REVIEW

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Lymphedema vs lipedema: Similar but different

ABSTRACT

Lymphedema and lipedema are chronic debilitating disorders that most commonly affect the upper and lower extremities. Although they can appear similar, they differ in important ways, which the authors of this article review and contrast.

KEY POINTS

Lymphedema can be primary (ie, inherited), but far more often it is secondary to damage to the lymphatic system, notably from cancer treatment.

Lipedema is a chronic, painful progressive disease characterized by an abnormal distribution of fat that affects the abdomen, buttocks, hips, legs, and arms disproportionately. The fat distribution is resistant to weight loss or limb elevation.

Lipedema is often confused with lymphedema, lifestyle-induced obesity, lipodystrophy, or lipohypertrophy. Its management must be multifaceted to support and improve the quality of life of the patient.

Although lymphedema and lipedema are traditionally seen as incurable, a better understanding of their pathophysiology and better diagnostic and therapeutic tools are challenging this view.

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*Ms. Smith, a 35-year-old woman with class 3 obesity, type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea, presented to our lymphedema-lipedema center with bilateral lower-extremity edema (***Figure 1***). She said her quality of life was poor because of swelling, heaviness, and pain in her legs. She also reported a history of varicose veins. What is your diagnosis?*

SIMILAR BUT DIFFERENT

Lymphedema, lipedema, and even simple obesity in the extremities can resemble each other superficially and are often confused for one another, but they differ in important ways (**Table 1**).[1–6] Here, we review the pathophysiology, diagnosis, and treatment of lymphedema and lipedema.

IS THIS LYMPHEDEMA?

Lymphedema is a progressive lymphatic disorder that is often underdiagnosed because many clinicians are not familiar with it. Delay in its diagnosis can lead to infection (cellulitis) or chronic complications such as loss of function and movement and psychological issues with body image and self-esteem.

The pathophysiology of lymphedema is complex and not completely understood. However, a current view is that "all edema is lymphedema."[7] This view emphasizes that the vascular and integumentary systems are connected through the lymphatic system and fluid is regulated by the endothelial glycocalyx layer. Accumulation of interstitial fluid, proteins, and glycosaminoglycans within the skin and subcutaneous tissue stimulates collagen production

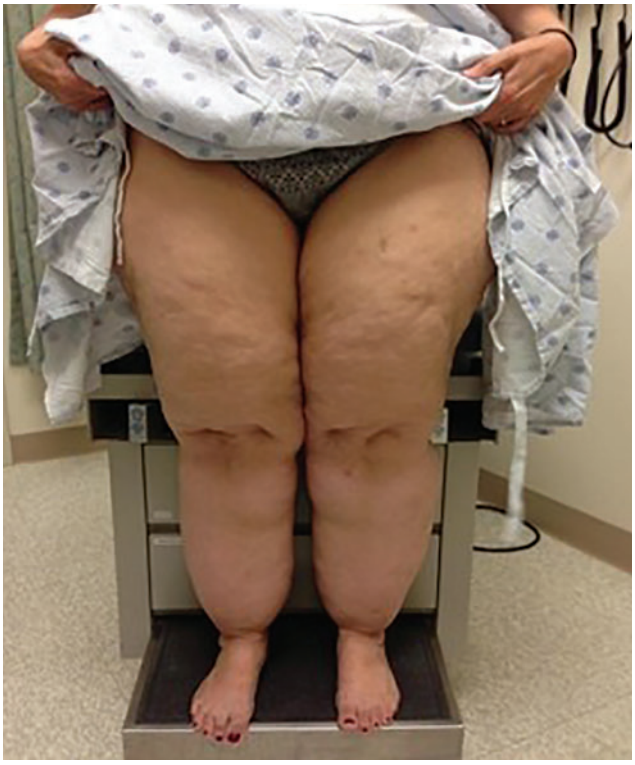


Figure 1. The patient had bilateral leg swelling with sparing of the feet. Note the ankle cutoff, or cuff sign. Her thighs also had a mattress-like appearance with numerous painful, palpable nodules.

by fibroblasts and disruption of elastic fibers. This subsequently creates skin-thickening fibrosis.[8]

Lymphedema can be classified as primary or secondary.

Primary lymphedema: Rare inherited disorders

Primary lymphedema (**Table 2**)[9] is a group of inherited conditions that affect the structure or function of the lymphatic system through hypoplasia, aplasia, or hyperplasia of the lymphatic vessel. The global prevalence of primary lymphedema is 1 in 100,000 individuals, and it is more common in women than men.[10] Genetic causes are found in 36% of patients with familial disease and 8% of patients without a family history.[11]

The subtypes of primary lymphedema can be grouped by age of onset: congenital (age < 2 years), praecox (2–35), and tarda (> 35). Congenital and praecox lymphedema can be further classified as syndromic (affecting other parts of the body) or nonsyndromic (not associated with an anomaly or other symptoms).[9]

As for the congenital subtypes, Milroy lymphedema is nonsyndromic and is associated with mutations in the *FTL4* gene.[9] Its symptoms are present at birth or are recognized within the first 2 years of life. The other 2 types of nonsyndromic primary lymphedema are Milroy-like lymphedema and hereditary lymphedema type 1B.

