heterogeneous presentation and anatomy of the condition and the lack of a diagnostic imaging exam that is easy to perform and interpret complicate its diagnosis.

There are gaps in our knowledge regarding lipedema management due to a lack of assessment for the impact of variable elements of the lipedema phenotype, such as obesity, venous disease, lymphatic insufficiency, and skin laxity, which each have an impact on patient outcomes.[9]

Polygenic susceptibility combined with hormonal, microvascular, and lymphatic disorders and loose connective tissue may be partly responsible for its development.[10] However, consistent information on lipedema pathophysiology is still lacking, and an etiological treatment is not yet available.

Objective

This review aims to outline current evidence regarding this enigmatic syndrome and gives a synopsis on the subjects that are still unknown. Thereby guiding further directions for research and treatment.

Method

A systematic literature search in PubMed and Embase with no date restriction was conducted in April 2023 using the

following search terms: ''lipedema'' AND (''pathophysiology'' OR ''symptoms'' OR ''diagnosis'' OR ''therapy'').

All articles published in English, German, French, or Spanish describing lipedema etiopathogenesis, clinical presentation, imaging, and treatment were included in this review. Reference lists in all relevant publications were examined and used to identify additional articles for inclusion. Using this search strategy, 488 articles were identified, of which 79 articles were included in this review.

Etiology

The etiology of lipedema is multifactorial and is influenced by genetic, hormonal, loose connective tissue, and vascular lymphatic factors.

Genetic

A positive family history *of similar "large legs" in female members* is reported in 15–73% of patients.[11-15] In a survey among lipedema patients, the relatives who were most often affected were grandmothers (35.4%) and mothers (29.7%), followed by aunts (23.0%), sisters (14.8%), and cousins (11.5%).[14] A genetic predisposition is thus assumed. Analyses of familial clusters suggest an autosomal dominant inheritance pattern with incomplete penetrance.[12,16]

Hormonal

Lipedema may manifest or aggravate at times of hormonal changes, such as pregnancy or menopause, suggesting an *estrogen-related etiology*.[13,15,17-19] A polygenically mediated change in the distribution pattern of alpha- and beta-estrogen receptors (ER) in the white fatty tissue of affected body areas (ER-α expression ↓, ER-β expression ↑) has been suggested.[20] The effect of contraceptives on the evolution of lipedema is unclear.

Loose connective tissue

Lipedema tissue has an enlarged extracellular matrix where proteoglycans reside, which bind sodium and water.[21] Water may thus collect in fat tissue by swelling of the fat cells and/ or collecting interstitial fluid, thereby producing edema of the fat cells and/or interstitium, a feature that has been demonstrated in the histopathology of biopsies and liposuction aspirate of lipedema patients.[5,6,19,22] Adipocytes are thus a major source of lymph production.[23]

Vascular lymphatic

Lymphatic fluid accumulation in the interstitium stimulates adipocyte growth, which causes hypoxia by compression of capillaries. Hypoxia results in adipocyte cell death and the recruitment of macrophages, which generates inflammation thereby stimulating fibrosis. Hypoxia also induces microangiopathy with an increase in capillary permeability resulting in fluid extravasation leading to edema. This fluid retention leads to a vicious cycle that further aggravates adipocyte growth.

Lymphatic malfunction plays a role in lipedema, as demonstrated by the biomarker Platelet factor 4 (PF4/ CXCL4).[24] Whether those lymphatic alterations are the cause or consequence of the disease or are secondary to the related obesity features is not yet known.

Pathogenesis

The pathophysiology of lipedema is poorly understood; nevertheless, it is described as lymphatic compromise in its initial stages and as frank lymphatic damage in the final stage of lipolymphedema.

One possible mechanism leading to the development of lipedema may involve one of increased adipogenesis.[8,25,26] Previous studies on lymphedema have demonstrated enhanced adipocyte growth in the setting of excess lymphatic fluid, thereby regulating lipid accumulation.[27,28]

The mechanism of lipedema might be a continuing deterioration in which the growing adipocytes keep slowing the lymphatic drainage, while it is still unclear whether the primary factor is the growing adipocyte or an intrinsic problem in the interstitial space or microlymphatic pathway.

Moreover, in other conditions with comparable or even more enlarged fat deposits, such as lipohypertrophy or adiposis, there is no reduction of the lymphatic flow.

