Obesity

Lipedema: A Call to Action!

Giacomo Buso [1], *Michele Depairon*[1], *Didier Tomson*[1], *Wassim Raffoul*[2], *Roberto Vettor*[3], *and Lucia Mazzolai*[1]

Lipedema is a chronic progressive disease characterized by abnormal fat distribution resulting in disproportionate, painful limbs. It almost exclusively affects women, leading to considerable disability, daily functioning impairment, and psychosocial distress. Literature shows both scarce and conflicting data regarding its prevalence. Lipedema has been considered a rare entity by several authors, though it may be a far more frequent condition than thought. Despite the clinical impact on women's health, lipedema is in fact mostly unknown, underdiagnosed, and too often misdiagnosed with other similarly presenting diseases. Polygenic susceptibility combined with hormonal, microvascular, and lymphatic disorders may be partly responsible for its development. Furthermore, consistent information on lipedema pathophysiology is still lacking, and an etiological treatment is not yet available. Weight loss measures exhibit minimal effect on the abnormal body fat distribution, resulting in eating disorders, increased obesity risk, depression, and other psychological complaints. Surgical techniques, such as liposuction and excisional lipectomy, represent therapeutic options in selected cases. This review aims to outline current evidence regarding lipedema epidemiology, pathophysiology, clinical presentation, differential diagnosis, and management. Increased awareness and a better understanding of its clinical presentation and pathophysiology are warranted to enable clinicians to diagnose and treat affected patients at an earlier stage.

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Introduction

Lipedema is a chronic and progressive disease that can lead to considerable disability, daily functioning impairment, and psychosocial distress (1,2). It affects almost exclusively women, starting most often between puberty and the third decade of life (3). Lipedema involves abnormal deposition of subcutaneous adipose tissue, leading to a bilateral, disproportional volume increase of lower extremities and, in some cases, of arms. Fat deposition typically spares hands, feet, and trunk. Pathophysiological mechanisms of lipedema remain to be fully elucidated (4). Additionally, given the lack of consistent diagnostic criteria, its prevalence is difficult to establish, though it is thought to be common. Lipedema is in fact highly underdiagnosed by health care providers, being frequently misdiagnosed as obesity or lymphedema, diseases with which it shares several features. This review aims to outline current evidence to elucidate lipedema epidemiology, pathophysiology, clinical presentation, differential diagnosis, and management. The overall aim is to increase awareness among physicians and gradually offer patients a diagnosis and proper management.

Epidemiology

The literature has shown both scarce and conflicting data regarding the prevalence of lipedema. Child et al. (5) suggested a minimum value of 1:72.000 within the general population, though this may represent an underestimation of the real distribution of the disease. Lack of current referrals is in fact responsible for the high rate of misdiagnosis of lipedema, which is frequently confused with other clinical entities, such as obesity and lymphedema. In a survey of 251 members of the Vascular Society of Great Britain and Ireland, only 46.2% of the consultants were able to recognize the disease (6). Foldi et al. (7) reported percentages up to 11% among women and postpubertal girls admitted to their clinic for lower limb swelling. Moreover, Forner-Cordero et al. (1) reported that 18.8% of patients presenting with the same clinical presentation, between 2005 and 2012, actually suffered from lipedema. Similar percentages were found in a previous study on patients hospitalized for lymphatic dysfunction (8) and in a more recent investigation on patients presenting with suspected lymphedema in a French department of lymphology (9). These data refer to a selected population and do not take into account the general population. Of note, a German cross-sectional study investigated lipedema prevalence in 62 professional women (10). The researchers detected the disease in 39% of women (including all stages), and prevalence remained consistent (up to 9.7%) even for moderate to severe clinical presentation.

Lipedema affects mostly women and usually starts in puberty. Some reports refer to lipedema onset following pregnancy or even menopause (5). Men with lipedema have been mentioned in the literature only in

[1] Angiology Division, Heart and Vessel Department, Lausanne University Hospital, Lausanne, Switzerland. Correspondence: Lucia Mazzolai (lucia.mazzolai@chuv.ch) [2] Plastic Surgery Division, Locomotor System Department, Lausanne University Hospital, Lausanne, Switzerland [3] Department of Medicine, Center for the Study and the Integrated Management of Obesity (EASO COM), Padova University Hospital, Padova, Italy.

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case reports, and male patients tend to have concomitant conditions associated with higher estrogen and lower relative testosterone levels, such as male hypogonadism and liver disease (4,11,12). Children can also be affected, and 6.5% of infants with a supposed diagnosis of lymphedema actually suffered from lipedema in a 2011 report (13).

