

## Lipedema: A Clinical Challenge-revisited

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### Authors' contributions

*This work was carried out in collaboration between all authors. Authors MO, AM, and NVD designed and wrote the first draft of the manuscript. All authors managed the literature searches. They read and approved the final manuscript.*

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Review Article

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## ABSTRACT

Lipedema is a disfiguring disorder with abnormal and progressive deposition of adipose tissue in the hips and lower extremities almost exclusively occurring in women. There is a hereditary tendency and a substantial variability in disease severity. Lipedema is often misdiagnosed as lymphedema or morbid obesity. The etiology and pathogenesis are not understood. Early diagnosis and treatment are critical to minimize physical and psychological morbidity. The diagnosis is usually made by history and clinical examination. Non-invasive imaging techniques such as computed tomography or magnetic resonance can differentiate lipedema from other causes of edematous lower extremities. Lymphoscintigraphy may be helpful in cases which are associated with lymphedema (lipo-lymphedema). Management with manual lymphatic drainage and compression therapy are considered the most appropriate treatment. Use of conventional liposuction is controversial since it may further damage the lymphatic vessels. Newer techniques such as tumescent micro annular laser assisted liposuction and water jet-assisted liposuction have shown some promising results. Variety of other surgical procedures combined with manual lymphatic drainage and tailored post-surgical care are under investigation.

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## 1. INTRODUCTION

Lipedema is a frequently misdiagnosed disfiguring disorder. The term “lipedema” was first used by Allen and Hines in 1940 who describe a syndrome of “fat legs and orthostatic edema” [1]. Different synonyms are reported in the literature, among which lipedema is the one most commonly used [2]. The syndrome is defined by a symmetrical localized subcutaneous deposition of fat which leads to a chronic progressive enlargement of the lower extremities [3]. Lipedema occurs almost exclusively in women, with a few rare cases reported in men. It normally begins insidiously around puberty and progresses gradually. However, the age of occurrence may vary substantially [3,4,5]. The condition is often confused with vascular diseases that affect the lower extremities such as lymphedema or venous insufficiency. Although in advanced cases, lipedema may be associated with secondary lymphatic insufficiency termed “lipo-lymphedema” [6].

Lipedema is neither well understood nor recognized by most health care providers resulting in significant under-diagnosis and mismanagement. This review will provide current and practical information to clarify this disease and also its management.

## 2. EPIDEMIOLOGY & GENETICS

The incidence of lipedema in the general population is not known, because the epidemiological studies are inconclusive. In most case series of patients referred to lymphedema clinics, the prevalence rate ranges from 10% to 23% [2,6,7]. However, most authors agree that lipedema is a misdiagnosed condition and the prevalence is most likely higher than reported.

Lipedema occurs predominantly in women and to our knowledge only a few men have been reported in the literature [3,6,8,9]. No racial preference is evident. Although a specific genetic defect has not been identified in lipedema, a family history of having “fat legs” is not uncommon, and varies widely in the medical literature from 16% to 64% of lipedema cases [2,3,7,10]. In pedigree analyses, Child et al. [8] found 10 of 67 (15%) of lipedema patients with at least one affected first degree relative. Seven of the analyzed families in that study had at least three affected members in two or more