Hypoxia, brought about by adipocyte hypertrophy, leading to endothelial dysfunction, plays a significant role in lipedema and is a major inducer of angiogenesis.[29] There is an increased capillary permeability due to microangiopathy and a diminished venoarterial reflex.[10,30] The venoarterial reflex protects the capillary bed from locally elevated hydrostatic pressure by constriction of the arterioles.[31] Fluid extravasation may be enhanced when this reflex is impaired.

The tissue edema can initially be compensated for by increased lymph drainage.[32-34] As the disorder progresses, the amount of fluid produced exceeds the transport capacity of the lymphatic system, and the pressure of the fat tissue itself causes obstruction of the lymphatic vessels and secondary lymphedema[35] with a reduced lymphatic flow as observed in lymphoscintigraphy of the lower extremity.[22,36,37] The stasis of extravasation of proteins causes first inflammation followed by fibrosis, leading to pathological changes in lymphatic capillaries typical in lipedema.[38]

The term “lipolymphedema” is used to describe the combined pathology during these stages.

Clinical presentation

Lipedema is a clinical diagnosis made on the basis of clinical examination findings.

In 1951 Wold et al.[13] proposed diagnostic criteria for lipedema, which include the following (Figure 1):

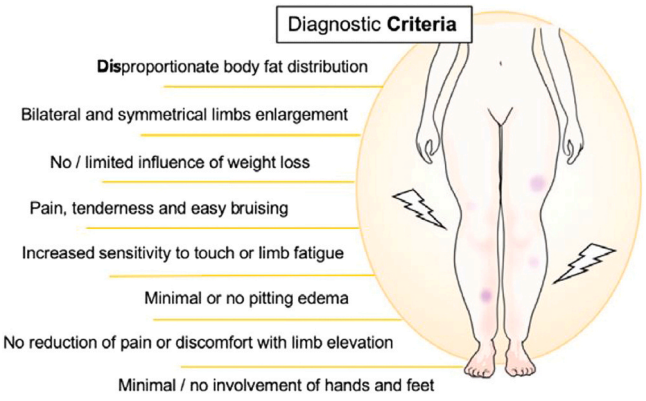

Figure 1 Criteria for lipedema diagnosis.
Reprinted with permission from Buso et al.[39] The final, published version of this article is available at https://www.karger.com/?doi= 10.1159/000527138.

(a) occurrence almost exclusively in women; (b) bilateral and symmetrical nature with minimal involvement of the feet; (c) minimal pitting edema; (d) pain, tenderness, and easy bruising; and (e) persistent swelling of lower extremities despite elevation or weight loss.

Based on distribution, five types of lipedema have been described (Figure 2).[10,11,41]

In type I, lipedema fat tissue accumulates around the hips and buttocks (saddle bag phenomena); in type II, accumulation involves the area from hips to knees; and in type III, a hip to ankle phenotype is observed. Approximately 30% of affected women have an additional involvement of arms (type IV), while it is rare to find fat dominating the calf region only (type V).

The types are determined by the segments of the lower body affected by abnormal adipose deposits rather than Allen and Hines' description of generalized lower-body involvement of the buttock, thighs, and lower legs.[4] These

