Review Article

Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome – systematic review

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Summary

Lipedema is a disproportinate, symmetrical fatty swelling characterized by pain and bruising existing almost exclusively among women. We undertook a systematic review of the available literature about lipedema, given the lack of knowledge and little evidence about this disorder especially among obesity experts. Diagnosis of lipedema is usually based on clinical features. Symmetrical edema in the lower limbs with fatty deposits located to hips and thighs usually appears at puberty and often affects several members of the same family. Main disorders considered for differential diagnosis are lymphedema, obesity, lipohypertrophy and phlebedema. Treatment protocols comprise conservative (decongestive lymphatic therapy) and surgical (liposuction) approaches. Early diagnosis and treatment are mandatory for this disorder otherwise gradual enlargement of fatty deposition causes impaired mobility and further comorbidities like arthrosis and lymphatic insufficiency.

Keywords: Decongestive lymphatic therapy, lipedema, liposuction, obesity.

Introduction

Lipedema was first described by Allen and Hines in 1940. This syndrome is characterized by symmetrical swelling, pain and frequent haematomas in the lower limbs and mainly affects women (1). It is an often misdiagnosed and poorly investigated disorder and only few publications have been devoted to this disorder. Nevertheless, it is very common and has an immense psychological impact. Patients often feel rejected by medical personnel, especially when they are stigmatized as being simply ‘obese’. The abundance of synonyms to refer to this condition indicates how little is known of this syndrome (e.g. adipositas dolorosa, lipomatosis dolorosa, painful lipohypertrophy) (2).

In a survey of 251 consultants, members of the Vascular Society of Great Britain and Ireland, lipedema was only recognized by 46.2% of them (3). Despite the increasing research in this disease, lipedema has not yet been included in the International Classification of Diseases (ICD) by the World Health Organization (4). The European Society of Lymphology has recently asked for its inclusion in the ICD.

Objective

We aimed to perform a systematic review of the available literature about lipedema, given the lack of knowledge and little evidence about this disorder.

Searching strategy

To undertake the study, we have collected information published about lipedema over the last 16 years (1995–
The search in the databases of clinical practice guidelines such as the National Guideline Clearinghouse (5), Guidelines Finder of the National electronic Library for Health of the NHS (6), CMA Infobase (7), CDR databases (8) and ACP Journal Club (9) did not bring any document. However, we found two documents in the Cochrane Library (10).

The terms ‘lipedema’ and ‘lipoedema’ do not appear in the MeSH Browser Database MEDLINE (11) nor in the EMBASE (12), therefore, the search was conducted with these same terms in the summary or title of the article in different databases: Web of Knowledge (13), Scopus (14), Cochrane Library (10) and Embase (12). The most relevant books on lymphedema have also been revised.

From the 97 documents found, 51 were excluded. The search in the databases provided us 46 documents after excluding 19 repeated or redundant papers, two articles in Chinese, two in Serbian, one in Russian, 12 with a different topic, seven patents not related to lipedema and eight abstracts in conferences.

Selection of studies and data

The articles were chosen by, firstly, reading the abstract and, subsequently data were analysed by reading the entire text through full-text resources or asking directly to the author.

The analysis of these documents reveals the increasing interest on the subject and that most have been written in Germany being a highlighted topic in the scientific literature on lymphology in this country. Most of the articles are reviews from others and original research is scarce.

Results

Epidemiology

Although there is no epidemiological data on the prevalence of lipedema, Földi described a prevalence of 11% in women, being extremely rare in men (1). Herpertz reports that lipedema accounted for 15% of patients in a lymphedema clinic (15). A recent study reports that 6.5% of the children with the referral diagnosis of lymphedema actually suffer from lipedema (16). According to our experience, from 843 patients seen in the unit since 2005, lipedema represents the 18.8% of the patients with enlargement of the lower limbs.

Clinical manifestations of lipedema

Lipedema is defined as a chronic disease that predominantly affects women and it is normally first noticed at puberty, pregnancy or menopause (1,17). In 97% of the cases, lipedema is located in lower limbs and in 31% in upper extremities (15).

Patients present a symmetrical and abnormal increase of adipose tissue from the hips, involving the buttocks as well as the regions of thigh and calf (Fig. 1c). The enlargement of the lower limbs is disproportionate in relation to the upper part of the body (18).

