



# An approach to lipedema: a literature review of current knowledge of an underestimated health problem

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## Abstract

Lipedema, which has been known as an adipose tissue disorder characterized by abnormal fat deposition, mostly affects women. This condition can easily be ruled out regarding its diagnosis because it is commonly misdiagnosed as obesity. True diagnosing and optimal management of lipedema show a great importance. As patients suffer from lipedema, not only experiencing physical symptoms such as tenderness or a feeling of heaviness but also psychological symptoms such as anxiety, they cause negative influences on quality of life of a person with lipedema. This paper tries to review all aspects of lipedema from diagnosis to management and assessment options.

**Keywords** Lipedema · Lymphedema · Body weight · Obesity

## Introduction

Lipedema can be described as a disorder affecting adipose tissue which can contribute to abnormal fat deposition in the subcutaneous layer by presenting swelling of the lower limbs bilaterally. It is commonly characterized as a tenderness to palpation and disproportional adipocyte hypertrophy in the lower limbs [1].

Lipedema mostly affects women; however, there are males also affected with lipedema. It was stated that the prevalence of lipedema is between 10 and 15% [2], while current reports indicated that nearly 11% of women are affected [3]. This condition can easily be misdiagnosed due to inadequate knowledge. Diagnosis of lipedema is typically confused with obesity. However, lipedema is not a direct cause or result of obesity. Mostly, patients with lipedema are told that this condition originated from their malnutrition or inadequate physical activity. The main difference between those is adipocyte

hypertrophy and swelling, which are resistant to decrease in lipedema when compared with obesity in which dietary modifications and exercise are effective [4].

Since the condition is commonly misdiagnosed, patients are struggling with ineffective and improper medical applications. As expected, failure to improve might cause frustration, psychological stress, anxiety, and so forth [5]. There has been a growing need for the understanding and familiarity of lipedema [6]. Therefore, this paper aims to review the current knowledge regarding all aspects of lipedema.

## Pathophysiology of lipedema

To date, there has been no evidence based on the pathomechanism of lipedema. It is believed that there is not only one direct effect or any factor regarding its pathophysiology. Lipedema is characterized by microangiopathy which causes increased capillary fragility and therefore increased protein permeability [7]. However, polygenetic susceptibility along with feminine hormonal changes plays a major role pertaining to the pathomechanism of lipedema [8]. In this way, estrogen might be the one responsible factor for its pathomechanism. Szel et al. [8] stated that endothelial barrier dysfunction and lymphangiopathy are the results for several genes which are controlled by estrogen. The same authors also hypothesized that neuropathy occurs in lipedema because of background innervation abnormalities and inflammation of

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sensory nerves since estrogen has an important role in region-specific sympathetic innervation of subcutaneous adipose tissue. Lipedema is also characterized by an increased sensitivity to palpation. Pathologically increased adipogenesis which might cause hypoxia could explain this phenomenon. Therefore, adipocyte necrosis and macrophages play a role in increased sensitivity [9, 10].

As lipedema mostly affects women, hormonal effects have been criticized and suggested [1]. This hypothesis might be highly acceptable due to estrogen affecting white adipose tissue directly via estrogen receptor alpha (ER $\alpha$ ) and G protein [11]. Gavin et al. [12] reported that diminished ER $\alpha$  and increased estrogen receptor beta (ER $\beta$ ) are present in the overweight to the obese premenopausal women in their buttocks. It is important because the waist to hip ratio was found directly linked to ER $\alpha$ /ER $\beta$  ratio. As it can be noted, lipedema has an impact on direct lower extremities, especially buttocks as being affected mostly. The distribution imbalance could also be the key answer to why patients with lipedema cannot improve with exercise.

As a following step, Gavin et al. [12] applied a sub-maximal exercise protocol in lipedema patients and monitored their lipolytic activity. They observed the more lipolytic activity in their abdominal region compared to the buttocks. Szel et al. [8] showed a detailed figure regarding the peripheral and central impacts of estrogen. Considering estrogen's central effect, having difficulty with weight loss in patients with lipedema can also be a relevant factor due to an altered estrogen receptor pattern centrally. Since neurons expressed ER $\alpha$ , they have also an important role in regulating to decrease food intake which might explain the difficulty with weight loss [5, 13].