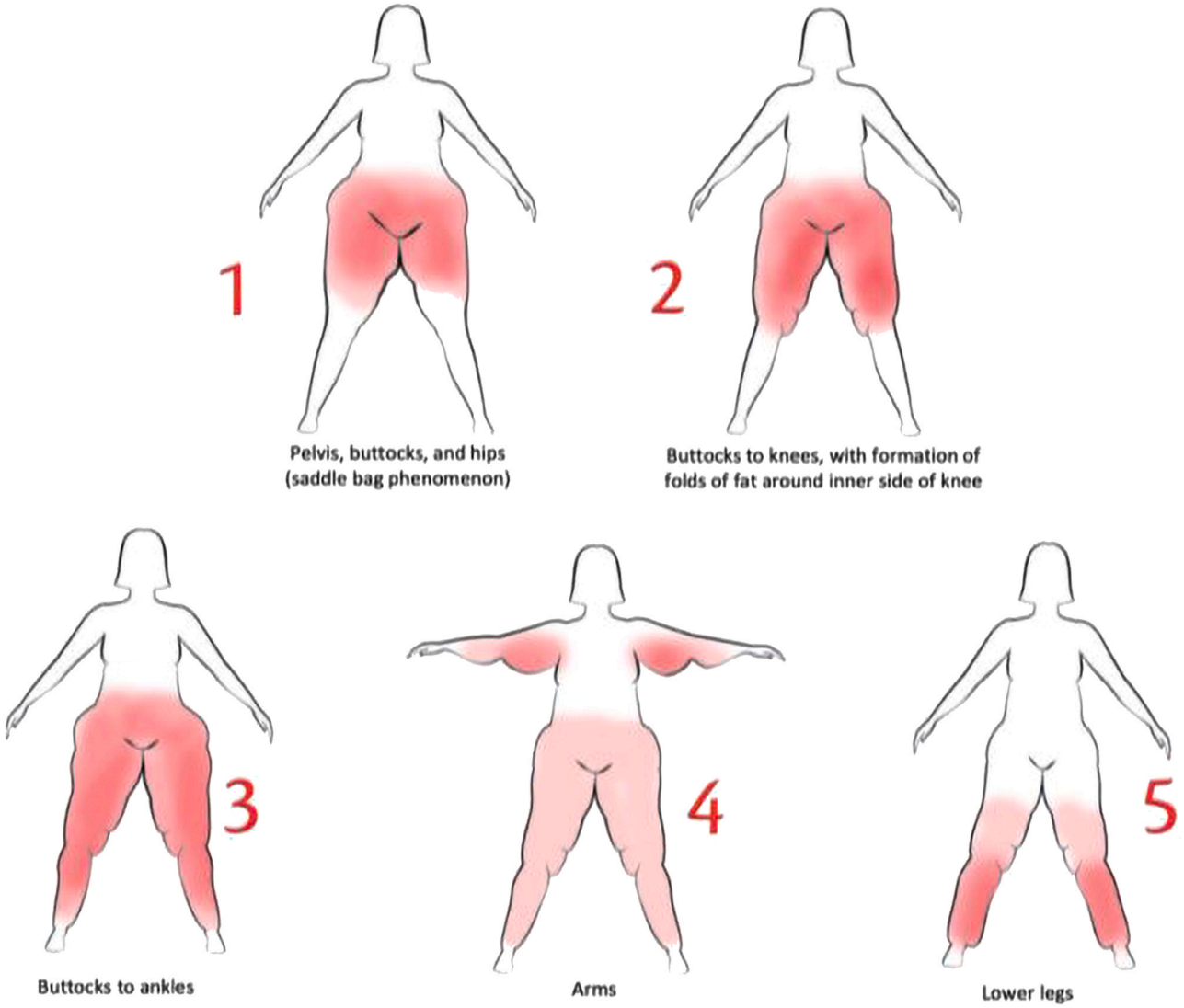

Figure 2 Lipedema types.
Reprinted with permission from Amato et al.[40]. The final, published version of this article is available at. https://journals.sagepub.com/doi/10.1177/02683555211002340.

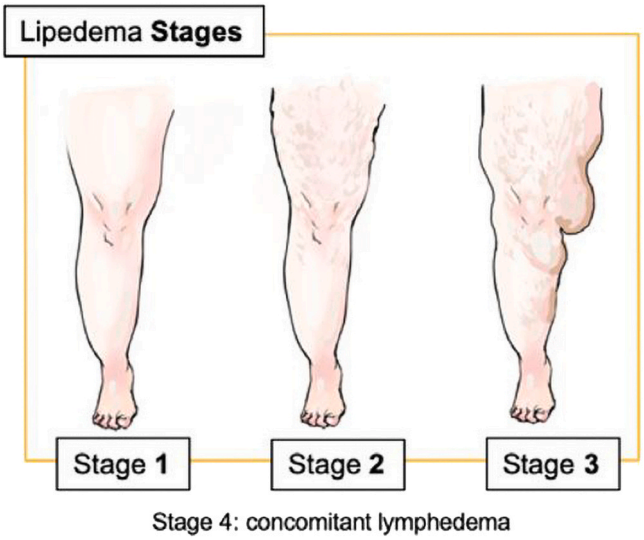

Figure 3 Lipedema stages.
Reprinted with permission from Buso et al.[39] The final, published version of this article is available at https://www.karger.com/?doi= 10.1159/000527138.

regional classifications are developed mainly for therapeutic follow-up purposes and have no pathophysiological basis.

Lipedema can be classified in four clinical stages based on morphological appearance (Figure 3).[5,20,42,43]

- 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 (Figure 4).
- Stage IV: lipolymphedema.