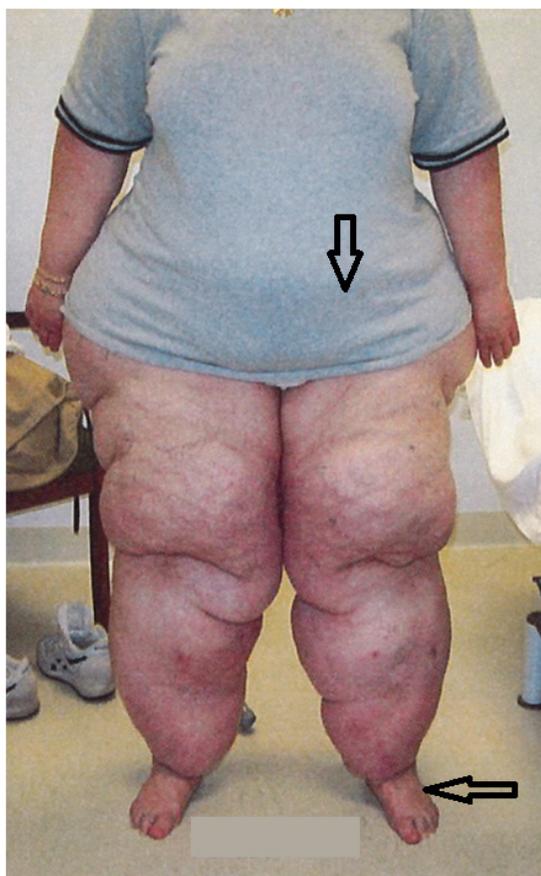
generations. This raised the possibility of a genetic predisposition with either an X-linked dominant inheritance or autosomal dominant inheritance with sex limitation. Furthermore, Bano et al. [11] described a male patient diagnosed with an inherited combined pituitary deficiency due to a PIT-1 mutation in association with a family history of short stature and lipedema affecting only females in four generations.

## 3. CLINICAL PRESENTATION

Heterogeneity of clinical presentation is common. Unfortunately, most cases are frequently misdiagnosed either as lymphedema, chronic venous insufficiency, or morbid obesity [12]. Many patients do not recognize the onset, which normally begins insidiously around puberty and sometimes after pregnancy or menopause suggesting a possible correlation with hormonal changes.

Lipedema is characterized by bilateral and symmetrical abnormal fatty depositions extending from the hips to the ankles with a unique sparing of the feet. The fat deposition is disproportionate to the upper body giving an appearance of “riding breeches” or “saddle bag” legs. (Fig. 1) In early stages rarely, some patients develop similar findings in the arms with sparing of the forearms and hands. (Fig. 2 upper arrows). In advanced cases the fat disposition spreads from the shoulder to the wrist.

The skin is usually spongy without pitting as is usually seen in lymphedema. The Stemmer’s sign (inability to pinch and lift a fold of skin at the base of the second toe) is negative. Patients may develop easy bruising with minimal trauma. The size and intensity of bruising may vary from a minor bruise to a large hematoma. Some patients develop petechiae in the arm after a blood pressure measurement (positive tourniquet test). However, mucosal bleeding is not seen. Pain and tenderness are important symptoms present in the majority of the patients. Most commonly, the pain is localized in the thighs and anterior tibial shins. However, other areas such as the lower abdomen may be affected. Most patients report a sensation of heaviness in the legs with moderate to severe sensitivity to touch or minor pressure. Interestingly, paresthesias may develop in the plantar aspect of the feet, an area not directly involved with lipedema.



**Fig. 1. Advanced case of lipedema with symmetrical abnormal fatty deposition of lower abdomen, hips, and lower extremities, which is disproportionate to the upper body (upper arrow) and unique sparing of the feet (lower arrow)**

In advanced disease, patients often develop moderate to severe orthostatic edema due to the combination of excessive fat accumulation and decreased mobility. The edema is usually aggravated by prolonged standing or sitting. Leg elevation has very minimal impact on reducing the swelling. When lymphatic orthostasis coexists with lipedema, the condition is referred to as "lipo-lymphedema". Stasis dermatitis with thickening of the dermis can develop in some patients. Skin discoloration is initially not apparent, however, in advanced lipedema some discoloration may occur. Due to secondary lymphatic dysfunction, lymphangitis (superficial infection without ulcerations) may occur as a rare complication of advanced lipedema. This can lead to the development of cellulitis (open skin ulcerations) which sometimes is difficult to treat. Furthermore, ambulation becomes difficult due to

the development of osteoarthritis in the hip and knee joints. As the disease progresses, psychological problems such as depression and eating disorders are frequently encountered. Poor cosmesis and difficulty with activities of daily living contribute to low self-esteem and depressive symptomatology [6,12].



**Fig. 2. Stage I lipedema with deposition of fat on both arms with sparing of the forearms and hands (upper arrows). Thickening of the fat at the ankle-cuffing sign (lower arrow)**

#### 4. STAGING

Although the staging of lipedema is not well developed, clinical observation demonstrates a continuum in the evolution of the disease. Our proposed description for the staging of lipedema is not perfect but it offers a clinical system that is relevant to the management of the disorder.