## Incidence and epidemiological burden of lipedema

Although there are plenty of patients suffering from lipedema, incidence rates and epidemiological studies are limited to show the exact rates. In related literature, few studies seem to have investigated lipedema in regard to its epidemiological burden. Forner-Cordero et al. [14] reported 18.8% of patients had lipedema, while Földi et al. [4] reported 11% of women are affected. Child et al. [1] reported a minimum number of 1:72,000 prevalence in the population.

Studies showed that lipedema can also affect males [7, 15]. Children can also be affected, as another finding arises according to the study in which infants were lead to consulting an

expert due to the suspected lymphedema, and it was found that 6.5% of infants had lipedema [16].

## Risk factors for lipedema

To date, exact risk factor(s) could not be put forward for lipedema. As lipedema commonly affects women, hormonal issues especially estrogen have been investigated. Polygenetic susceptibility and female hormonal imbalances are hypothesized regarding the pathophysiology of lipedema. As mentioned above, estrogen has crucial roles through weight control and subcutaneous adipose tissue [8]. Males with lipedema, however, when they were analyzed, liver disease or testosterone hormone imbalances were found [1, 15].

Positive familial history has been also reviewed. Although positive family inheritance is not proven for lipedema, the rate of having a positive family history in lipedema patients ranged from 16 to 64% [17]. Child et al. [1] investigated 330 family members; in 10 out of 67 of them who were affected by lipedema, family history was positive. They concluded that positive familial history incidence was at least 15%. Since all lipedema patients who had positive familial history were female, X-linked dominant or autosomal inheritance of lipedema is the one which should be focused on in detail.

Obesity or being overweight often leads to misdiagnosis of lipedema. In Child et al. [1] study, 77% of lipedema patients were classified as overweight or obese according to the World Health Organization classification based on their body mass index (BMI). Fife et al. [7] also reported similar conclusions with the Child et al. [1] study. Most of their lipedema patients showed a high level of BMI. However, resistance to dietary modifications in lipedema is the main difference when compared with obesity [5]. Moreover, there are patients with lipedema having a normal BMI range [1, 7].

## Clinical presentation of lipedema

Lipedema is characterized by the symmetrical involvement of the lower limbs (Fig. 1). Although obesity is a well-known symmetrical fat distribution, being obese is not mandatory for patients to suffer from lipedema. The legs, thighs, and buttocks are the main affected areas, yet the feet are not affected, in general. In the progression of lipedema, microangiopathy, vasculopathy, and lymphangiopathy may include lymphedema, which is called, from that point, "lipo-lymphedema." In turn, feet are affected [7] (Fig. 2). This is because microangiopathy, capillary fragility, and hypoxia cause tenderness.



**Fig. 1** Symmetrical involvement of both lower extremities in a 60-year-old female patient with lipedema



**Fig. 2** Lipo-lymphedema: note that feet are affected in a 38-year-old female

Tenderness can result in sensitivity to palpation, which is stated in the literature as “painful fat syndrome.” Seventy percent of patients with lipedema reported tenderness [7]. Knee pain is also reported to be the explanation of fat pads which they can be frequently localized in the medial side of the knee along with the perimalleolar area [7] (Fig. 3).

common, can be described as large bulges or lobes placed on the hip region or lower extremities [17–19]. A few patients can show a mixed type of both phenotypes as stated in researches [7].

Five major types of lipedema have been reported overall. Type I affects the pelvis, buttocks, and hips; type II runs from the buttocks to the knees with a

#### Clinical Presentation

- Symmetrical involvement of both lower limbs
- Associated lymphedema with progression: lipo-lymphedema
- Symmetrical involvement of both lower limbs at early stage
- Arm involvement at late stage (30% of cases)
- Adiposity growth take place in extremities rather than trunk (whereas growth is spread in obesity)
- Adipose tissue is resistant to diet and exercise (whereas in obesity not)
- Tenderness and sensitivity to palpation: Painful fat syndrome

#### Classification of lipedema

Staging and classification of lipedema might be helpful through the treatment process of patients [7]. Földi et al. [4] suggested a concept which includes two main phenotypes of lipedema, i.e., “columnar” and “lobar” phenotypes. Columnar phenotype, which can be described as an enlargement of the lower extremity portions through conic sections, seems to be more frequent in prevalence. Lobar type, which is observed rather less