The majority of patients experience their first symptoms mostly during puberty up to the beginning of the third decade.[10] The reported delay between lipedema onset and the correct diagnosis varies between 10 and 15 years.[10,15,44]

Hypermobile joints are present in 50% of women with lipedema consistent with a connective tissue disease, such as hypermobile Ehlers-Danlos syndrome.[45] Reduced elasticity of the skin[46] and aorta[47] in women with lipedema confirm lipedema as a connective tissue disease.[48]

Comorbidities

The prevalence of obesity (37.6%[15]), hypothyroidism (27-36%[14,15,48]), migraine (23%[15]), and depression (23-25.5%[14,15]) is often increased in lipedema. To what extent there is a causal connection between lipedema and these disorders or whether they are just an epiphenomenon of obesity remains unclear.[14] Interestingly, patients with lipedema display a less severe cardiovascular profile in contrast to obesity.[45]

Differential diagnosis

Lipedema is often regarded as an extension of simple obesity or erroneously diagnosed as one of the non-systemic causes of enlarged lower extremities, e.g., lymphedema or mixed lymphovenous disease. Confusion often exists concerning the differential diagnosis, which includes[17]:

Lipohypertrophy (similar disproportion, symmetric, but no edema and no pain),

Herpetz et al. described lipohypertrophy as increased symmetrical subcutaneous fat deposits, mostly on the legs

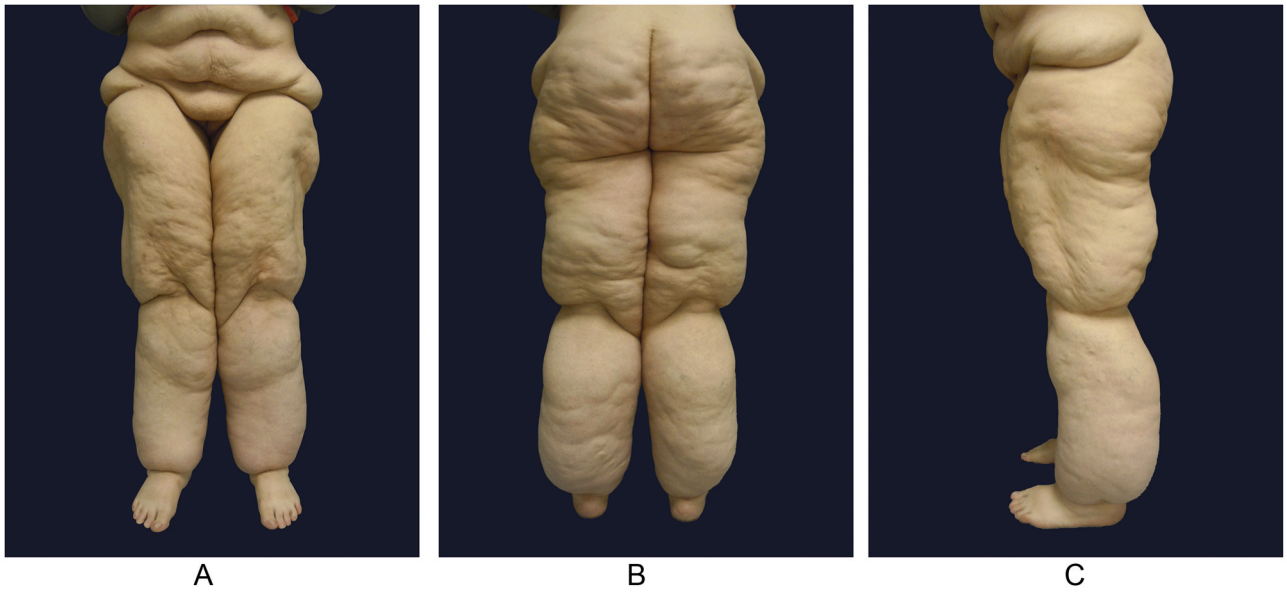

Figure 4 A 34-year-old patient with type 3, stage 3 lipedema. A, frontal; B, dorsal; and C, side views.

and arms in women. The difference between lipohypertrophy and lipedema is the absence of edema and pain in lipohypertrophy.[29]

Primary lymphedema (asymmetric, decreased lymphatic flow, positive Kaposi–Stemmer skin fold sign, no pain, and no bruising), In contrast to lymphedema, Stemmer's sign (i.e., the inability to pinch a fold of skin at the base of the second toe due to thickening of the skin and subcutaneous tissues) is negative, and lipedema is always symmetrical. Lymphedema commonly responds to compression therapy, while lipedema responds poorly to compression therapy. The skin in patients with lymphedema is brown, warty, and sclerotic, while the skin in lipedema is commonly intact.