Pathophysiology

Little is known about lipedema pathophysiology, although some studies have suggested that polygenic susceptibility combined with hormonal, microvascular, and lymphatic disorders may be partly responsible for its development. Therefore, adipose tissue enlargement might not be the initial step in affected patients but rather the consequence of lymphangiopathy and/or microvascular dysfunction, starting a vicious cycle and resulting in persistent alterations in lymphatic and blood microcirculation. Hypothetical pathophysiological mechanisms responsible for lipedema development have been reviewed by Szél et al. (4). Several genes under the influence of estrogen, involved in vasculo- or lymphangio-genesis, may play a role in endothelial dysfunction and lymphangiopathy. Additionally, it could be tempting to speculate that imbalanced estrogen-mediated mechanisms of weight control in the central nervous system may be involved, at least partly, in lipedema pathogenesis, as 17β-estradiol's actions in the brain are known to contribute to the regulation of body energy homeostasis, particularly in females (14). Estrogen also plays a pivotal role in region-specific sympathetic innervation of subcutaneous adipose tissue. An intriguing hypothesis is that local inflammation of sensory nerves and adipose tissue dysfunction may act together and be responsible for the neuropathy typically found in this condition. Nonetheless, in light of the lack of high-quality scientific research on lipedema pathophysiology, opinion and consensus largely dominate the literature, and some of the proposed mechanisms need to be taken carefully with a critical view.

Genetic background

In 60% of patients suffering from lipedema, genetic background with familial predisposition has been described (15). Studies have suggested that positive family history in affected patients ranges between 16% and 64% (16). Furthermore, a clinical report on 330 family members found a possible autosomal dominant inheritance with incomplete disease penetrance, though genes involved have not been identified, and the unusually high prevalence of BMI consistent with obesity in the study raises questions about its applicability in the absence of obesity (5).

Lipedema was first described by Allen and Hines in 1940 as a condition characterized by "abnormally poor resistance to the passage of fluid into the tissue from the blood thus permitting oedema to occur" (17). This assertion suggests the presence of a connective tissue disorder with impaired adipose tissue elastic recoil, allowing fluid to collect rather than exit into lymphatic circulation (18). Williams syndrome, a genetic disease presenting with lipedema phenotype in both males and females, among other clinical features, is associated with loss of several genes, including *ELN* for elastin, which is an important component of connective tissue (19). Coherently with the hypothesis of an etiological role for loss of elasticity in lipedema, aortic stiffness develops in this condition (20) as well as in Williams syndrome (21). Research on both humans and animal models has suggested possible involvement of other genes. A study by Harvey et al. (22) showed that mice with functional inactivation of a single allele of the homeobox gene *PROX1* (which plays a critical role in embryonic development and functions as key regulatory protein in neurogenesis and heart, eye lens, pancreas, and lymphatic system development) displayed both defective lymphatic vasculature and subcutaneous and intra-abdominal fat accumulation (particularly around lymph nodes and in other regions rich in lymphoid tissue). In two animal models of hereditary lymphedema, mice carrying a vascular endothelial growth factor receptor 3 (*VEGFR3*; also known as FMS-like tyrosine kinase 4 *[Flt4]*) heterozygous missense inactivating mutation, or expressing a soluble form of this receptor, developed hypoplastic dermal lymphatics and concomitant thickening of subcutaneous adipose tissue (23,24). An additional candidate in lipedema development may be *PIT1* (encoding a transcription factor involved in the specification of the lactotrope, somatotrope, and thyrotrope phenotypes in the developing anterior pituitary gland; also known as POU class 1 homebox 1 *[POU1F1]*). *PIT1* mutation was found in a family in which short stature and leg swelling affected females through four generations (11). In line with this finding, González-Parra et al. (25) reported that modifications in circulating levels of sex hormones influenced *PIT1* expression. Along the same line, Foldi et al. (7) observed higher rates of lipedema after surgery for pituitary adenomas. Mutation of *NSD1* (encoding a protein enhancing androgen receptor transactivation), responsible for Sotos syndrome (26), has been reported to cause estrogen-mediated formation of lipedema fat tissue. Finally, *BMP2* (encoding a secreted ligand of the transforming growth factor-beta superfamily of proteins and playing a central role in osteoblast differentiation and cartilage development) is regulated by estrogen (27) and mediates inflammatory reaction with ensuing edema (28). *BMP2* also induces adipogenesis through peroxisome proliferator-activated receptor gamma (29); moreover, its administration in neurosurgery to stimulate lumbar spine fusion was hypothesized to be responsible for acute epidural lipedema (30).

Hormonal influence

Because women are mainly concerned and the disease starts predominantly at puberty, it would be tempting to speculate that lipedema's pathophysiology is largely influenced by sex hormones. Estrogen is known to directly modulate lipid metabolism in white adipose tissue, mainly through estrogen receptor alpha and beta (ER-α and -β), and G-protein-coupled estrogen receptors (31). In light of the different distribution of androgenic and gynoid adiposity, effects of sex hormones are plausibly anatomical region specific. A study by Van Pelt et al. (32) showed that intravenous bolus of conjugated estrogen led to higher levels of basal lipolysis in the abdominal region compared with the femoral one. A subsequent study in premenopausal women with overweight or obesity found decreased ER-α and increased ER-β protein levels in the gluteal region compared with the abdominal one. Furthermore, researchers observed that the waist-hip ratio was inversely associated with gluteal ER-β protein levels and directly correlated to the gluteal ER-α–ER-β ratio (33). These findings may explain, at least partially, both the predilection of lipedema for the female sex and the peculiar distribution of adiposity, suggesting that defective ER expression, distribution, and signaling pathway may be involved in lipedema development. Another crucial aspect that needs to be clarified is the low response of lipedema fat tissue to extreme diet and physical exercise (34). Hormonal influence should play a role. Indeed, estrogens act as central mediators for food intake and energy consumption in the hypothalamus. In particular, ER-α is expressed mainly by pro-opiomelanocortin neurons of the arcuate nucleus (35), which plays a crucial role in food intake regulation through alpha-melanocyte-stimulating hormone secretion (36,37). Research has shown that brain-specific deletion of ER-α in female mice causes both hyperphagia and hypometabolism,