Lymphedema praecox encompasses 6 conditions. Meige disease, or hereditary lymphedema type 2, is the most common primary lymphedema and is the only lymphedema praecox condition that is nonsyndromic.[9] Lymphedema praecox has autosomal-dominant inheritance, affects women more than men, and has a variable onset.[9] At onset, patients present with inflammation and symptoms that can include distichiasis (eyelashes growing from the meibomian glands on the posterior lamella of the eyelid), ptosis (drooping eyelids), and yellow nails. The 5 other conditions are hereditary lymphedema type 1C, lymphedema-distichiasis syndrome, yellow nail syndrome, and hypotrichosis-lymphedema-telangiectasia syndrome. These all have distinct features (**Table 2**).[9]

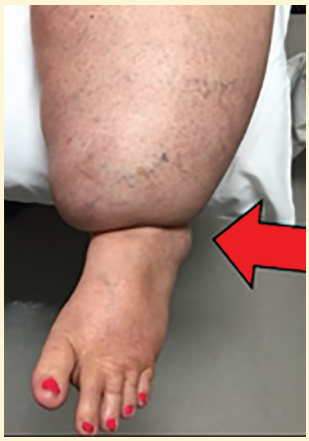
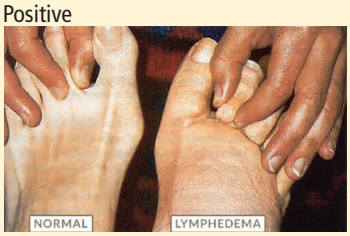
Lymphedema tarda manifests after age 35 and is due to underdevelopment of the lymphatic pathways. It may present with unilateral or bilateral edema, and it is believed to be triggered by an infection or trauma.[9] Lymphedema praecox and lymphedema tarda have been associated with mutations in the *FOXC2* gene.

Secondary lymphedema is more common

Secondary lymphedema is triggered by disruption or overload of the lymphatic system. It is more common than primary lymphedema, affecting approximately 1 in 1,000 Americans.[10] Risk factors include cancer treatment such as radiation therapy and lymphatic resection for cancer of the breast, head, or neck and other malignancies; soft-tissue infection (bacterial, parasitic, and cellulitis); chronic venous insufficiency; injury; trauma; and surgery.[12]

The incidence has been most studied in patients with cancer. The risk of lymphedema after breast cancer treatment varies widely, with estimates ranging from 14% to 40%.[13] There are no specific clinical features that can distinguish those who will develop lymphedema from those who will not, but several factors have been associated with an increased risk: dissection of the axillary nodes, with or without extensive breast surgery; radiotherapy to the breast or the axillary, subclavicular, or internal mammary lymph nodes; infection or postoperative complications related to surgical wounds or drains; ipsilateral venous compromise; advanced or recurrent cancer; traumatic insult to the arm; taxane-based chemotherapy; number of positive lymph nodes; and capsular invasion by a tumor.[13,14]

TABLE 1
Lipedema, lymphedema, and obesity compared

	Lymphedema	Lipedema	Obesity
Sex affected	Both men and women	Almost exclusively women	Both men and women
Family history	Present in primary lymphedema, absent in secondary	Present	Present or absent
Edema	Nonpitting (early) or pitting, unilateral or bilateral	Nonpitting, bilateral	Bilateral
Swollen feet	Present	Absent unless patient has lipolymphedema or phlebolymphedema	Present
Increased fatty tissue	Absent	Present and usually nodular	Present
Abnormal distribution of adipose tissue	Possible	Present in arms, abdomen, buttocks, and legs	Possible
Tenderness and pain	Absent	Present	Absent
Tendency to develop hematomas	Absent	Present	Absent
Cuff sign[a]	Negative	Positive 	Positive
Stemmer sign[b]	Positive 	Negative	Negative
Weight-loss treatment	Recommended to reduce lymphatic harm	May not reduce size of affected region but is recommended to minimize complications and if metabolic syndrome is present	Recommended

[a]Tissue enlargement stops abruptly at the ankle or wrists (arms affected in up to 80% of patients).
[b]Inability to pinch a fold of skin at the base of the second toe compared with the opposite foot.

Based on information from references 1–6.