Phlebedema/ chronic venous disease (pathological vein function tests, pitting edema, improvement of symptoms and swelling with leg elevation, and, in advanced stages, skin changes with typical brown coloration (dermite ocra), white scars (atrophie blanche), and ulcers.[10]

Phlebedema is associated with chronic venous incompetence, swelling of the lower leg, varicosities, and induration.[49] Lipedema and chronic venous disease often coexist; 25–50% of women with lipedema have concomitant venous disease.[13,48] Many symptoms of lipedema mimic venous symptoms, including the feeling of heaviness and swelling in the legs.

Both diseases could exacerbate each other. Advancing age, female gender, and BMI compound an underlying relationship between lipedema and chronic venous disease.[48]

Obesity (increased volume on the trunk, increased weight, body mass index $> 30\,kg/m^2$, often no obvious disproportion, no edema, and no pain).

Dercum's disease (increased volume, pain, but no edema).

Dercum's disease (adiposis dolorosa) is a clinical condition that partly overlaps with lipedema, as the two share cardinal features such as spontaneous or palpation-induced pain and bruising. At its onset, Dercum's disease is characterized by multiple painful lipomas with possible progression into circumscribed or general diffuse fatty deposition. It is usually accompanied by recurrent headaches and depression, which are less frequently described in lipedema.[10,50,51]

Launois-Bensaude benign symmetric lipomatosis (increased accumulation of fatty tissue with typical disproportion, mostly localized in the neck (type I), shoulders and upper arms (type II), or pelvic region (type III), no pain, no edema).[2]

Imaging

In lipedema, the medical history and clinical examination do not always indicate the nature or extent of the underlying abnormality (i.e., the anatomical extent, pathology, and cause). Furthermore, the clinical distinction between lipedema, lymphedema, phlebolymphedema, and lipolymphedema can be difficult. Diagnoses often coexist, further complicating the diagnosis of lipedema, which is currently made on clinical grounds alone. Imaging can be useful to differentiate lipedema from other similarly presenting diseases, although a diagnostic imaging exam for lipedema is currently still lacking.

Ultrasound

Ultrasonography represents a minimally invasive cost-effective tool that can be of great value to distinguish lymphedema from lipedema. Lymphedema presents with increased dermal thickness and decreased echogenicity, while lipedema is characterized by an increased thickness of the subcutaneous tissue.[7,52,53] For the diagnosis of lipedema, Campos et al.[40] proposed cut-off values of the subcutaneous tissue thickness of 11.7 mm for the pre-tibial region, 17.9 mm for the anterior thigh, and 8.4 mm for the lateral side of the leg.[40]

Lymphoscintigraphy

Lymphoscintigraphy can be useful in the differential diagnosis of edema, allowing the exclusion of clear lymphatic dysfunction. Patients suffering from lipedema have an abnormal lymphoscintigraphic pattern, with a slowing of the lymphatic flow.[22,37,38,54–56] More severe lipedema may be associated with greater lymphatic transport abnormalities.[55] A frequent asymmetry between the lower extremities is also noticed in the lymphoscintigraphic findings in contrast to the bilateral clinical presentation of the disease.[29] Depending on the pattern of the adipocyte tissue expansion in each limb, different degrees of lymphatic transport abnormalities may be observed. Further study is needed to identify causative factors behind differences in disease expression between patients.[55] Interestingly, Van de Pas et al.[38] found a symmetrical lymphatic function after liposuction.

MR imaging

Magnetic resonance imaging may have an important role in differentiating lipedema from lymphedema and in evaluating mixed forms of lipedema such as lipolymphedema and lipophlebolymphedema.

Lipedema is characterized by an increased layer of subcutaneous fat without changes in signal intensity between T-2 and T-1 weighted images, confirming that the tissue does not contain excess fluid.[49,57]

MR lymphangiography

MR lymphangiography is an accurate minimally invasive imaging modality to delineate pathologically modified lymphatic pathways in patients with lipedema and lipolymphedema.