thus enhancing abdominal obesity (35,38). Further research is needed to elucidate whether an altered ER pattern and/or signaling pathway at a central level may explain typical resistance to weight loss in patients with lipedema.

Microangiopathy

Although not pathognomonic, and in spite of a lack of high-quality scientific data, microangiopathy has been considered a typical histological feature of lipedema by some researchers (7). This vascular alteration may be a consequence of the primary endothelial dysfunction through hypoxia mechanism with subsequent increased vascular fragility, similar to what was observed in patients with diabetic retinopathy (39). Angiogenesis has several stimulators, including VEGF. In a study by Siems et al. (40), the authors found that average VEGF plasma levels were significantly above normal in patients undergoing shock-wave therapy for lipedema, thus suggesting a role for pathological angiogenesis in disease development. Increased oxidative stress was also described in patients with lipedema, displaying increased serum concentrations of malondialdehyde (a marker of lipid peroxidation). Therefore, angiogenesis and increased capillary permeability may be consequences of imbalanced adipogenesis, leading to abnormal fat expansion and subsequent tissue hypoxia. In line with this hypothesis, Suga et al. (41) carried out immunohistochemical analyses in lipedema fat tissue and observed the presence of necrotizing adipocytes and infiltration of macrophages forming crown-like structures. Additionally, they described enhanced proliferation capacity of adipose-derived stem, progenitor, and stromal cells, likely promoting adipogenesis. Interestingly, a recent study by Al-Ghadban et al. (42) found that patients with lipedema and without concomitant obesity displayed hypertrophic adipocytes, increased numbers of macrophages and blood vessels, and dilation of capillaries in thigh fat compared with healthy controls. Such findings suggest that inflammation and angiogenesis may occur independently of obesity in lipedema and support the role of an altered microcirculation in the manifestation of the disease.

Notably, increased free fatty acid levels may induce endothelial dysfunction and altered transendothelial transport (43,44), while leptin modulates angiogenesis under hypoxic conditions, having a direct effect on endothelium and VEGF expression (45,46).

The autoregulatory veno-arterial reflex (preventing edema formation) (47) should also be dysfunctional in patients with lipedema (7). Concerning this intriguing aspect, a pivotal role may be played by an overproduction of adipocyte-derived relaxing factor, released by periadventitial adipose tissue and activating voltage-dependent potassium channels hyperpolarizing smooth muscle cell membranes (48).

Despite these interesting hypotheses, the existence and real contribution of microangiopathy in lipedema are still speculative and need to be confirmed by further and more exhaustive research.

Lymphangiopathy

Patients with lipedema display features of lymphedema, particularly in advanced stages (34). A study by Bilancini et al. (49) demonstrated an abnormal lymphoscintigraphic pattern with slowing of lymphatic flow in 12 lipedema-affected women, similar to what was observed in patients suffering from primary lymphedema. Amann-Vesti et al. (50) used fluorescence microlymphangiography and observed multiple microlymphatic aneurysms at the thigh, ankle region, or foot in 12 patients with lipedema. Enlarged lymphatic vessels with a beaded appearance were found by magnetic resonance lymphangiography in affected participants (51). Functional and morphological abnormalities of lymphatic capillaries were also described by Foldi et al. (7), while Wollina et al. (52) showed podoplanin-negative subcutaneous lymphatic vessels in two patients with lipo-lymphedema. Lastly, morphological studies using indirect lymphangiography have documented typical changes, although not pathognomonic, in the form of flame-shaped contrast medium deposits in patients with lipedema (53).

Besides these findings, the exact role of lymphangiopathy in lipedema has not been yet determined. It is well known that adipocytes grow significantly in the presence of lymphatic fluid (54). Nougues et al. (55) observed enhanced rabbit adipocyte differentiation and lipid accumulation by adding mesenteric lymph and chylomicrons to culture medium. Other studies on animal models have demonstrated that lymphangiopathy might actually enhance fat deposition (22,23).

Conversely, imbalanced and prolonged adiposity enlargement may also lead to microlymphatic disturbances, as observed by Blum et al. (56) in mice fed with a chronic high-fat diet. Expanding adipocytes produce some lymphangiogenic factors, such as VEGFC (57), which may induce lymphatic hyperplasia (58). Lastly, in hypoxic environments, hypoxia-inducible factor 1 enhances fibrosis (59), thus potentially compromising lymphatic drainage in dysfunctional adipose tissue.