TABLE 2
Primary lymphedema: Genetic basis and key features

	Gene affected	Key features
Congenital		
Milroy lymphedema (hereditary lymphedema type 1A)	*FTL4 (VEGFR3)*	Nonsyndromic
Hereditary lymphedema type 1B	Unknown	Nonsyndromic
Milroy-like lymphedema (hereditary lymphedema type 1D)	*VEGFC*	Nonsyndromic
Congenital lymphedema syndromes	Varies	Specific to syndrome
Lymphedema praecox		
Meige disease (hereditary lymphedema type 2)	Unknown	Nonsyndromic
Lymphedema distichiasis syndrome	*FOXC2*	Ptosis, secondary eyelash formation, corneal abrasions
Primary lymphedema with myelodysplasia (Emberger syndrome)	*GATA2*	Myelodysplasia, congenital deafness may be present
Hereditary lymphedema type 1C	*GJC2*	Myelodysplasia, congenital deafness may be present
Hypotrichosis-lymphedema-telangiectasia	*SOX18*	Vascular malformations including aortic dilation and cutaneous telangiectasias, hypotrichosis
Yellow nail syndrome	Unknown	Triad of yellow-green nails, respiratory symptoms, and lymphedema
Lymphedema tarda	*FOXC2*	Unilateral or bilateral lymphedema presenting after age 35

Adapted from reference 9.

Among survivors of head and neck cancer, more than 90% experience lymphedema internally (larynx and pharynx), externally (face or neck), or both in the first 18 months after treatment.[15,16] Other cancers associated with lymphedema include sarcoma, gynecologic cancers, and malignant melanoma.

Another common cause of lymphedema, especially in poor, tropical countries, is filariasis due to the parasitic roundworm *Wuchereria bancrofti* occupying the lymphatic vasculature.[17]

Chronic venous insufficiency can also lead to secondary lymphedema, as extracellular fluid cannot return to the venous system and overloads the lymphatic system. In fact, according to clinical practice guidelines,[12] all patients with chronic venous insufficiency should be considered to have lymphedema. If untreated, it can permanently damage the lymphatic architecture, resulting in flow-obstructive lymphedema with worsening swelling.

The risk of lymphatic dysfunction also increases with body mass index, as obesity decreases the uptake of lymphatic fluid by the lymphatic vessels, resulting in buildup of subcutaneous deposits.[18]

Relevant and rigorous epidemiologic studies are lacking, limiting a true estimate of the prevalence of secondary lymphedema. A retrospective analysis of hospital admissions for lymphedema in the United States from 2012 to 2017 showed that 92% of the 165,055 total admissions reported were for cellulitis, and 77% of the patients were admitted via the emergency department.[19] The median age was 62 years, and the inpatient mortality rate was 0.03%. Although the mortality rate is low, the numbers indicate that secondary lymphedema affects a significant number of patients and imposes a financial burden on hospital systems.

LYMPHEDEMA IS USUALLY DIAGNOSED CLINICALLY

A thorough history and physical examination can often point to the correct diagnosis.[20,21] When collecting a history, it is crucial to ascertain the onset and location of the swelling and any of the following:

- Axillary or inguinal injury
- Surgical procedures, particularly lymph node dissection
- Radiation therapy
- Chemotherapy
- Trauma to the affected area
- History of bacterial or parasitic infection or cellulitis
- Travel to an area with endemic filariasis
- History of malignancy
- Family history of congenital lymphedema.

Clinical signs of lymphedema

Lymphedema progresses through stages:

- Stage 0 (latency)—patient is considered at risk; disease is latent or subclinical; swelling is not evident despite impaired lymph transport
- Stage 1 (spontaneously reversible)—spontaneous early accumulation of fluid high in protein content; pitting may occur; swelling is reduced with limb elevation
- Stage 2 (spontaneously irreversible)—pitting may be present depending on degree of fibrosis; limb elevation does not reduce swelling
- Stage 3 (lymphostatic elephantiasis)—trophic skin changes are present; acanthosis, fat deposits, and warty overgrowth often develop.[20]

Thus, there is soft pitting edema early on (**Figure 2**), and fibrosis and induration in later stages. Clinical signs include *peau d'orange* skin changes, lymphorrhea, lymphangioma, papillomatosis, hyperkeratosis, cellulitis, and the Stemmer sign (inability of the examiner to grasp the skin at the base of the second digit of the foot or hand).[20]

Examine the axillary or inguinal areas for scars, which may denote injury to the lymphatic system from radiation treatment. Further examination may reveal vascular malformations or cutaneous problems such as hyperkeratosis, lymphorrhea, and, in more severe cases, skin breakdown. If you suspect primary lymphedema, look for syndromic characteristics such as the following:

- An extra row of eyelashes, eyelid ptosis, yellow nails (lymphedema distichiasis syndrome)
- Sparse hair, cutaneous telangiectasias (hypotrichosis-lymphedema-telangiectasia syndrome)
- Generalized edema, visceral involvement, developmental delay, flat faces, hypertelorism (widely spaced eyes), and a broad nasal bridge (Hennekam syndrome)
- Short stature, webbed neck, and a broad chest (Turner syndrome).[20]