Patients complain that edema in lower limbs may worsen in the afternoon or evening and that increased swelling is often related to orthostasis or heat. Patients have increased sensitivity to pain and spontaneous or minimal trauma-induced bruising. Other symptoms include plantar arch

![Figure 1](image-url) 1a and b show that lymphedema can be unilateral or bilateral, while lipedema is always bilateral (c).
abnormalities, cold skin and spontaneous or minor trauma-induced pain. As lipedema progresses, increasing lower limb weight may lead to hip and knee joint damage that can develop to orthopaedic disorders and gait alterations with impaired mobility (Fig. 4d).

In severe forms when lipedema remains untreated, increased lymphatic load continually exceeds lymphatic transport capacity resulting the decompensation of lymphatic system therefore uni-, or much more typically, bilateral lymphedema can develop. Evidence for lymphedema is the presence of swelling of the dorsum of the foot, a positive Stemmer sign (the inability to pinch a fold of skin at the base of the second toe due to thickening of the skin and subcutaneous tissues) or deep skin-folds. The combination of lymphatic insufficiency and lipedema is called lipo-lymphedema or lympho-lipedema depending on the terminology (Fig. 2). Concomitant severe venous insufficiency is rare; however, varicosity is often seen among lipedematous patients (19). Lipedema often co-exists with obesity and the clinical diagnosis may be confused as simply obesity.

Diagnosis

Diagnosis of lipedema is usually made on the basis of clinical features (20). Usually, the medical history and clinical examination are enough to suspect the diagnosis. Symmetric lower limb edema, with deposit of fatty tissue in the hips and legs, usually appears at puberty and often affects several female members of the same family: mother, sisters, grandmother, etc. (Fig. 3). Self-reported positive family history of lipedema varies between 16% and 64% (21). In our series, 25 of 73 patients presented familiar lipedema history. These strong familial background suggests that lipedema is a genetic disorder (22).

Other important hallmarks of lipedema comprise pain on palpation and frequent bruises occurring spontaneously or provoked by minimum blows due to capillary fragility.

To make a reliable clinical diagnosis, it is important to differentiate disorders that present with swelling and fat deposits (Table 1).

Lipedema appears to be a distinct clinical entity but may be confounded with lymphedema. The following descriptions pinpoint the most significant differences between lymphedema and lipedema (23,24):

- Lymphedema can be either unilateral or bilateral (Fig. 1a,b), while lipedema is always bilateral (Fig. 1c).
- Lymphedema patients commonly present a positive Stemmer sign, whereas in pure lipedema, Stemmer sign is negative, the feet are spared and the fat deposits begin abruptly above the ankles (cuffing sign; Fig. 2).
- Lymphedema is usually painless, whereas lipedema patients report spontaneous or even minimal pressure-induced tenderness.
- Lipedematous skin gets easily bruised.

Lipedema is distinguished from obesity because it usually appears in lower limbs, more rarely in arms, whereas obesity may affect the whole body with an increased body mass index (BMI) while lipedema can occur in patients with a normal BMI. This is important to recognize since lipedema is frequently misdiagnosed as obesity resulting in disturbed eating behaviour such as anorexia, or other self-image perception alterations. Lipedema, unlike obesity, hardly ever responds to low-calorie diet (25). Dietary counselling is advisable as a preventive measure against further weight gain (26). Medical history of most patients shows that the majority has a history of dieting and exercising.

![Figure 2](image-url)
without any considerable benefit on the contours and shape of affected limbs.

Lipedema might also be mistaken with Morbus Dercum as they share their cardinal hallmarks, the spontaneous or palpation-induced pain and bruising. At the onset Dercum’s disease is characterized by multiple painful fatty masses or lipomas with a possible progression into circumscribed or general diffuse type. However, it appears between the ages of 35 and 50 years, Morbus Dercum is considered as a postmenopausal condition. The most common locations of painful fatty depositions are the limbs, trunk, the pelvic area and the buttocks (27,28). Morbus Dercum usually has several typical accompanying symptoms like recurrent headache and depression that have never been described in lipedema (29). In differential diagnostic procedure, lipohypertrophy should also be considered. The most apparent feature is found in its painless condition (30). Lipedema is often preceded by symmetrical lipohypertrophy. The differential diagnostic hallmarks between lipohypertrophy and lipoedema are the absence of edema and pain in lipohypertrophy; however, there are painful subtypes of lipohypertrophy (31).