Taking into account these findings, research is still needed to clarify whether a persistent and progressive damage of the microlymphatic vessels because of adipose tissue expansion (16), rather than a primary lymphatic defect, may be responsible for the lipo-lymphedema state.

Adipogenesis

As already mentioned, previous research has reported enhanced adipose stem cell proliferation in patients with lipedema, which is likely responsible for the massive adipose tissue enlargement typically found in this condition (41). More recently, stromal vascular fraction obtained by liposuction from 52 affected women revealed a significant increase in adipose stem cell number (60). Interestingly, approximately half of these cells seemed to originate from perivascular cells, while 20% of them showed characteristics of pericyte-like cells. These findings are of particular relevance, as Li et al. (61) previously demonstrated that perivascular-derived cells from adipose tissue exhibited very low adipogenic differentiation potential compared with the preadipocyte subpopulation. Likewise, Hu et al. (62) found that a subpopulation of these latter cells also showed lower adipogenic potential. In line with these results, *in vitro* adipogenic differentiation potential assessed by the degree of lipid droplet accumulation on adipogenic induction was significantly reduced in patients with lipedema compared with healthy participants (60).

Intriguingly, several studies have demonstrated impaired preadipocyte differentiation in patients with obesity (63). Several hypotheses have been proposed to explain why some patients are unable to expand their adipose tissue in a healthy manner. Like other organs and tissues, it has been supposed that adipose tissue growth must be accompanied by a parallel expansion of its vascular network. Notably, several researchers have demonstrated a capillary reduction in the subcutaneous adipose tissue of patients with obesity (64,65). This phenomenon may lead to hypoxia

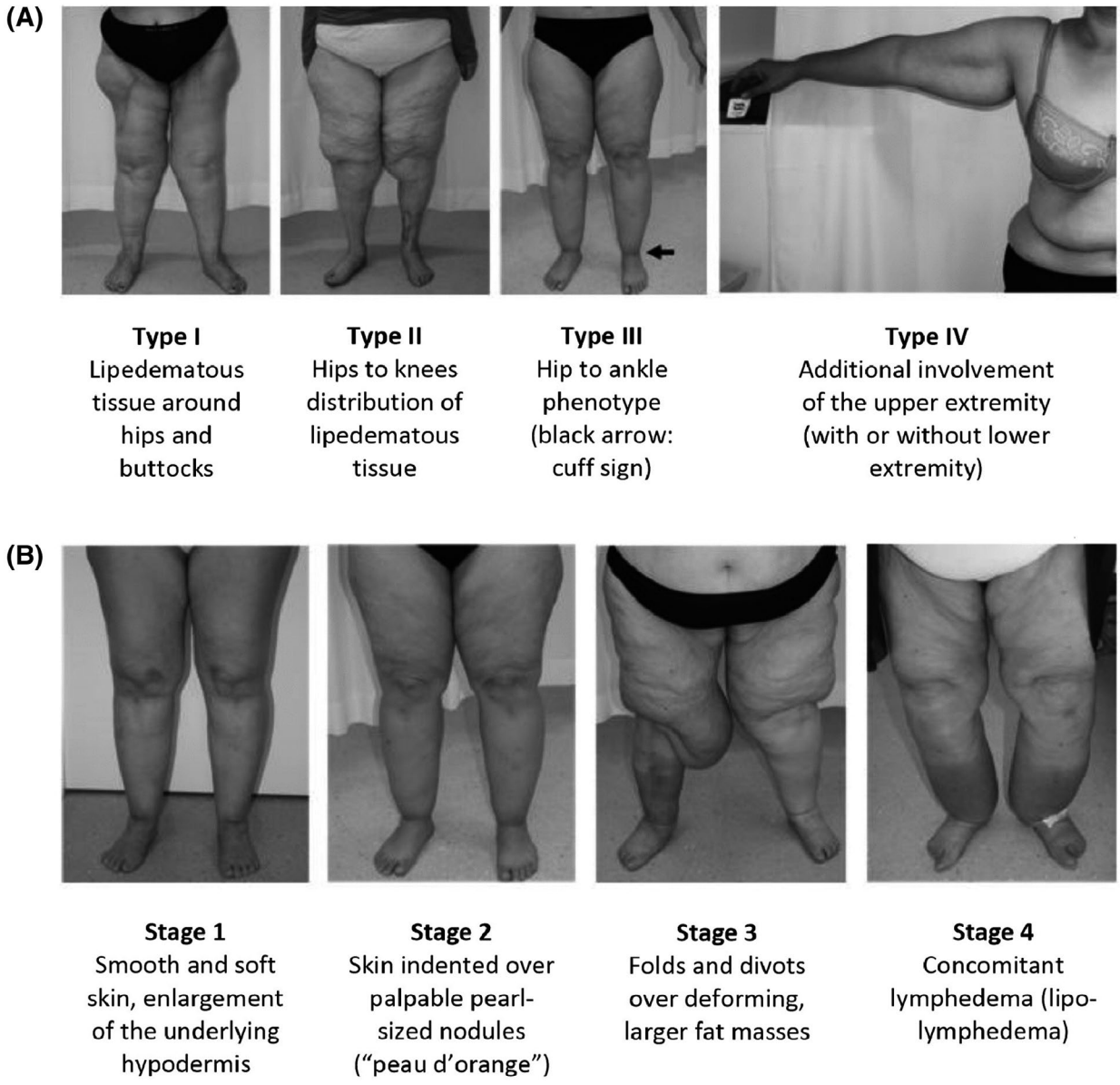

Figure 1 **(A)** Types and **(B)** stages of lipedema.

and impaired secretion of adipokines, thus contributing to adipose tissue low-grade inflammation, which may in turn affect the adipogenic program. However, whether these series of events are shared by obesity and lipedema remains unclear.