**Stage I** is characterized by a "loose" accumulation of fat without deformation of the regular skin. At this stage, it could be difficult to differentiate lipedema from obesity. However, in lipedema the subcutaneous tissue is spongy with some

nodular changes in the fat which are felt with palpation. The thickening of the fat at the ankle (cuffing sign) could be recognized (Fig. 2).

**Stage II** is more frequently recognized because of the increased nodularity and consistency of the accumulated adipose tissue with an irregular skin surface. Formation of fatty lobules on the medial distal and proximal thigh and thickening of the fat around the ankle (cuffing sign) is usually observed. The feet are invariably spared (Fig. 3). Similar fat deposition might be rarely seen in the upper extremities without affecting the forearms or hands (Fig. 2). Tenderness over the anterior tibial shin may be observed during this stage.



**Fig. 3. Stage II lipedema with formation of fatty lobules around knee and medial distal thigh (upper arrow) and thickening of the fat around the ankles (lower arrows)-cuffing sign**

**Stage III** is the most frequently encountered and diagnosed stage. The amount of deposited fatty tissue is excessive and more lobular giving the appearance of riding breeches. (Figs. 1 and 4) The feet continue to be spared and there is a thickening of fat at the ankle (cuffing sign). Deformation of the skin surface is quite evident. In rare cases the upper extremity could be affected with deposition of fat from the shoulders to the wrists. The hands usually are spared. Other skin changes such as discoloration and induration can be seen if orthostatic edema

develops. A pitting edema indicates lymphatic involvement (lipo-lymphedema).

## 5. IMAGING STUDIES

The diagnosis of lipedema is usually made clinically; however, imaging studies might be helpful to distinguish lipedema from other causes of leg swelling [13]. Generally, standard angiography does not show morphologic abnormalities of the large lymphatic, venous, or arterial vessels that are specific or diagnostic of lipedema [14]. In lipedema, quantitative radionuclide lymphoscintigraphy reveals a mild degree of slow lymphatic drainage when compared to lymphedema, in which lymphatic function is significantly impaired [10,15,16]. Fluorescent microlymphography reveals extremely distended pre-lymphatic spaces that are referred to as microlymphatic aneurysms of lymphatic capillaries in the affected region [17]. High-resolution cutaneous ultrasonography may help to differentiate lymphedema from lipedema. In patients with lipedema, the skin thickness and echogenicity are normal, while lymphedema is characterized by dermal thickening and hypochoic subcutaneous tissue [18].



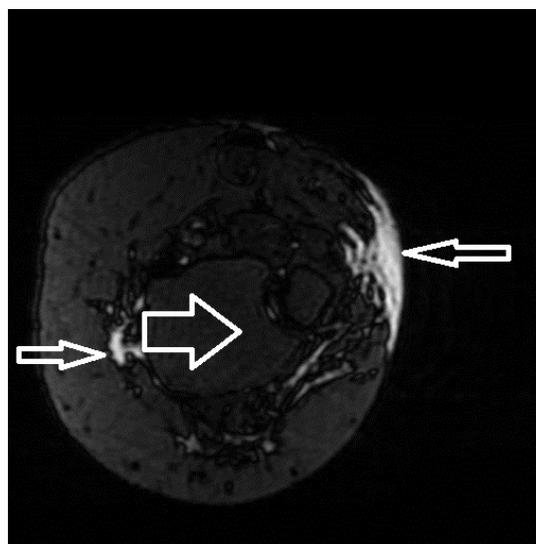
**Fig. 4. Patient with stage III lipedema with the appearance of more lobular fatty deposition and "riding breeches". Skin changes are frequently seen (arrow)**

Computed tomography (CT) is another imaging technique used to distinguish lipedema from lymphedema. The soft tissue edema, skin thickness, and interstitial fibrosis (honeycomb

pattern) are very specific to lymphedema and not present in early lipedema [19,20,21].

lymphedema and obesity. Other conditions for differentiation are shown in (Table 2).