In the study of Lohrman et al.,[35] clinically pure lipedema was characterized by an increased layer of subcutaneous fat in the leg, with a maximum mean diameter of 4.4 cm at the level of the lower leg and 7.7 cm at the level of the upper leg. Enlarged lymphatic vessels up to a diameter of 2 mm were found, indicating a subclinical status of lympohostasis.[35] Lymphatic vessels showed a beaded appearance (microlymphatic aneurysms of lymphatic capillaries).[35,58,59]

Table 1 Studies assessing the effectiveness of liposuction for lipedema treatment.

Author	N	Age	Mean BMI	Lipedema stage	Technique	No. operations	Mean amount of fat	Mean weight loss	Median FU	Pain	Cons treatm po
Rapprich, 2010[33]	25	38	NR	NR	TL	1-5 (mean 2.5)	1909$	6.9% VR	6 mo	↓↓↓	16%
Wollina, 2010[34]	6 (LE+DD)	58	38	II, n = 2 III, n = 4	TL	1-4	2808 ml	NR	6-48 mo	↓	NR
Schmeller, 2012&[2]	112	39	NR	I, n = 35 II, n = 75, III, n = 2	TLA	1-7	9846 ml or 3077 ml per session	4.3 kg	4 yrs	↓↓↓	77%
Wollina, 2012[70]	18 (LE + 1 DD)	47	35.3	I, n = 1 II, n = 6 III, n = 11	TL + LATL	1-4	TL 4200 ml LATL 2600 ml/session	7.8 kg	18 mo	↓↓↓	N/A
Baumgartner, 2016 &[71]	85	40	NR	I, n = 24 II, n = 61	TLA	NR	NR	NR	8 yrs		70%
Dadras, 2017[72]	25	45	35.3	I, n = 1 II, n = 11 III, n = 13	TL	1-7, mean 3	9914 ml		16/37 mo	↓↓↓	N/A
Münch, 2017[73]	141	37	26.6	NR	WAL + sed	NR	4200 ml	3.4 kg	36 mo	↓↓↓	95%
Bauer, 2019[14]	209	38	NR	II, n = 209	TL	1-9, Average 3	10.1 L= average amount of total fat	NR	12 mo	↓↓↓	49.3%
Wollina and Heinig, 2019[74]	111	44	NR	I, n = 7 II, n = 50 III, n = 48	TLA	NR	Median 4700 ml	LC -6 cm	2 yrs	↓↓↓	84
Ghods, 2020[15]	106	41	31.6	I= 11 II= 61 III= 34	TL	Median 3	6355 ml/operation 17,887 ml throughout entire surg treatment		34 mo after 1st operation	↓↓↓	
Witte, 2020[75]	63	35	28.4	I (29%) II (71%)	WAL	1 (10%) 2 (33%) 3 (38%) 4 (19%)	12,922 ml	5.6 kg	22 mo*	↓↓↓	44%

*mean; mo, months; $, amount of pure fat; VR, volume reduction; NR, not reported; TL, tumescent liposuction; TLA, tumescent local anesthesia; WAL, water-assisted liposuction; LATL, laser-assisted tumescent liposuction; LE, lipedema; DE, Dercum's disease; LC, limb circumference; FU, follow-up; sed, sedation; cons treatm, conservative treatment; po, postoperative; &, indicates same study population but different follow-up times.

Dual-energy X-ray absorptiometry (DXA)

Dual-energy x-ray absorptiometry, measuring regional body composition, provides quantification and distribution information about total and regional fat, lean, and bone mass, thus representing a useful tool for diagnosis, staging, and follow-up of lipedema patients.[60]

Analysis by Dietzel et al.[60] suggested that fat mass in the legs adjusted for BMI was the best index for diagnosing lipedema, with a cut-off value of 0.46.[60]

However, BMI analysis may be misleading since it considers total weight without considering regional fat distribution, which is a hallmark of lipedema. Buso et al.[39] therefore optimized diagnostic efficacy by dividing the amount of leg fat mass by total fat mass and presented this index with a cut-off value of 0.383.

These references may be particularly helpful for a differential diagnosis in otherwise doubtful cases.

Treatment

An etiological treatment for lipedema is currently still lacking. Treatment is focused on symptom reduction, functional limitation amelioration, and prevention of disease progression.