Clinical Presentation and Cardiovascular Risk

Localization of lipedema fat tissue is of gynoid type, with typical involvement of the hips, buttocks, thighs, and lower legs, resulting in a disproportion between the upper and lower body (i.e., a waist-hip ratio < 1). Distinct features of lipedema are a sharp separation between normal and abnormal tissue at the ankle ("cuff sign") and significant disproportion in circumference between the hips and waist ("riding breeches"). Based on distribution, five types of lipedema have been described (Figure 1A). In type I, lipedema fat tissue accumulates around the hips and buttocks; in type II, accumulation involves the area from hips to knees; and in type III, a hip to ankle phenotype is observed. Approximately 80% 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). In terms of severity, four stages have been described (Figure 1B). In stage 1, skin may be smooth and soft, but the underlying hypodermis is enlarged; in stage 2, skin may be indented over palpable pearl-sized nodules ("peau d'orange"); and stage 3 is characterized by folds and divots over deforming, larger fat masses, frequently associated with functional limitations. The development of concomitant lymphedema defines the stage 4 (18). The lipo-lymphedema, or lipedema stage 4, is usually

the result of a long-term evolution of the disease from subclinical to clinically manifested lymphedema, thus representing a more advanced stage in most cases. Besides edema of the feet, with a pathognomonic positive Stemmer sign, stage 4 may be accompanied by other common features of advanced lymphedema, such as cellulitis or papillomatosis. Overall, disease progression is heterogeneous and highly variable from one individual to the other. Indeed, some women develop minor lipedema, stabilizing over time, while others exhibit gradual disease progression with sudden stress-induced exacerbation (i.e., pregnancy or surgery) (16).

The most common complaints of patients are easy bruising and moderate to severe pain at digital pressure on affected limbs. Most individuals also experience spontaneous pain. Orthostatic edema is another cardinal sign, which may be responsible for leg heaviness, fatigue, and discomfort. Swelling and pain worsen during warm weather and exercise, and they are not alleviated by limb elevation. Conversely, pain is significantly reduced by lipoaspiration (66). In a single case report (67), the presence of pain was attributed either to mechanical forces or to biochemical effects on sympathetic nerve fibers, with inflammation playing a leading role in this scenario. Microangiopathy with inappropriate blood supply to peripheral nerves may also contribute to protopathic sensibility disturbance (67).

Women with lipedema are at an increased risk for developing morbid obesity, and obesity itself is regarded as a risk factor for lipedema (68). Despite overexercise and extreme dieting, weight loss measures exhibit minimal effect on the abnormal body fat distribution in patients with lipedema. This often results in eating disorders, increased risk for depression, and other psychological complaints, which are commonly reported in this condition (34).

Excessive fat on the buttocks, hips, thighs, and lower legs also impacts the gait of patients with consequent malalignment of the mechanical leg axis, thus resulting in joint stress (69). This often provokes knee valgus osteoarthritis, antalgic gait, and feet overpronation. Hypermobility, which appears to be prevalent in the population with lipedema, can further enhance these complications (70). Additionally, skin lesions, maceration, and infection may occur because of bulging tissue and deep skin folds (71).

Interestingly, patients with lipedema display a less severe cardiovascular profile (18). Pinnick et al. (72) showed that gynoid fat negatively correlated with insulin resistance after total fat adjustment, whereas the opposite was found for abdominal fat. Furthermore, a previous study by Mekki et al. (73) found lower fasting triglyceride-rich lipoprotein, lower triglyceride levels, and smaller chylomicron particle size after a mixed test meal providing 40 g of triglycerides in women with a gynoid fat distribution compared with those with an android distribution. These findings suggest that lipedema fat tissue, which has typically a gynoid distribution, may have protective effects against metabolic dysfunction; however, the authors did not specify whether some of the included patients had lipedema.

Low prevalence of diabetes has also been described in patients suffering from lipedema despite an average BMI of 39 ± 12 kg/m^2 (70). Additionally, a recent study on 46 affected patients found that the majority of them had a normal lipid profile, while only 11.7% had total cholesterol ≥ 240 mg/dL (18), compared with higher percentages (up to 33.5%) in the general female population.

The same study found that less than 30% of women with stages 2 or 3 lipedema had hypertension, which was even absent in patients with stage 1. Interestingly, national data have suggested hypertension rates of 32.4% in women of any BMI aged 40 to 59 years and even higher hypertension rates (up to 60%) in Caucasian women with obesity and a mean age of 63 (18). Nonetheless, patients with lipedema were shown to develop aortic stiffness in one study (20), which seems to contradict these findings. Geographic differences of women included in the these studies may partly explain such apparently contradictory findings. Further research is needed to clarify these aspects.