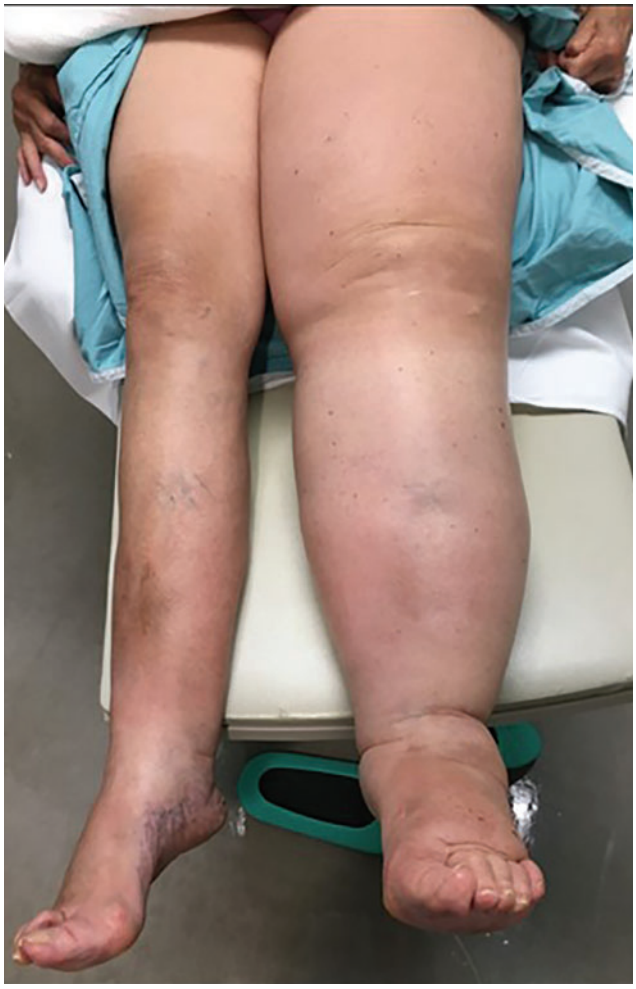


Figure 2. Lymphedema. Note the exaggerated skin creases at the base of the toes of the left foot and pitting edema in the anterior mid-thigh. There is also a dorsal hump on the top of the left foot.

Imaging and tests

Tissue biopsies and urine and blood tests are not required for the diagnosis of lymphedema but may help define underlying causes of the lower- or upper-extremity or abdominal edema.

Ultrasonography, computed tomography, magnetic resonance imaging. In most patients, lymphedema is diagnosed with a detailed history and physical examination, but many undergo ultrasonography to evaluate the venous system or computed tomography (CT) before their referral to a specialist. These

TABLE 3
Management of lymphedema diagnosed clinically or by lymphoscintigraphy

Refer to vascular medicine or surgery, plastic surgery, or both

Start conservative therapy

- Refer to physical therapy and consider manual lymph drainage
- Continuous compression garment use (circular vs flat knits)

Assess response to therapy at 6 months

- If symptoms are improved, continue conservative therapy, including compression garment use with annual prescription depending on patient compliance
- If symptoms do not change or if they worsen, consider referral to surgery for debulking or excisional or suction-assisted lipectomy in healthy patients at low surgical risk

Adapted from reference 26.

imaging tests are not recommended because they have low sensitivity for detection of lymphedema.[13] Reported signs of lymphedema on CT and magnetic resonance imaging (MRI) include thickening of the skin, a honeycombed pattern in the subcutaneous tissue, and the absence of edema within muscular compartments.[22–24]

MRI has greater specificity than lymphoscintigraphy for detecting delayed lymphatic drainage and greater sensitivity for delineating lymph vessels.[13] CT and MRI may help rule out causes such as deep venous thrombosis, chronic venous insufficiency, or malignancy.

Near-infrared lymphography is a newer method for assessing lymphedema that uses indocyanine green fluorescent dye. It is used as an adjunctive tool in lymphatic microsurgery.

Radionuclide lymphoscintigraphy is now generally considered the gold standard for diagnosing lymphedema, but it is not widely available.[12] It is an invasive procedure that requires injecting radiolabeled sulfur colloid subcutaneously into the interdigital region of the toes or fingers of the affected limb and using a gamma camera to assess the lymphatic vasculature and function. In patients with lymphedema, it shows absent or delayed radiotracer transport, backflow, or poorly visualized lymph nodes.

Other tests such as tonometry (which measures tissue's resistance to compression) and perometry (which measures overall limb volume including muscle and fat) may help confirm the diagnosis and allow for better assessment of edema volume vs limb volume, but are not commonly used or available.[12,20]

TREATMENT FOR LYMPHEDEMA

Early diagnosis and treatment can help slow the progression of this disease. Patients should be referred to a lymphedema specialist to learn about evidence-based coping strategies.[25] An approach to management is outlined in **Table 3**.[26]

Conservative treatment

Complete decongestive therapy is the primary treatment for lymphedema and helps reduce limb volume and fibrotic tissue. It encompasses manual lymph drainage, compression garments, exercise, skin care, and psychological support.