Therapeutic approaches also aim at impacting factors negatively influencing lipedema progression, such as obesity, lymphedema, venous insufficiency, and decreased physical activity.[10]

Treatment of lipedema is based on two pillars: conservative decongestive treatment (CDT) and surgery. According to international guidelines, conservative treatment should always be initiated.[42,48,61-63] Manual lymph drainage (MLD), compressive garments, and physical exercise should improve lipedema tissue by increasing lymphatic flux, which in turn increases the movement of glycosaminoglycans from the extracellular matrix into lymphatic vessels.[48] These measures can offer some symptom relief (less tenderness and tightness) and reduce capillary fragility, resulting in a reduction of petechiae and hematoma formation following minor trauma.[64] However, the long-term benefit is questionable and in the absence of edema even doubtful since CDT has no effect on adipose tissue[25,41] In addition, compression may not be tolerated by lipedema patients because of pain.

If symptoms persist liposuction should be considered to reduce the volume of adipose tissue in lipedema. It is the only treatment that slows progression of lipedema and ideally would be performed before complications and disabilities from lipedema develop.[48] However, several articles suggest that liposuction could induce lymphedema due to destruction of the lymphatic vessels, especially classic dry liposuction.[65,66] Tumescence or water-jet-assisted liposuction (WAL) is therefore often recommended to spare the lymphatic vessels. Cadaver studies have shown markedly reduced injury to lymphatic structures when the tumescent technique was used and when the liposuction cannula is oriented longitudinally instead of radially with regard to the vessels.[66,67]

Compared to more conventional liposuction the water-assisted technique better respects the anatomical structures without damaging them.[3,68,69]

It is recommended that liposuction be performed in multiple sessions since extensive amounts of adipose tissue have to be removed.

To date, all studies show clinical improvements for women with lipedema using tumescence or WAL techniques (Table 1).[2,14,15,33,34,70-75]

Liposuction is effective in the treatment of lipedema and significantly improves symptoms (pain, sensitivity to pressure, tendency to swelling, and restriction of movement) and quality of life, with a lasting benefit, even after an 8-year follow-up.[71]

It also improves lymphatic symptoms, reducing the need for conservative therapy,[2,14,33,71,74-76] and it does not decrease lymphatic drainage as shown by lymphangioscintigraphy.[38,77] However, conservative therapy must be consistently continued even after surgery in order to avoid or slow down the progression of the disease.

Lipedema reduction surgery may be less effective in advanced stages of lipedema[61,72,74] and in women with lipedema and severe obesity,[2,71,76,78] although recent data demonstrate a greater reduction of symptoms in more advanced cases.[74,79]

Fat embolism after liposuction has been observed in up to 8.5% of patients undergoing liposuction. There are no data indicating a higher risk of fat embolism in liposuction for lipedema compared to esthetic indication.[74]

With increasing age, skin laxity after liposuction may occur. Skin laxity is also a serious problem after massive weight loss. Patients with advanced lipedema after liposuction usually have a vertical tissue excess propagated by the looser adherence of skin and adipose layers of the medial thigh.

Secondary surgical procedures to correct this skin laxity might become necessary but carry an increased risk of lymphatic vessels destruction. It is important to objectify the presence of lymphedema preoperatively to detect subclinical lymphatic insufficiency that could decompensate after surgery. The vertical scars in post-bariatric reconstructive surgery follow the anatomical course of the lymphatics and are thus expected to be less problematic with regard to lymphatic drainage than transverse incisions. An imaging study to objectify the effect of excess skin resection on the lymphatics could answer this hypothesis.

A combination of lymphovenous anastomosis and debulking surgery might offer improvement in physiologic drainage of excessive lymphatic fluid and removal of excess adipose tissue, respectively.[55] Combining these techniques may reduce cellular and metabolic load on the lymphatic system while adding capacity to the system of lymphatic transport by bypassing the native routes of lymphatic flow and increasing the drainage of the limb. Removal of lymphatic fluid may in turn decrease adipogenesis, as lymphatic fluid has been shown to upregulate adipose generation and differentiation.[55]

Conclusion

Many questions remain to be answered regarding lipedema. Its diagnosis remains a challenge due to its heterogeneous

presentation, co-existing diseases, and the lack of objective diagnostic imaging. Liposuction appears to be an effective treatment. Further directions for research include the effect of surgery on lymphatic drainage.

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Ethical approval

Not required.

Declaration of Competing Interest

None.

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