**Fig. 3** Fat pads localized in the medial side of the knees in a 44-year-old female



**Fig. 4** Type III lipedema runs from buttocks to the ankles in a 57-year-old female

specific fat pads and folds especially around the medial side of the knee; type III runs from the buttocks to the ankles (Fig. 4); type IV, arms (Fig. 5); and type V affects the isolated lower leg. Among these, types 1, 2, and 3 are seen more common as compared with the rest two [3]. To cluster the lipedema severity, Herbst



**Fig. 5** Type IV lipedema: note that the hands are spared in a 62-year-old male

et al. [5] suggested four stages: intact skin surface with enlarged hypodermis attributed as stage I; nodular shape changes in subcutaneous fat with uneven skin attributed as stage II; huge nodular fat growths around the thighs and knee side which cause contour deformity attributed as stage III; and an advanced level of lipedema, describing the existence of lipo-lymphedema as stage IV.

#### Classification and Treatment Lipedema

- Lobar and Columnar phenotypes

-*Columnar: enlargement of lower extremity portions through conic sections*

-*Lobar: large bulges or lobes placing on hip region or lower extremities*

- Type I to V lipedema

**Type I:** Pelvis, buttocks, hips

**Type II:** Buttocks to the knees with a specific fat pads and fold around the knee

**Type III:** Buttocks to the ankles

**Type IV:** Arms

**Type V:** Isolated lower leg

Herbst et al [5]. Classification

- Intact skin surface with enlarged hypodermis **stage I**,
- Nodular shape changes in subcutaneous fat with uneven skin **stage II**,
- Huge nodular fat growths around thighs and knee side which cause contour deformity **stage III**,
- Advanced level of lipedema, describing the existence of lipo-lymphedema as **stage IV**
- **Treatment of Lipedema**

#### Conservative Approach

- Complex Decongestive Therapy (Manual Lymph Drainage (MLD), Skin Care, Multilayer Compression Bandaging, Exercise)
- Compression garments
- Pneumatic Compression

#### Surgical Approach

- Debulking surgeries
- Lipoaspiration
- Tumescant Lipoaspiration

## Diagnosis of lipedema

Lipedema is often misdiagnosed by clinical professionals. Distinguishing lipedema from obesity is not always easy, yet some major differences can help the clinician [6, 9]. It has been reported that there is no need for further imaging modalities like magnetic resonance, ultrasound, computed tomography, and lymphoscintigraphy to diagnose lipedema [20].

Lipedema has mostly been associated with obesity. In lipedema, adiposity growth in extremities rather than the trunk is much more common when considered obesity, where the growth is spread and proportionate in general [3]. As lipedema mostly affects the lower extremities, the difference could be accepted as a primary sign of lipedema. Another difference can also be expressed in



**Fig. 6** Lymphedema of the right lower extremity shows itself as “asymmetrical” in a 47-year-old female

such a way that adipose tissue is resistant to exercise and diet in lipedema, whereas in obesity, exercise and diet modifications are shown as effective [4]. To differentiate obesity from lipedema, BMI might also be helpful. Child et al. [1] indicated that patients with lipedema generally had a higher level of BMI, yet some patients with lipedema also had BMIs in a normal range. On the other hand, lymphedema can also be thought in the diagnosis, although in advanced cases, lipedema might have also lymphedema. However, there is a major difference in that lymphedema generally responds to compression therapy, whereas pure lipedema does not [6]. In addition, lymphedema shows itself as asymmetrical (Fig. 6), while lipedema is symmetrical. Stemmer sign, which can be used to diagnose lymphedema in physical examination, is negative in lipedema patients, while in lymphedema, this sign generally is positive due to the affected foot [6, 21]. Pain is common in lipedema, as described in the literature as “painful fat syndrome” due to increased capillary fragility that is often in lipedema when compared with lymphedema in which pain is uncommon [3, 5, 7, 22].

In summary, Herbst et al. [5] suggested some diagnostic criteria which might be helpful to detect lipedema as follows: worsening swelling with orthostasis in summer time, telangiectasias or “spider veins” which can be seen on the surface of the skin and affected arms in cases at the rate of 30%, and inefficacy with caloric restriction or diet.

## Assessment of lipedema

Beginning with a thorough documentation and taking a detailed medical history in the assessment of lipedema are suggested. Since the pathophysiological background of the condition is not well known, possible mechanisms should be considered and documented [17].