Manual lymph drainage involves massage of the affected limb. It enhances lymphatic contractility, redirects lymph flow through nonobstructed cutaneous lymphatics, and helps increase lymph flow and reduce limb volume. Manual lymph drainage sessions are done at least 3 times per week for no less than 4 weeks.[27]

Compression garments and bandaging should be applied after manual lymph drainage. This includes multilayered (short-stretch) compression bandaging to prevent fluid from reaccumulating after the limb volume is reduced. A single-center, randomized, nonblinded study of compression therapy and education vs education alone showed that compression therapy resulted in a lower incidence of recurrent cellulitis in adults with chronic edema of the leg.[28] However, most quality-of-life measures did not differ between groups.

Compression garments should be chosen with the help of a lymphedema professional, and they must be fitted properly.[12] If improperly fitted or too tight, they can cause more swelling and limit blood flow, which may worsen lymphedema. In the evening, some patients may need short-stretch garments or intermittent pneumatic compression devices to obtain maximal benefit.

Garments can be circular or flat knit; the choice depends on the severity of lymphedema and limb shape. Circular compression garments are seamless, tube-shaped, and not as dense or stiff as flat-knit garments. They provide more compression at the ankle and less at the thigh. Circular compression garments are often employed in patients with mild swelling and normal-shaped legs. Flat-knit elastic compression garments are thicker and stiffer and, being custom-made, tend to be more expensive. They are better for patients with severe lymphedema. The stiff compression allows the garment to cross skin folds without cutting into the adjacent skin. Typical indications include significant differences in leg circumference, deep skin folds, and edema of the toes and forefoot.

Light exercise can help patients maintain or lose weight, promotes protein absorption via muscle contraction, and promotes lymph drainage. Examples are stretching, walking, aquatic therapy, aerobics, and other low-impact exercises.

Skin hygiene is key to preventing secondary infections (cellulitis). Instruct the patient to wash the affected limb daily, apply moisturizer, and use antifungal agents between the toes.

Psychological support should be provided to patients who may face loss of function, restriction of movement, or disfigurement with loss of body image and self-esteem.

Drug therapy

Benzopyrones historically have been used to treat lymphedema by limiting the amount of fluid that collects in subcutaneous tissue. They are believed to increase macrophage activity and hence lysis of tissue protein, leading to reabsorption of fluid and prevention of fibrosis.[29] They can be taken orally or applied topically. However, owing to poor reporting and limited information in randomized controlled trials, a Cochrane meta-analysis could not conclude that they were effective in treating lymphedema.[29]

Diuretics may be used with physical therapy in the initial phases of treatment, but because their benefits are minor, long-term use is not recommended. Diuretics may induce imbalances in fluid and electrolytes and increase the protein concentration in the lymphatic fluid, potentially increasing the risk of fibrosis due to protein accumulation. An interdisciplinary and shared decision-making approach is needed for patients with underlying cardiac or renal insufficiency.[30]

Antibiotics are used if an underlying acute infection is suggested, especially if there are clinical signs or symptoms (erythema, high fever, pain), or if a complete blood count indicates leukocytosis or blood and skin cultures reveal a bacterial infection. Antibiotics should be discontinued once the white blood cell count has returned to normal to avoid excessive treatment.[31]

Analgesics should be used to control pain. Prolonged use of nonsteroidal anti-inflammatory drugs should be avoided, however, to minimize cardiovascular, renal, and gastrointestinal toxicity and their side effect of causing swelling.

Other agents that can be considered include antifibrotic agents and anti-transforming growth factor beta-1 antibodies, which have been shown to be effective in regulating fibrosis and severity of lymphedema in mouse models[32] and some clinical trials. These medications may not be readily accessible to all patients but may be available to participants in clinical trials; this may be a beneficial option and should be discussed with patients, if available.

Nonconservative and surgical therapies

Patients should be referred to a vascular or lymphedema specialist or clinical lymphologist, as well as a surgeon (plastic surgeon) knowledgeable in lymphedema surgery.

Low-level laser therapy is used to improve lymphatic motility and prevent tissue fibrosis. It uses a wavelength between 650 and 1,000 nm to deliver low-level doses to target tissue.[33]

Extracorporeal shockwave therapy is noninvasive and activates vascular endothelial growth factor and fibroblasts. It may help reduce edema and skin fibrosis and has been proposed to be used with complete decongestive therapy.[34]

Surgical therapies encompass physiologic procedures that attempt to restore or increase lymphatic clearance and ablation procedures that remove excess subcutaneous tissue to facilitate conservative procedures. Examples are removal of edematous tissue by an open technique or liposuction or lymphatic reconstruction including lymph vessel-to-vein anastomosis or lymph node-to-vein anastomosis.[35,36]

Debulking involves resection of excess skin and expanded subcutaneous tissue down to the muscle fascia. It is being used in combination with other treatments in earlier stages of lymphedema to reduce the volume of the arms and legs and improve quality of life. It is also recommended in end-stage lymphedema in a multidisciplinary holistic approach to improve quality of life. However, limb edema may return, and patients may develop complications from debulking such as ulceration, keloids, and lymphatic fistulas.