Assessment and Diagnosis

The diagnosis of lipedema is based on clinical evidence and exclusion criteria. In 1951, Wold et al. (17) proposed a list of six diagnostic criteria, which were extended in 2017 in the first Dutch guidelines, based on clinical experience and literature evidence (74). In Table 1, we propose a slightly modified version of the list recently published by Halk and Damstra (74).

TABLE 1 Diagnostic criteria of lipedema

Medical history (A) (criteria of Wold et al. (17))	
A	**1** Disproportionate body fat distribution
	2 No or limited influence of weight loss on fat distribution
	3 Limb pain and bruising
	4 Increased sensitivity to touch or limb fatigue
	5 Nonpitting edema
	6 No reduction of pain or discomfort with limb lift
Physical examination (B, C, D, E)	
B	**Proximal part of the lower limb**
	1 Disproportionate fat distribution
	2 Circumferentially thickened cutaneous fat
C	**Distal part of the lower limb**
	1 Proximal thickening of subcutaneous fat
	2 Distal thickening of subcutaneous fat, accompanied by slender instep (cuff sign)
D	**Proximal part of the arm**
	1 Significantly thickened subcutaneous fat in comparison with vicinity
	2 Sudden stop at elbow
E	**Distal part of the arm**
	Thickened subcutaneous fat, accompanied by slender back of hand (cuff sign)
Extra criteria	
F	**1** Pain when applying bimanual palpation
	2 Distal fat tissue tendrils of the knee (popliteus)

Modified from Halk and Damstra (74).
Diagnosis is highly probable when present: A (1 to 6) + (B [1 + 2] or C [1 + 2] or D [1 + 2] or E).
In the absence of at most two of these criteria (A to E), the presence of the extra criteria F(1) or F(2) also support the diagnosis.

To correctly follow up patients, Reich-Schupke et al. (71) recommended using clinical parameters such as daily activity index, weight, BMI, waist-hip ratio, waist-height ratio, and limb measurements of circumference and volume (e.g., perometer). Interestingly, 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 (75,76). In a study by Dietzel et al. (75) comparing patients with lipedema and obesity, the amount of fat in the leg and in the gynoid region was significantly higher in patients with lipedema once adjusted for BMI. The optimal cutoff value for leg fat mass per BMI to identify lipedema was considered to be 0.46. This reference may be particularly helpful for a differential diagnosis in otherwise doubtful cases (75). Figure 2 shows a potential diagnostic and therapeutic work-up for patients with suspected lipedema.

The differential diagnosis of lipedema includes conditions presenting with swelling or excessive adiposity of lower limbs, mainly represented by lymphedema and obesity (Table 2). In cases of more advanced edema, other classical causes (i.e., chronic venous insufficiency, idiopathic cyclic edema, edema because of cardiac, hepatic, or renal disease, myxedema, and orthostatic edema) should also be considered.

In lymphedema, the skin is usually altered and thickened, while it remains relatively normal in lipedema. Nevertheless, distinguishing lipedema from lymphedema may be difficult because the two conditions may coexist in advanced stages of disease. Compared with lymphedema, digital pressure typically induces pain in patients with lipedema. Lymphoscintigraphy and green indocyanine lymphofluoroscopy may show impaired lymphatic flow in the affected extremity of patients with lipedema. Impaired lymphatic flow in affected patients is generally less severe than in patients with lymphedema, and imaging may show lymphatic dysfunction that is not yet clinically evident (77,78). In light of these findings, imaging techniques may be considered as a useful tool when diagnosis is doubtful or for lipedema staging. Magnetic resonance imaging, computed tomography, and high-resolution cutaneous ultrasonography have been also used to differentiate lymphedema from lipedema, although these are seldom applied in the clinic (79,80).

Recognizing lipedema among all conditions characterized by excess adiposity in the lower limbs is particularly challenging. BMI may be helpful in differentiating it from obesity, though patients with lipedema may develop obesity at later stages. In a study by Child et al. (5), BMI of the majority of patients with lipedema was consistently within the obesity class II (BMI = 35-39.99, 27%) or class III (BMI > 40, 50%) range. A distinctive feature of lipedema consists of high resistance to lower limb volume reduction following overexercise, extreme dieting, and even bariatric surgery (81). Other characteristic hallmarks are easy bruising, typical anatomical fat distribution, and presence of the "cuff sign."

Dercum 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 disease is characterized by multiple painful lipomas with possible progression into circumscribed or general diffuse fatty deposition. It is usually accompanied by recurrent headache and depression, which are less frequently described in lipedema (82). Although considered a postmenopausal condition by some researchers, Dercum disease has also been described in premenopausal women and even in men (70). Despite some apparent differences, sharp discrimination with lipedema may be complex in clinical practice, and particular awareness on Dercum disease is needed to avoid misdiagnosis.