Critical issues should be addressed in medical history related to lipedema. The onset of duration and symptoms, progression or exacerbation of symptoms, and previous treatment modalities (if taken) can be given as examples in critical issues. One of these, the evaluation of family history, is the most important part of the documentation because lipedema has been commonly related to the familial history [23]. After a detailed medical history was taken, physical examination of lipedema helps clinicians to diagnose properly along with deciding the best management options. For instance, the onset of symptoms and progression might shed light to differentiate lipedema from obesity.

In the physical examination, the extent of the swelling, asymmetry/symmetry of the swelling, surgical scars or other skin conditions, fat pads, visible signs of chronic venous insufficiency (i.e., telangiectasias and spider veins) should be carefully observed and documented. Physical examination provides a great deal of importance within the context of differential diagnosis, as lipedema generally spares the feet unless lipo-lymphedema manifests. Symmetrical involvement of swelling should also be carefully criticized after the elimination of systemic conditions (i.e., renal failure) during taking a medical history due to the symmetrical involvement of extremities in lipedema. Apart from these, Peau d’orange skin changes, leakage of fluid (lymph fistula), and firmness or fissures should be inspected and be well documented [18].

Palpation of the affected sites can give crucial points to differentiate lipedema from other conditions (i.e., lymphedema). Evaluating swelling asymmetry which can be assessed by bilateral circumferential measurement of the affected extremities in different reference points might help to differentiate lipedema from lymphedema. Pitting edema, which is not common in lipedema, can be assessed with Godet’s sign test, during which generally 30-s pressure is enough to test whether one has pitting edema or not. However, lipedema patients are not well tolerated to pain and pressure due to the fragility of the skin. Stemmer’s sign, which is a pathognomic sign to differentiate the existence of lymphedema, should also be performed in lipedema. The inability to pinch the skin of the second or third finger makes this test positive. In the case of lipo-

lymphedema or lymphedema itself, Stemmer sign would be positive [21, 24].

Wold et al. [23] suggested the series of symptoms related to lipedema: Gender, i.e., women seem more likely; mostly overweight; painful limbs (affected areas); diet-resistant weight; and resistant to elevation are the items which should be noted in medical history, as well as easy bruising, negative Stemmer's sign, sparing of the feet, non-pitting edema, and symmetrical enlargement of the extremities which are the criteria for the physical examination.

Lohrmann et al. [20] also concluded as magnetic resonance lymphangiography can be used, as it is the least-invasive procedure among imaging modalities showing lymphatic function. However, well-improved and safe technologies utilized to differentiate or evaluate management modalities might be helpful [25, 26].

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## Assessment and Diagnosis of Lipedema

### Assessment of Lipedema

#### Detailed medical anamnesis

- The onset of duration and symptoms,
- Progression or exacerbation of symptoms,
- Previous treatment modalities (if taken)
- Estrogen Disorders or imbalances

#### Physical Examination

- The extent of the swelling,
- Asymmetry/symmetry of the swelling,
- Surgical scars or other skin conditions,
- Fat pads, visible signs of chronic venous insufficiency (i.e. telangiectasias, spider veins etc.)
- Godet's sign test (pitting edema)
- Stemmer's sign (lymphedema)

#### Imaging and other modalities

- Magnetic Resonance Imaging
- Ultrasound
- Tissue Dielectric Constant
- Dual Energy X-ray Absorptiometry

### Diagnosis of Lipedema

- Gender (i.e. women seem more likely)
  - Mostly overweight,
  - Painful limbs (affected areas),
  - Diet-resistant weight and resistant to elevation
  - Easy bruising,
  - Negative Stemmer's sign,
  - Sparing of the feet,
  - Non-pitting edema,
  - Symmetrical enlargement of the extremities
- 

## Promising modalities in the assessment of lipedema

### Magnetic resonance imaging

Magnetic resonance imaging (MRI) is helpful to show dermal thickening and fluid accumulation especially in

cases with lymphedema component; however, although normal skin thickness can be observed in MRI in patients with lipedema, increased fatty tissue might be a precipitator [27]. Duewell et al. [28] indicated that MRI can show diffuse fatty hypertrophy in patients with lipedema. MRI is recommended because of its safe application, non-invasive feature, and higher sensitivity which improve to differentiate different clinical cases [27].