Suction-assisted protein lipectomy removes fatty deposits and lymphatic solids in patients with chronic lymphedema and functional problems in the limb. It is most often used in advanced stages of lymphedema, and patients must faithfully wear their compression garments afterward.[35]

IS THIS LIPEDEMA?

Lipedema (adiposis dolorosa, or the painful fat syndrome) is a loose connective tissue disease. Its estimated prevalence is about 1 in 72,000 individuals (although this is likely a significant underestimate),[37] and it has a marked female predominance, affecting an estimated 1 in 9 adult women.[38]

The etiology and pathophysiology of lipedema are not well understood, but it is thought to be triggered

by hormonal changes during puberty, childbirth, or menopause; stressful lifestyle changes; or alteration in tissue associated with surgery or trauma. Estrogen is theorized to play a role, as it regulates lipid and glucose metabolism and female-associated adipocyte distribution.[39] In addition, very few men are affected.[40,41]

A cross-sectional study found the prevalence of lipedema increased with weight and body mass index,[42] and obesity is believed to be an aggravating factor for lymphatic harm and edema leading to lymphatic overload.

Lipedema is characterized by increased palpable nodular and fibrotic adipose tissue deposits in the abdomen, buttocks, hips, and limbs. Hypermobility of the joints and sparing of the hands and feet (also known as the "cuff phenomenon") are classically present. Lipedema is also characterized by a feeling of heaviness in the affected areas and a worsening of symptoms over the course of the day. Lipedema is bilaterally symmetrically distributed and is associated with pain and easy bruising. Increased perception of pain is possibly due to dysregulation of local-regional sensory nerve fibers resulting from inflammatory and hypoxic mechanisms.[3]

Lipidema is thought to have a genetic predisposition, with autosomal-dominant inheritance and sex limitation.[3]

Often confused with other disorders

Lipedema is often confused with obesity, lipodystrophy, lipohypertrophy, or lymphedema. Lipodystrophy is a disorder that causes abnormal fat distribution.[4] It can include lipohypertrophy, a disorder characterized by lumps of fat or scar tissue under the skin caused by repeated injections or infusions in the same area.

Misdiagnosis can delay treatment for decades and increase the risk of complications such as recurrent infections, ulcers, or worsening of the lymphatic system.[21,43] Often, women with this condition are told that their symptoms are a result of their inability to control their diet or due to their sedentary lifestyle. This can result in increased fixation on weight, false accusations of poor compliance, and "fat shaming," leading to psychosocial distress, anxiety, depression, eating disorders, and social isolation.

Diagnostic evaluation

A detailed history should consider family history of lipedema. This includes the onset of weight gain and disproportionate body fat distribution; pain, tenderness, or heaviness of the arms or legs; easy bruising or vascular fragility; difficulty in losing weight despite diet and exercise or bariatric surgery; and no reduction of pain or discomfort with limb elevation.

Comorbid conditions should also be assessed, eg, hypermobility of joints, loss of tissue elasticity, lymphedema, obesity, metabolic disease, and vascular disease.[43]

In the physical examination, note any symmetric tissue enlargement; painful, palpable tissue nodules on the arms, abdomen, and legs; sparing of the hands or feet (the cuff phenomenon); hypothermia of the skin; telangiectasias; and a negative Stemmer sign. Pitting edema is noted when there is underlying venous insufficiency or lymphedema. Nonpitting bilateral edema is often found in lipedema. It is characterized by swelling, usually in the limbs, that does not indent when pressure is applied. If nonpitting edema is suspected, thyroid tests should be done to rule out myxedema due to hypothyroidism.[1]

Clinical criteria for the diagnosis of lipedema, proposed by Wold et al[5] and amended by Herbst[44] and Kruppa et al,[3] are as follows:

- Female patient (almost exclusively)
- Bilateral, symmetrical, disproportionate fatty tissue hypertrophy of the limbs and abdomen
- Sparing of the hands and feet (cuff phenomenon)
- Minimal pitting edema
- Can involve the arm (in about 30% of cases)
- Negative Stemmer sign (ie, the examiner can pinch or tent the skin at the base of the second toe or finger, unlike in lymphedema, in which the Stemmer sign is positive and the examiner can't pinch this area)
- Feeling of heaviness and tension in affected limbs
- Pain and tenderness on pressure or touch
- Easy bruising and a tendency to form hematomas
- Stable limb circumference despite weight reduction or caloric restriction
- Worsening of symptoms over the course of the day
- Telangiectasias and visible vascular markings around fat deposits
- Hypothermia
- Hypermobile joints.