Schingale distinguishes five types of presentation of the lipedema (32):

- Type I: adipose tissue increased on buttocks and thighs.
- Type II: the lipedema extends to the knees with formation of fat pads on the inner side of the knees.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Differential diagnosis of lipedema</th>
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<tbody>
<tr>
<td>Gender affection</td>
<td>Location</td>
</tr>
<tr>
<td>Lipedema</td>
<td>Women, puberty</td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td>Women, puberty</td>
</tr>
<tr>
<td>Primary</td>
<td>Both; often at puberty</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>Both</td>
</tr>
<tr>
<td>Phlebedema</td>
<td>Both</td>
</tr>
<tr>
<td>Obesity</td>
<td>Both</td>
</tr>
<tr>
<td>Morbus Dercum</td>
<td>Both (female/male ratio: 30/1)</td>
</tr>
</tbody>
</table>

BMI, body mass index; LL, lower limbs; T, trunk; UL, upper limbs.
• Type III: lipedema extends from the hips to the ankles.
• Type IV: involving the arms and legs.
• Type V: lipo-lymphedema.

Based on inspection and palpation, lipedema can be classified in three clinical stages according to severity (25) (Fig. 4):

• Stage I: the skin surface is normal and the subcutaneous fatty tissue has a soft consistency but multiple small nodules can be palpated.
• Stage II: the skin surface becomes uneven and harder due to the increasing nodular structure (big nodules) of the subcutaneous fatty tissue (liposclerosis).
• Stage III: is characterized by lobular deformation of the skin surface due to increased adipose tissue. The nodules vary in size and can be distinguished from the surrounding tissue on palpation. The phenomenon of ‘peau d’orange’ can be seen by pressing the skin.

Complementary tests
Complementary tests can provide data on the differential diagnosis of lipedema and severity.

Laboratory tests
General blood tests are recommended because some patients may also suffer from underlying medical conditions that are responsible for the further deterioration of their symptoms (33). Thyroid function should be tested as there is an association between lipedema and sub- or clinical hypothyroidism (34).

Streiten test
Cardiac, renal and venous insufficiency should be excluded before starting the test. The patient drinks 20 mL water per kg of body weight and remains in an upright position for 4 h. During this observational period urine is collected. The leg volume is measured before and after the test. Normal healthy subjects excrete more than 60% of the ingested water and the leg volume does not increase with more than 350 mL/leg. Pathological results indicate the existence of increased permeability of blood capillaries. Based on the result of Streiten test together with clinical features, the diagnosis of lipedema can be suspected (34,35).

Duplex ultrasound examination of lipedema shows a thickened subcutis with increased echogenicity, whereas in lymphedema, the typical echo-less gaps are not compressible. High-resolution cutaneous ultrasonography shows that in patients with lipedema, dermal thickness and echogenicity were normal, while increased dermal thickness and decreased echogenicity were associated with lymphedema (36). The sonography is sometimes superior to clinical examination and can be chosen as the second step in diagnosis of all non-systemic forms of edemas of the legs (36,37).

Other radiological examinations may also help in the differential diagnosis of lipedema. According to Monnin-Delhom et al., computed tomography scan has a sensitivity of 95% and specificity of 100% for the diagnosis of lipedema. Skin thickening can appear in lipedema, but subcutaneous fluid accumulation, the honeycomb pattern and muscle enlargement are not seen in lipedema, while these features are typical for lymphedema (38).

Magnetic resonance imaging (39,40) and its modified form, magnetic resonance lymphangiography are of practical importance to evaluate the lymphatic circulation when the lymphatic involvement is unclear (41).

Lymphoscintigraphy can be useful in the differential diagnosis of edema, allowing the exclusion of clear lymphatic dysfunction (42–44). Lymphatic insufficiency can be seen in long-standing lipedema without lymphedema-like morphologic abnormality (45) (Fig. 5).

Pathology and pathophysiology
Földi and Földi have proposed that microangiopathy in the area of the affected adipose tissue results in higher permeability to proteins and increased capillary fragility leading to spontaneous and minor traumatic injury-induced formation of bruising (1). Siems et al. detected nearly fourfold higher levels of plasma vascular endothelial growth factor (VEGF) levels at baseline than normal values of plasma VEGF (46). VEGF controls angiogenesis and hypoxia is a potent inducer of angiogenesis and this factor may play a significant role in lipedema, too (26). The detected high baseline levels of both malonyldialdehyde and protein carbonyls are indicative of severe pre-existing oxidative stress and likely represent an accelerated lipid peroxidation in lipedematous tissue. Existing diminished venoarterial reflex also contributes to haematoma formation. Bano et al. have recently found a Pit-1 mutation in members of a family with lipedema (47) and screening of lipedema family members strongly suggests inheritance (22). In adipose tissue morphological examinations, Suga et al. found robust CD68+ macrophage infiltration in lipedematous adipose tissue with loss of adipocytes due to necrosis and simultaneous proliferation of adipose-derived stem cells (Ki67+ CD34+). These results suggest massive adipogenesis with concomitant hypoxia resulting in necrosis and macrophage recruitment (48).