Magnetic resonance imaging (MRI) is a valuable procedure for differentiating lipedema from lymphedema, venous insufficiency, or obesity [22,23]. It is capable of analyzing multiple and subtle tissue characteristics and thereby provides better definition of soft tissue than with other imaging techniques. MRI can distinguish fat from water or from proteinacious fluid differentiating lipedema from obesity [24]. Specialized fat-saturating imaging techniques may be used to reduce the signal intensity of fat and enhance the visibility of edema [25]. Lipedema demonstrates homogeneous thickening of the subcutaneous fat whereas lymphedema displays circumferential soft tissue edema with thickening of the skin (honeycomb pattern) [26]. In lipedema, the subcutaneous tissue contains abundant fat and little water (Fig. 5). When the water volume increases, it indicates the presence of lipo-lymphedema; a condition that is eligible for manual lymphatic drainage.



**Fig. 5. MRI image of below the knee, right leg of patient with lipo-lymphedema. The white area represents fluid in the fat (small arrows). Dark areas represent saturated fat (large arrow)**

## 6. DIFFERENTIAL DIAGNOSIS

Lipedema is commonly mistaken for obesity or lymphedema. (Table 1) summarizes the most significant clinical differences between lipedema,

**Table 1. Differential diagnosis of most common misdiagnosed diseases**

<b>Patient History</b>	<b>Lipedema</b>	<b>Lymphedema</b>	<b>Obesity</b>
Sex	Exclusively Women	Men & women	Men & women
Age of onset	Around puberty or young adulthood	Any age	Any age
Positive family history	Possible	Only in congenital or primary	Common
Effect of elevation & compression	None to Minimal	Minimal to moderate	None
Response to dieting	None	None	Significant
History of cellulitis or lymphangitis	Rare	Frequent	None
<b>Clinical findings</b>			
Areas involved	Mostly hips and legs (feet spared)	Any extremity	Entire body
Malleolar fat pad	Present	Absent	Absent
Symmetry	Always bilateral	Usually unilateral	Diffuse
Skin consistency	Soft and spongy	Thick and firm	Soft
Pitting edema	Only in advanced stages	Always present	Absent
Pain and tenderness	Common	Absent	Absent
Easy bruising & hematoma	Common	Absent	Absent

**Table 1 continued .....**

Foot involvement	Absent	Always present	Absent
Stemmer's sign	Absent	Present	Absent
Metabolic comorbidities	Unrelated	Unrelated	Common
<b>Imaging studies</b>			
Lymphangiography	Normal	Abnormal	Normal
Lymphoscintigraphy	Normal or very mild lymphatic impairment in some patients	Abnormal with delayed lymphatic drainage, and dermal backflow with large lymphatic collaterals	Normal
CT scan	Normal skin thickness No subdermal fibrosis Marked hypertrophy of homogenous subcutaneous fat	Dermal thickening Fluid accumulation in the subcutaneous tissue Interstitial fibrosis (honeycomb appearance)	Homogeneous thickening of the fat with normal skin thickness
MRI	Homogenous thickening of fat tissue Normal skin thickness No subcutaneous edema	Dermal thickening Fluid accumulation in subcutaneous tissue with fibrosis (honeycomb appearance)	Homogenous thickening of fat tissue Normal skin thickness

*Other conditions associated with swelling or adipose deposition also should be considered [27]*

**Table 2. Other conditions for differentiation**

	<b>Phlebedema</b>	<b>Rheumatic edema</b>	<b>Immobility edema</b>	<b>Constitutional variants of normal leg form</b>
Underlying disease	Varicose veins post thrombotic syndrome	Chronic polyarthritis Fibromyalgia	Various conditions which could lead to reduced mobility	Wide range of ethnically-determined leg forms
Clinical characteristics	Uni or bilateral edema	Uni or bilateral edema Flaring or immobilizing joint pain	Sever edema of the lower legs	Tendency to have lipohypertrophy of the legs and gluteal regions without displaying signs of lipedema
Skin changes	Hyperpigmentation Purpura Leg ulcers Derma sclerosis	Occasional bacterial or non-bacterial circumscribed lesions (plaques)	Hyperpigmentation Dermatitis Leg ulcers	
Imaging diagnosis	Color-coded duplex sonography			

**7. PATHOPHYSIOLOGY & PATHOGENESIS**

The precise mechanism for the development of lipedema remains unknown. Several hypotheses have been proposed including microangiopathy, adipogenesis, and genetic mutations.