Laboratory tests and imaging

There are currently no specific imaging criteria or biomarkers available to confirm the diagnosis of lipedema, but a combination of imaging tests is used to strengthen the diagnosis.[43]

Laboratory tests should be obtained to exclude heart, kidney, liver, thyroid (hypothyroidism), hormonal, or edema-promoting disturbances such as secondary effects of medications (eg, calcium channel

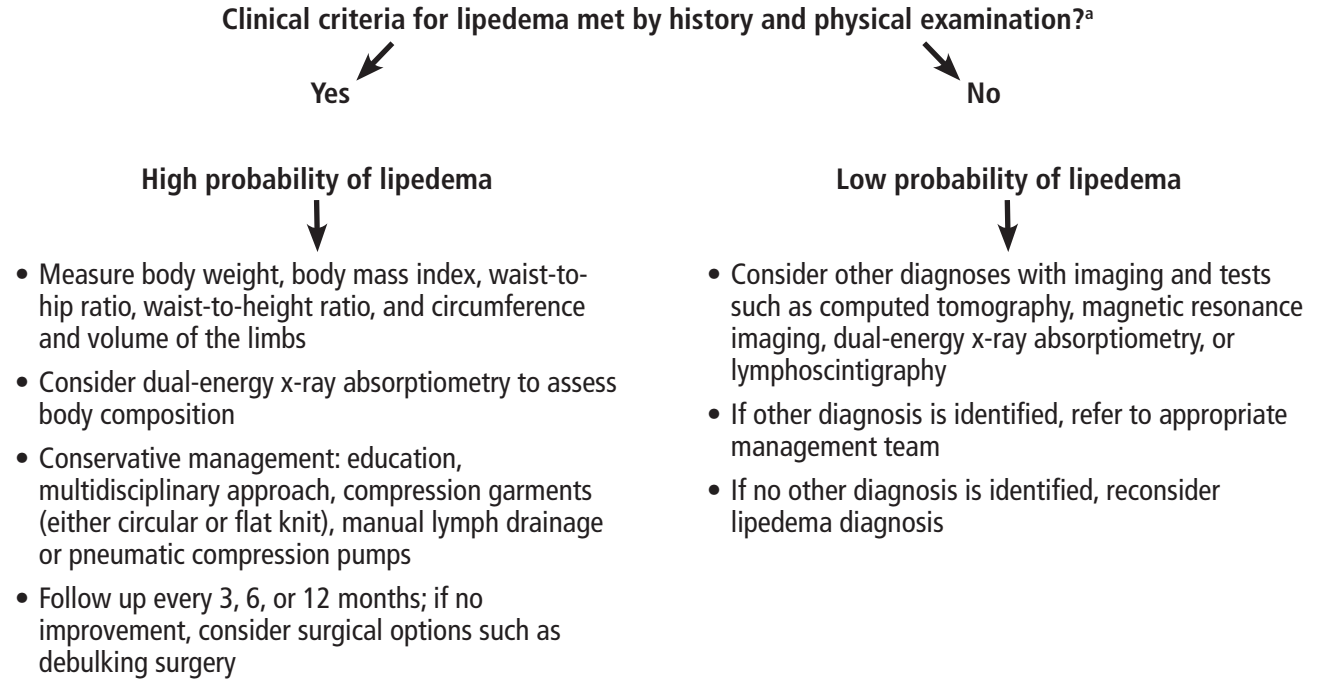


Figure 3. Algorithm for lipedema management.

[a]Not all of the clinical criteria for the diagnosis of lipedema must be present (see "Diagnostic evaluation" in the "Is This Lipedema?" section of this article), but a combination of the criteria is often present.

Adapted from reference 6.

blockers, gabapentin, and oral corticosteroids). Serum selenium levels are often checked because selenium deficiency due to oxidative stress can lead to tissue injury by inflammation, apoptosis, or necroptosis.[45]

Ma et al[46] identified platelet factor 4 as a promising diagnostic marker of lymphatic malfunction that could help in diagnosing and clinically differentiating lymphedema, lipedema, and obesity. Furthermore, it was found at higher levels in women with lipedema even if they were not overweight or obese. Thus, elevated levels of platelet factor 4 may provide evidence of underlying lymphatic structural and functional vasculature dysfunction in the pathogenesis of lipidema. It is not routinely used in practice as a diagnostic marker, but research continues on this topic.

Imaging tests such as ultrasonography, CT, or MRI can be used to study the skin and subcutaneous tissue. Ultrasonography can show thinner skin and increased thickness and hypoechogenicity of subcutaneous fat toward the medial calf and distal extremities. CT can show fatty hypertrophy in the lower extremities, and MRI can show dilation of lymphatic vessels in the legs. Indirect lymphography, functional lymphatic scintigraphy, and fluorescence microlymphography can be used to evaluate the structure and function of the lymphatic system.[3]

Dual-energy x-ray absorptiometry can be useful in assessing fat mass and lean body mass to rule out lipedema.