Therapy
Standard conservative therapy for lipedema has been based solely on clinical experience and relies on decongestive lymphatic therapy (DLT). Its elements are the gentle massage technique called manual lymph drainage (MLD),
Figure 4 Stages of lipedema. (a) 14-year-old girl in stage 1. (b) 35-year-old woman in stage 2. (c) 55-year-old woman in stage 3 and (d) 68-year-old woman with elephantiasis and important disability.
Figure 5 Lymphoscintigraphic findings in lipedema (a), primary lymphedema with a lymphatic aplasia in the left lower limb (b) and lymphedema secondary to gynaecological cancer (c).
physical exercise, multilayered and multicomponent compression bandaging and meticulous skin care. MLD directs the lymph away from the edematous parts and reduces the volume of the limb by diminishing the persistent lymph stasis, increases protein resorption and opens lymphatic collaterals (49). In selected cases DLT can be combined with intermittent pneumatic compression (IPC). It improves predominantly venous flow and decreases lymph production upon reduction of capillary afterload (50).

Sustained compression efficiently decreases capillary filtration. One uncontrolled trial of complex decongestive physiotherapy in lipedema showed that the maximally achievable reduction was around 10% of the original leg girth (45). In another clinical study, MLD-based DLT was compared with MLD plus IPC-based DLT once daily therapy in a 5-day course. Each treatment modality resulted in significant limb volume reduction (6.2% and 8.9% respectively; \( P < 0.05 \)); however, no significant difference was proven between the two regimens \( (P < 0.07) \) (53). There is also evidence to support the capillary fragility reducing effect of MLD plus IPC-based DLT. Capillary fragility was measured as the number of petechiae evoked by Parrot’s angiosterrometer before and after conservative therapy. The application of decongestion resulted in a considerable reduction of the number of petechiae. Mean ± SD number of petechiae was 13.95 ± 10.17 at baseline and 8.775 ± 6.88 after DLT \( (P < 0.001) \). Lipedematous legs of the control group were treated only with moisturizers and this therapy failed to show any improvement in capillary fragility \( (P > 0.05) \) (51–54).

There are different aspects of surgery in lipedema. Mild- to-severe forms of commonly associated varicosity could be subjected to varicose vein surgery. It is rather controversial, however, lipedema remains a relative contraindication to varicose vein surgery because it may worsen swelling and may be associated with complications such as delayed wound healing (55). Originally, debulking or conventional liposuction under general anaesthesia were contraindicated because of the risk of iatrogenic damage to the lymphatics (56).

In a new era of lipoaspiration using tumescent local anaesthesia, large amounts of fluid (saline, lidocaine, adrenaline, etc.) are infiltrated in the subcutaneous tissues. Tumescent liposuction efficiently removes excess adipose tissue and less likely damages lymphatic vessels than conventional lipospiration. Novel techniques as power-assisted liposuction with machine-powered 30–40 cm long and 3–4 mm wide metal cannulas oscillating in and out or vibrating fast using multiple insertions with limited amount of aspirated fat (53,55) or water jet-assisted liposuction have been shown to improve safety (57). Besides heavy decongestion, liposuction drastically improves pain perception, mobility and range of motion, especially at knee joints and results appear to be sustained (58,59).

In advanced stages of lipedema, extensive amounts of fat are deposited; therefore, multiple sessions of surgery are necessary. The German Phlebological Society recommends liposuction as a part of therapeutic armamentarium in the management of lipedema (17). Recent reports show the long-term efficacy of liposuction in maintaining the volume of the limb (60), emphasizing the use of compression garment 24 h per day after the procedure (61); however, conservative decongestion could be either stopped or its frequency could be substantially decreased (55). Tumescent liposuction results the most potent benefit for lipedematous limbs without serious side effects (55).

Conclusions

Current knowledge about lipedema as a hidden epidemic is scarce, but the scientific interest is increasing. More studies are required to know the real prevalence and to reach an earlier diagnosis of this disorder. Diagnosis and treatment should be made as early as possible to prevent complications associated with increased functional and cosmetic morbidity.

Conflict of Interest Statement

No conflict of interest was declared.

References

Lipedema: from clinical presentation to therapy. A review of the


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