Another common condition that can be confused with lipedema is chronic venous disease (83). Classic hallmarks of this entity include 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. Notably, swelling also involves the ankles and feet in these patients, with a typical negative Stemmer sign. Varicose veins are also frequently observed in lipedema patients and cannot be used for differential diagnosis (5,17).

Treatment

Given the lack of sufficient information regarding pathophysiology and the relatively scarce experience in terms of management, therapeutic options for lipedema remain limited (3,4,41). Main goals include symptom reduction, functional limitation amelioration, and prevention of disease progression. In the absence of an etiological treatment, therapeutic approaches also aim at impacting factors negatively influencing lipedema progression, such as obesity, lymphedema, venous insufficiency, and decreased physical activity (84). Management of the patient's expectations through education is essential. Psychological support is recommended (16,85,86). Surgical approaches may be limited to selected cases.

Conservative treatment

An active lifestyle should be encouraged, and a multidisciplinary approach to obesity, including dietary modification, is important to consider (84). Although dietetic strategies cannot prevent the disproportional fat distribution, they may reduce local inflammation, thus ameliorating symptoms and improving general well-being and overall health (83). Lifestyle changes cannot reduce fat deposition; however, obesity prevention is crucial because further adipose tissue deposition scarcely responds to diet and exercise. Notably, there is no specific diet for lipedema. However, because insulin promotes lipogenesis and insulin resistance worsens edema formation, a diet avoiding glycemic and insulin peaks and allowing adequate intervals between meals (i.e., isoglycemic diet) may be desirable. Weight loss should not be achieved at the expense of muscle mass (87-89). Aquatic physical activity seems to be particularly beneficial in patients with lipedema because water pressure promotes lymph drainage and buoyancy reduces the load on the joints of lower limbs, decreasing the risk of future orthopedic complications.

To ameliorate therapeutic outcomes, the use of compression garments represents another milestone of conservative treatment and is often able to reduce the pain and discomfort of affected limbs. In patients with lipo-lymphedema, complex decongestive lymphatic therapy (CDP) may be also useful (1). CDP consists of manual lymph drainage associated with multilayered and multicomponent compression bandaging, meticulous skin care, and physical exercise. In selected patients, combination with intermittent pneumatic compression has been shown to improve venous flow and decrease lymph production (90). In a clinical study comparing CDP with and without intermittent pneumatic compression, researchers found significant lower limb volume reduction with both approaches (6.2% and 8.9%, respectively; $P < 0.05$) (91). According to a recent Canadian study (92), treatment of bilateral lymphedema can be