TREATMENT FOR LIPEDEMA

Patients should be referred to a specialist knowledgeable in the disorder to better assess the stage and to personalize treatment (**Figure 3**).[6,43] They should be informed that a conservative approach may help relieve symptoms but will have minor effects on the appearance of the extremities. Studies have shown that conservative management results in only about a 5% to 10% volume reduction.[3]

It is important to routinely measure body weight, body mass index, waist-to-hip ratio, waist-to-height ratio, and circumference and volume of the limbs to monitor response to treatment.

Conservative treatment

Conservative management consists of treating current underlying medical problems, plus the following:

TABLE 4
Lipedema: Clinical stages and compression recommendations

Stage	Characteristics	Compression recommendations
1	Smooth skin, homogenous increase in subcutaneous tissue, cool skin in certain areas Subdermal pebble-like feel due to underlying loose connective tissue fibrosis Small nodules Edema reverses with elevation Circadian rhythmicity	Micromassage compression garment 10–20 mm Hg as needed
2	Irregular or uneven skin surface (skin dimpling) Palpable nodules (may be walnut size) Nodular change of subcutaneous tissue Tissue begins to hang off the arm, wrist cuff sign Reversible or irreversible edema Moderate to severe fibrosis Circadian rhythmicity	Micromassage compression garment 20–40 mm Hg if pain, swelling, or heaviness is present
3	Tender subcutaneous nodules Pronounced increase in circumference with loose skin and tissue Bulging protrusion of fat mainly at inner and outer thighs and knees Marked sclerosis and fibrosis Often concomitant lymphedema with a positive Stemmer sign (lipolymphedema)	Micromassage compression garment 20–40 mm Hg as tolerated if pain, swelling, or heaviness is present May have to layer different garments

Based on information from references 4,5,43.

- **Anti-inflammatory diet**
- **Education** on self-management of diet and exercise
- **Physical exercise** or referral to physical or occupational therapy to help improve mobility, muscle strength, gait, and balance; exercise prescriptions should be tailored to the patient's needs with the guidance of a physical therapist
- **Avoiding medications that increase fluid retention** such as nonsteroidal anti-inflammatory drugs and hormone replacement therapy
- **Manual lymph drainage**, sequential pneumatic compression pumps, or both should be considered to improve lipedema tissue and decrease pain[43]
- **Compression garments** (either circular or flat knit). Flat knits are often used in patients with severe lipedema and should be prescribed with the help of a therapist familiar with lipedema (**Table 4**)[4,5,43]
- **Weight management** with medications for weight loss (glucagon-like peptide-1 receptor agonists, phentermine, phentermine-topiramate, naltrexone-bupropion, or other appetite suppressants)
- **Metformin** is recommended for patients with metabolic complications, as it inhibits hypoxia-induced fibrosis in adipose tissue[43]

- **Selenium supplements** may be beneficial, as this element plays an important role in inflammation and immunity
- **Emotional support** and counseling for anxiety, depression, and social isolation
- **Adjunct therapy** for comorbidities.

Nonconservative or surgical treatment

Interventive or surgical treatment is becoming more widely available, but insurance often does not cover it. Patients are encouraged to see a specialist in vascular medicine, lipedema, or lymphedema to make informed decisions on interventive or surgical therapy, preferably before complications and disabilities develop.

Liposuction removes abnormal lipedema tissue while sparing blood and lymphatic vessels. It is useful when lipedema does not respond to conservative measures. It also improves symptoms, mobility, gait, and quality of life, and it is the only treatment that slows the progression of the disease.[43]

Bariatric surgery should be considered in patients who have a body mass index of 40 kg/m^2 or more—or 35 or more if they have type 2 diabetes or other serious weight-related problems—and for whom a nonsurgical weight management approach has failed.

CASE REVISITED

After visiting our lymphedema-lipedema clinic and undergoing an extensive physical evaluation that showed nonpitting edema, varicose veins, cuff sign at her wrist and ankles, hypermobile joints, and painful, palpable nodules involving her abdomen, arms, and legs, she was diagnosed with lipedema.

We discussed a personalized therapeutic plan in detail with the patient. As part of a multidisciplinary approach, a dietitian referral was placed to educate her about nutrition programs to aid with weight loss. She also saw an exercise physiologist to learn about a personalized exercise regimen that could help her overcome her physical limitations. Her endocrinologist started her on a glucagon-like peptide-1 receptor agonist to optimize her glycemic control and modify her cardiometabolic and renal risk factors. These steps helped her lose 50 pounds over the subsequent 6 months. Treatment of her lipedema included manual lymph drainage and compression garments, and within 6 months she underwent liposuction. The patient reported a reduction in her leg pain and size and an overall improvement in her quality of life.

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Dr. Makin has disclosed teaching and speaking for Bayer. Dr. Burguera has disclosed serving as an advisor or review panel participant and as a research principal investigator for Novo Nordisk, Inc. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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