### Ultrasound

High-resolution cutaneous ultrasonography is known as a safe, non-invasive method to track changes. Showing dermal edema is possible by using ultrasonography. Naouri et al. [26] investigated the applicability of ultrasonography in patients with lipedema and lymphedema in their controlled study. It is hypothesized that normal ultrasonographic findings can be achieved in lipedema and whether ultrasonography is helpful to differentiate lipedema from lymphedema. Dermal thickness and echogenicity were found to be normal in patients with lipedema while in lymphedema, the dermal thickness was found to be increased and echogenicity was decreased. No difference was found between lipedema and healthy controls regarding the parameters mentioned above. It is concluded that high-resolution ultrasonography can be used to differentiate lipedema from lymphedema.

### Tissue dielectric constant

Tissue dielectric constant (TDC) has been gaining attention due to its easy and safe applicability. A hand-held control unit generates a 300-MHz electromagnetic wave which passes through tissues via contacted probe of the skin. An electromagnetic wave is partially absorbed by the tissues while the rest of them reflected the control unit. Absorption mainly based on tissue water molecules, an electrical parameter called "Tissue Dielectric Constant (TDC)" can be achieved from the reflected wave. This parameter is directly linked to the local tissue water. TDC ranges from 1 to 78.5 while air and pure water TDC values are 1 and 78.5, respectively [29–31]. Birkballe et al. [25] studied whether TDC method can differentiate lipedema from lymphedema. In their study, they compared lipedema subjects with treated and untreated lymphedema in addition to healthy controls. They found that TDC values of untreated lymphedema were significantly higher than others. Setting off a cut-off value as 40, it was shown that this value could be useful to differentiate lipedema from lymphedema in

the ankle and lower leg measurements. However, there was not enough study related to lipedema measurements with TDC despite many studies existing related to lymphedema with TDC [32–34]. Applying to this safe and non-invasive device could be useful to track changes in sub-tissue fluid content which might be a difference-making element because sub-tissue fluid accumulation is not in common in lipedema [25].

### Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DEXA) body composition measurement has been shown to be successful to monitor upper extremity lymphedema after breast cancer. DEXA is known as valuable, as it can differentiate lymphedema from lipedema by determining sub-tissue fluid proportion. On the other hand, DEXA has been discussed as a more non-invasive procedure than lymphoscintigraphy or other radiological modalities in addition to a lower dose of radiation [35–37]. Dietzel et al. [38] showed that patients with lipedema had a higher DEXA index after adjusting BMI of the legs and gynoid region when compared with the healthy controls. The risk ratio was found as 1.3 between lipedema and controls. They concluded that optimal cut-off value per BMI was 0.46, which might be useful to differentiate lipedema.

## Treatment of lipedema

### Conservative approach

Treatment of lipedema aims to reduce the symptoms and limitations related to the condition along with preventing progression [39]. In this manner, complex decongestive therapy (CDT) has been used for both lipedema and lymphedema. CDT consists of four main components as manual lymph drainage, skin care, multilayer compression bandaging, and exercise. CDT is accepted as the standard care for lipedema along with lymphedema in Europe. Ten percent of maximal reduction of circumference when considered the original leg girth can be achieved with CDT [40]. In addition to CDT, pneumatic compression devices are suggested as helpful in the treatment of lipedema by improving venous blood flow. It was reported that these devices can also be safely used in home settings after educating patients. Szolnoký et al. [41] evaluated the pneumatic compression effect by combining manual lymph drainage. They found no significant superiority to one another regarding the treatment effect, yet both

modalities were significantly effective on limb volume reduction. When considered, reducing the edema with compression applications is the main goal of the treatment in patients with lymphedema; unlike in lipedema, patients might not be able to tolerate pressure due to their skin hypersensitivity. Besides, lipedema is characterized by fatty deposition which does not respond to external pressure [4, 40, 41].

Compression garments, which are the mainstay to sustain CDT effects, should be worn every day. Nevertheless, it was shown that only 38% of patients with lipedema wear their compression garments every day. Tenderness and hypersensitivity are the ones to be thought as hindering factors related to not complying to use compression garments, yet it is also known that symptom alleviation and improving physical abilities could be achieved by compression [42, 43].