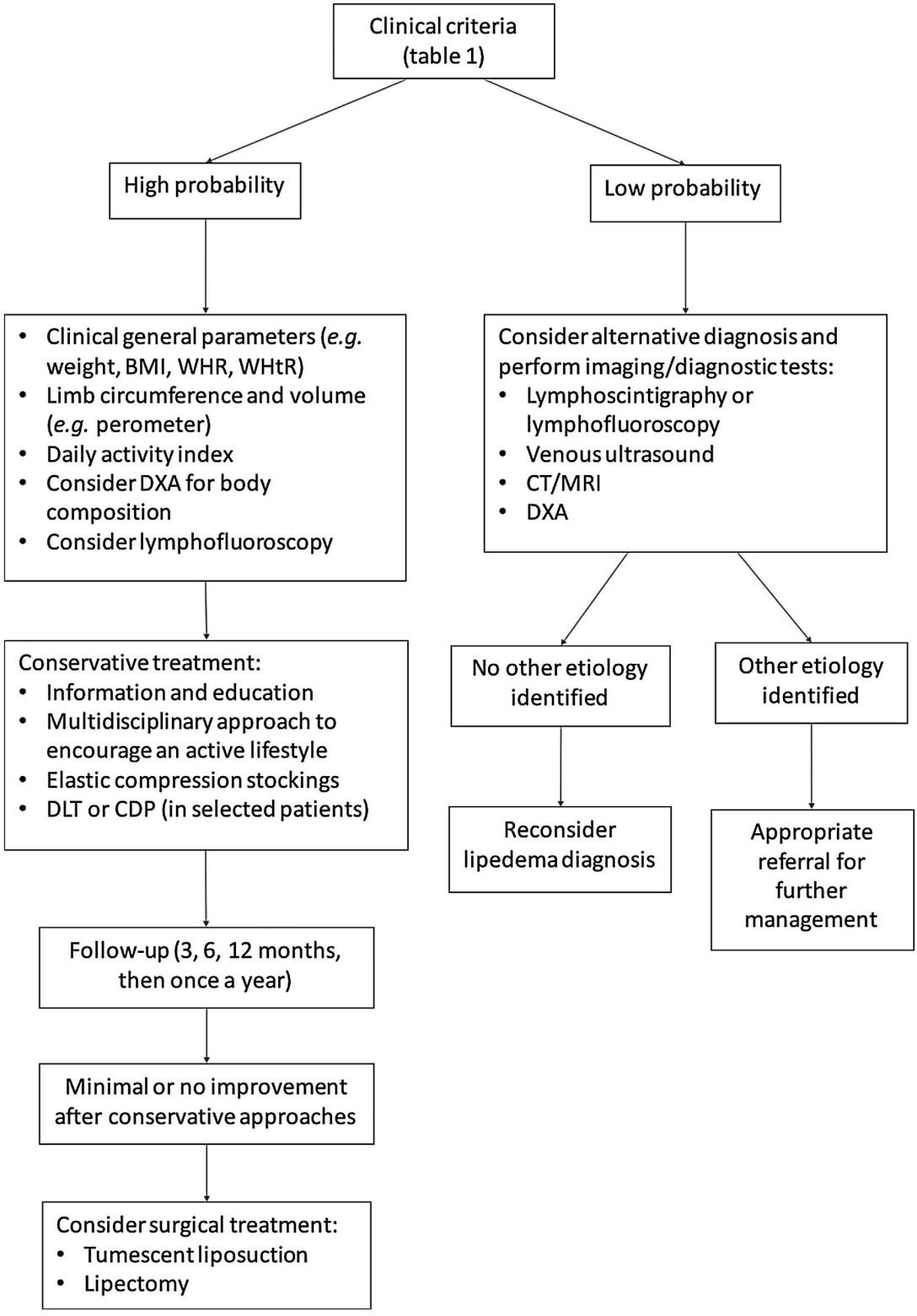

Figure 2 Algorithm for work-up in patients presenting with suspected lipedema. DLT, decongestive lymphatic therapy; CDP, complex decongestive physiotherapy; WHR, waist-hip ratio; WHtR: waist-height ratio; DXA, dual-energy x-ray absorptiometry; CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 2 Differential diagnosis of lipedema

	Lipedema	Lymphedema	Obesity
Increase in fat	+++	(+/+++)	+++
Disproportion	+++	+	(+)
Edema	+/+++	+/+++	(+)
Tenderness to pressure	+++	–	–
Easy bruising	+++	–	–

+ to +++, present; (+), possible; +/+++, variable severity; –, not present.

significantly more time-consuming, costly, and challenging than that of unilateral limbs; this is also true for patients with lipo-lymphedema.

Pharmacological options, including beta-adrenergic agonists, corticosteroids, diuretics, flavonoids, and selenium, have also been suggested (34,93), although their real efficacy in this condition remains to be elucidated.

Surgical treatment

For patients with minimal or no improvement following conservative approaches, the following two surgical options may be considered: liposuction and lipectomy (94). Notably, techniques employed in lipedema patients differ from those adopted for cosmetic purposes (15,66,95). Early procedures, such as dry liposuction, carry an inacceptable risk of lymphatics damage in patients suffering from lipedema (96). Following introduction of tumescent local anesthesia (TLA), super-TLA, and vibrating cannulas, this risk has considerably decreased. Several investigations have shown that TLA is highly effective in terms of both cosmetic and functional outcomes. Schmeller et al. (15) described an average reduction of 9,846 mL of subcutaneous fatty tissue after treatment, with an additional amelioration of sensitivity to pressure, edema, bruising, functional limitation, and cosmetic complaint ($P<0.001$). Moreover, no serious complication occurred following the procedure, with wound infection rates of 1.4% and bleeding rates of 0.3% (15). Very recently, Wollina et al. (97) reported on 111 patients mostly with advanced lipedema treated by microcannular liposuction in tumescent anesthesia between 2007 and 2018. They described a median total amount of lipoaspirate of 4,700 mL, a median reduction of limb circumference of 6 cm, and a median pain level lowering from 7.8 to 2.2 at the end of treatment as well as improved mobility and bruising. Serious adverse events were observed in 1.2% of procedures, with infection and bleeding rates being 0% and 0.3%, respectively (97).

Although some studies have reported better outcomes in the early stages of lipedema compared with advanced ones (15), consistent criteria to identify the ideal timing or patient characteristics for liposuction are lacking. TLA requires specialized skills and should be performed only in specialized centers. In advanced lipedema stages, multiple sessions are frequently necessary to remove larger amounts of adipose tissue and prevent recurrent fat deposition. Unfortunately, lipedema surgical treatments are still too often not reimbursed by health insurance companies, thus representing an expensive option for the overwhelming majority of patients (74). In addition, despite several promising short-term results, only a few studies have evaluated the long-term efficacy of TLA for lipedema treatment (15,98,99). Future research with longer-term outcomes will help support the role of liposuction in the management of such a condition.

In complicated and advanced cases of lipedema with severe mechanical limitations, a more invasive surgical approach consisting of excision of large localized deposits of lipedema fat tissue ("lumps") as a debulking procedure (lumpectomy) may be considered (52). Nevertheless, it has to be noted that this technique may be associated with the development of secondary lymphedema (100).

Conclusion

A call to action for increasing awareness about this widespread and too often misdiagnosed disease is urgently needed. Health care providers should be prompted to diagnose lipedema as early as possible and to offer patients the best management solutions. Best management includes a multidisciplinary approach, involving vascular medicine specialists, plastic surgeons, obesity and endocrinology specialists, and physiotherapists. In parallel, there is a strong need to conduct specific studies to better understand the pathophysiology of lipedema and to design specific therapeutic strategies.

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