There is an intimate relationship between adipose tissue biology and the vascular system, especially the lymphatic vessels [27,28]. With angiography there are no anatomical abnormalities evident of the large lymphatic or venous vessels that are specific or diagnostic of lipedema [14]. The lymphatic drainage is inversely proportional to the size of the

adipocytes [1]. Dynamic lymphoscintigraphy shows slow lymphatic drainage which never approaches the level of lymphatic impairment observed in true lymphedema [10,15]. Additionally, there is a higher permeability to proteins and increased capillary fragility with formation of micro-aneurysms of the lymphatic capillaries [17]. Hence, the high content of protein and fat in the lymphatic fluid leads to a low-grade inflammation with subsequent interstitial fibrosis resulting in a non-pitting orthostatic edema. This may also explain easy bruising with minor trauma. Nevertheless, whether the slow lymphatic flow or the formation of lymphatic micro-aneurysms in lipedema is primary or secondary to adipocytes accumulation remains unknown.

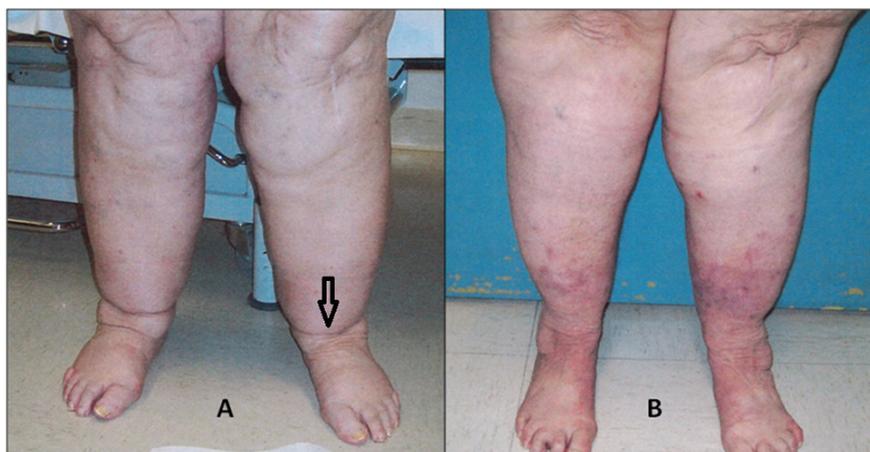
In addition, the adipose tissue biopsies usually demonstrate irregular clusters of elastic fibers, adipocytes necrosis with micro-cyst formation, and an increased number of mast cells [29, 30]. The adipocytes are surrounded by crown-like structures containing necrotic adipocytes with an accumulation of macrophages (CD 68+); similar to what is seen in obesity [31,32]. Macrophages in adipose tissue have been shown to produce vascular endothelial growth factors (VEGF) in response to inflammatory stimuli and hypoxia [5,32,]. It has been suggested that the massive enlargement of adipose tissue in lipedema creates a hypoxic environment leading to angiogenesis and adipocytes dysregulation [30]. This may contribute to the previously described histological findings such as capillary fragility, lymphatic micro-aneurysms, and abnormal

elastic fibers with an increased number of mast cells.

## 8. MANAGEMENT

Lipedema is a difficult condition to treat, especially since most cases are misdiagnosed and inappropriately treated as lymphedema or obesity. Patients usually present to a lymphedema clinic much later at an advanced stage of disease. Since lipedema is a progressive form of fat deposition, early diagnosis offers an opportunity for better management. Therefore, staging is a very important step for the management of lipedema. Lasting improvement and long remission can be expected only in patients detected early. Otherwise, gradual progression of fatty deposition leads to debilitating impaired mobility and secondary lymphatic insufficiency.