### Surgical approach

The surgical approach for lipedema varies. Debulking surgeries or other techniques which aim to reduce the excessive amount of fluid in interstitial spaces have been performed in lymphedema. However, in lipedema, excessive fatty tissue deposition instead of excessive fluid accumulation takes place. Since conventional liposuction or debulking surgeries show a great risk to damage functional lymphatics, it should be noted that these operations could lead to lipo-lymphedema [44]. Instead of conventional lipoaspiration, tumescent lipoaspiration has been shown to be effective to remove excess adipose tissue by less damaging the lymphatics [17]. Novel techniques such as water-jet liposuction and power-assisted liposuction were proven to improve pain, the perception of symptoms, physical ability, and range of motion, and these effects were also shown to be sustainable in a long-term period [19]. Tumescent liposuction is rather a safe method in addition to its long-term sustainable parameters such as quality of life, pain, and volume reduction [45]. Nevertheless, researchers stated that these procedures cannot be applied to all patients and each operation should be individualized because multiple sessions might be required in some patients with chronic advanced stage lipedema [46]. Although lipoaspiration was shown to be effective to improve the quality of life and symptoms, adjuvant compression garments might be necessary to sustain surgical treatment achievements in some patients [47]. It should also be noted that weight control is crucial after surgery because excessive weight can be deposited in the lower limbs [7]. By doing so, dietary changes along with

active lifestyle habits in addition to compression should be integrated into the daily lives of patients with lipedema although lipedema fat is resistant to diet. In addition, dietary and lifestyle modifications can help one's well-being and improve prognosis [17].

## Other issues in lipedema

### Psychological aspect of lipedema

Lipedema has been an underestimated health problem due to misdiagnosis of the condition or thinking the issue is just as being fat or obese. Patients with lipedema try to improve their condition with strict dietary and exercise modifications. However, these were not able to improve lipedematous fat due to the resistant nature of fatty tissue. Patients are having difficulty to find proper outfits and those all efforts contribute to depression [7]. Fetzer et al. [48] indicated a tremendous impact on the mental health of patients with lipedema. Eighty-five percent of patients with lipedema reported that lipedema has a huge impact on their mental health and coping skills. Decreased self-esteem, lack of confidence, and even the tendency to suicide were also reported. According to the National Health Service, cognitive behavior therapy which is characterized by collaborative psychotherapy sessions, might be helpful to help patients with lipedema [42].

### Quality of life

Patients suffer from lipedema try hard to find any option regarding its treatment. Worthless tries upon exercise and diet along with inadequate knowledge regarding lipedema diagnosis frequently drag them into a hopeless state. Pain and tenderness, which might be thought as restrictors of one's physical ability and willingness to be active, were reported to be highly correlated with decreased quality of life. In addition, as lipedema progresses, lipo-lymphedema and related severe conditions also contribute to decreased quality of life with anxiety problems, depression, and even mental health deterioration [5, 17, 49, 50]. Dudek et al. [51] reported that life satisfaction and quality of life were found to be highly correlated with social connectedness. The same authors also pointed out pain and tenderness, which should be managed thoroughly within the aspect of lipedema.

## Conclusion

Since lipedema affects patients in many ways, managing these problems is crucial to integrate an optimal holistic health care. Therefore, a prompt diagnosis and being familiar to lipedema are important regarding managing the condition properly. Lipedema is commonly misinterpreted as obesity, though it has many different aspects when compared with obesity. Even though the exact mechanism of lipedema is not known, possible mechanisms regarding its etiology need to be undertaken in further studies in detail. Patients who suffer from lipedema can face many problems in different aspects. Physical, psychological, and esthetic problems are a few of the problems which may affect one's quality of life in addition to physical ability. Therefore, daily life activities can also be affected. Although surgical techniques have been developed by technology, educating patients in pre- and post-surgery periods regarding the condition and the need for a sustainable management plan should be addressed. Consequently, approaching lipedema in a multidisciplinary attitude is crucial. In this sense, discriminating between the clinical signs and the differences of lipedema is of great importance. Thus, reducing health care costs and improving one's quality of life can be achieved by multidisciplinary management.

**Patient consent** Patients provided written consent for the use of their images.

**Conflict of interest** Alper Tuğral and Yeşim Bakar declare that they have no conflict of interests.

**Ethical approval** For this type of study, a formal consent from a local ethics committee is not required.

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