Conservative management with the combination of manual lymphatic drainage (MLD) and compression therapy is widely considered the most effective treatment [33]. This management is mainly effective in the early stages of the disease. It is divided into two distinct phases, an intensive phase and a maintenance phase. The intensive phase consists of MLD, multilayered compression bandaging, physical exercise, and meticulous skin care. The MLD involves gentle massages to mobilize the lymph away from the edematous area and reduce the lymphostasis. Compression therapy with multilayered short-stretch bandaging to maintain the calf muscle pumping mechanism is usually started when the pain and tenderness decrease.



**Fig. 6. A female with lipo-lymphedema stage II. (A) Before treatment, (B) after completion of conservative management (manual lymphatic drainage plus compression therapy). Cuffing sign is not present after treatment (arrow)**

Intermittent pneumatic compression (IPC) has been shown to produce similar results and represent an adjunctive role to MLD. This combination has been proven to decrease leg volumes, capillary fragility, and pain intensity, even if no pitting edema has been observed (Fig. 6). This may further prevent the progression to lipo-lymphedema.

The maintenance phase incorporates properly measured and well-fitted compression garments to stabilize the initial outcome and prevent relapse. High pressure compression stockings should be avoided. This may result in hemorrhagic complication. The response to therapy depends particularly on the extent of fibrous tissue formation within the adipose tissue and the skin. In the advanced stages, scar formation with a thickness of 3 mm or more in the adipose tissue interferes with MLD. Intense MLD may result in subcutaneous or cutaneous bleeding. In this case, MLD should be directed to the surrounding non-fibrosed areas rather than towards the scar tissue. Special techniques such as shock wave therapy or ultrasound may be performed to soften the scar tissue [34].

In more advanced stages, the patients' condition is further complicated by limited mobility, skin changes, and infections. Therapeutic efforts are mainly focused on palliation of pain and improving coping and daily living skills. When lipo-lymphedema develops, skin ulcerations and cellulitis may become a chronic problem, especially in patients with diabetes and peripheral vascular disease. In such cases, prolonged treatment with antibiotics before and during MLD may be beneficial. Furthermore, psychological counseling and social support are essential in the management of these patients who frequently suffer from low self-esteem and depression.

An exercise program should be tailored to the patient's ability and stage of disease. Swimming and low impact aerobics may produce gratifying results. Although prevention of obesity is very important to prevent further complications such as diabetes mellitus, hypertension, and heart failure, excessive weight loss may lead to an even greater discrepancy between the legs and the upper body. Dieting, laxatives and diuretics are usually not effective in lipedema.

Surgical techniques have been attempted with limited and controversial results. Conventional liposuction may lead to worsening of the edema

due to further damage to the lymphatic vasculature [35]. However, newer techniques such as tumescent liposuction and water jet-assisted liposuction have shown promising results in reducing the leg volumes and severity of symptoms without damaging the lymphatics [36-39]. However, occurrence of methemoglobinemia after tumescent anesthesia even as a temporary adverse effect should be considered with caution. The evaluation of the patient's relevant benefit in the treatment of lipedema is important and use of instrument such as patient benefit index will facilitate the evaluation procedure [40]. All these surgical techniques are considered experimental and require appropriate experimental protocol. Good clinical results obtained from globally accepted protocol will support the experimental procedure and convert it to standard treatment.

## 9. CONCLUSION

Lipedema is a frequently misdiagnosed disorder of fatty deposition. The adipose tissue is disproportionately distributed in the lower extremities compared to the upper body. There are distinguished clinical features which are present in all cases. The patients with the disorder are almost exclusively women. The onset in the majority of patients is around puberty which may suggest a correlation with hormonal changes. In addition, some cases demonstrate hereditary tendency, although the genetic pattern in most patients with lipedema is not clear. Recognition of the clinical features at an early stage of disease allows for more effective and efficient management. Conservative therapy, including MLD, should be started as soon as possible to prevent functional and cosmetic complications. More studies are required to identify the pathogenesis of the disorder and thereby leading to more effective therapy. A uniform surgical technique and eligibility criteria for the surgical procedure should be mandatory which will decrease heterogeneic patterns of the studied patient population. This could be included in the agenda of annual surgical meetings where the surgical protocol should be discussed and recommended.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

Not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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