

Evaluation and Management of Patients with Leg Swelling: Therapeutic Options for Venous Disease and Lymphedema

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Abstract

Keywords

- ▶ edema
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Lower extremity swelling is a common condition which has a variety of etiologies and can be challenging to diagnose and manage. Swelling is usually the result of the accumulation of interstitial fluid in the subcutaneous tissues. Common etiologies include systemic, superficial, and deep venous, and lymphatic disorders. Leg swelling can occur bilaterally or unilaterally, with venous disorders being one of the most common causes of unilateral lower extremity edema.

The modern understanding of lower extremity swelling is based on the notion that all swelling is lymphedema. The traditional Starling principle described swelling as occurring when filtration of fluid driven by hydrostatic pressure in the arterial end of the capillaries exceeded the absorption of fluid driven by plasma oncotic pressure on the venous end of the capillaries.¹ More recent evidence demonstrates that there is little plasma oncotic pressure-mediated reabsorption of fluid and all lower extremity swelling is caused by the imbalance of interstitial fluid production and the capacity of the lymphatics to clear it.^{1,2} Therefore, when analyzing a patient with lower extremity swelling, consideration of factors that can lead to increased filtration or diminished lymphatic capacity is the best way to determine the cause of the swelling.

Chronic swelling is a common issue, especially in the elderly patient population. Chronic edema has a significant negative effect on overall quality of life.³ Therefore, efficient and accurate strategies to diagnose its cause(s) and evidence-based recommendations for treatment should be utilized. The diagnosis of lower extremity swelling can be challenging, as edema can sometimes be multifactorial in etiology, and patients can be referred to vascular specialists to assist in diagnosis and management. Although severe symptomatic swelling should be treated, for mild chronic swelling that is not life or limb threatening and without significant negative

impact on quality of life, a conservative approach to its management is reasonable.

Causes of Lower Extremity Swelling

There are a wide variety of etiologies of lower extremity swelling. When evaluating patients, it is helpful to consider swelling as unilateral or bilateral to efficiently determine its causes; certain etiologies are more likely associated with bilateral lower extremity swelling, although asymmetric swelling can be related to combinations of bilateral and unilateral causes (→ **Table 1**). The most common cause of lymphedema in the United States is “phlebolymphe-
dema,” which is lymphedema secondary to longstanding venous obstruction or reflux.⁴

Clinical Evaluation

A patient with swelling should be assessed for a personal and family history of varicose veins, thrombosis, and lymphedema, as well as a personal history of malignancy including any surgery and radiation that could affect lymphatic drainage. Prior cellulitis is very suggestive of the presence of lymphedema. Patients should be queried for symptoms or a history of heart failure, renal, hepatic and thyroid disease, obesity, obstructive sleep apnea, as well as causes of

Table 1 Common causes of chronic lower extremity swelling

Unilateral	Bilateral
Primary venous reflux, superficial or deep	Right-side heart, renal or hepatic failure
Postthrombotic syndrome (deep vein obstruction and reflux)	Medications
Lymphedema, primary and secondary	Central venous obstruction (postthrombotic, congenital or mass)
Nonthrombotic iliac vein obstruction (including mass compressing an iliac vein)	Hypoalbuminemia or proteinemia
Calf muscle pump impairment (musculoskeletal or neurological)	Lymphedema
Vascular malformations	Obesity
Overgrowth syndromes	Medications
Complex regional pain syndrome (reflex sympathetic dystrophy)	Lipedema
Mass, soft tissue, or bone	Immobility

hypoalbuminemia, such as a malabsorption syndrome.⁵ Medications can also contribute to edema, including anti-hypertensives (specifically calcium channel blockers and amlodipine in particular), corticosteroids, chemotherapeutic agents, and nonsteroidal anti-inflammatory drugs, among others.⁵

Physical examination should be performed with attention to the cardiac and pulmonary systems, as well as noting the presence of central obesity which can impede venous drainage from the lower extremities.⁶ Thorough examination of both lower extremities and the pelvis should be performed. The exam should note the distribution, extent, and severity of swelling including recording the circumferences of the ankles, calves, and thighs using a reproducible method that can be used to follow the response to therapy. Chronic swelling of the entire limb suggests that a more central venous etiology is possible; it is essential to include an examination of the lower pelvis to look for collaterals that would support such a diagnosis. Recent-onset swelling has a broader differential diagnosis. While it is important to consider venous thrombosis as a cause, it is also important to consider a mass compressing a central vein in certain patients, especially in young and elderly patients with abdominal or pelvic symptoms, unexplained weight loss, or adenopathy. Musculoskeletal and neurological disabilities, such as reduced ankle range of motion or hemiparesis, can lead to swelling by decreasing the utilization of the calf muscle pump.⁷ Obesity, especially central abdominal obesity, can be a primary cause of edema, as it results in increased abdominal and pelvic compartment pressures, impeding venous drainage of the lower limbs.⁶ In addition, obese patients also tend to be more sedentary, thereby engaging their calf muscle pump less often.

Examination of the skin of the lower extremities can help identify the underlying etiology of the edema. Signs of venous insufficiency include varicose veins, hyperpigmentation, eczema, atrophy blanche, lipodermatosclerosis, and

healed or active ulcerations. Thin, shiny skin with bilateral edema and pretibial myxedema (demarcated papules or nodules with skin thickening and induration) can be suggestive of endocrine disorders. Obesity can be a cause of bilateral swelling with skin changes typical of venous insufficiency in the absence of venous disease.

Swelling of the dorsum of the foot and toes suggests lymphedema. Specific signs include the Stemmer sign (inability to pinch skin between the dorsum of the foot and base of the second toe) which is reflective of skin thickening of Stage II and III lymphedemas, hypertrophy of the fatty layer, “ski jump” toe nails, and hyperkeratotic skin changes in late stages.³ Lipedema is a common but poorly understood condition that primarily affects adult women who bilaterally have large legs from the waist to just above the ankles as a result of excessive fat deposition.⁸

Laboratory Evaluation

Laboratory evaluation can be a valuable supplement in evaluating lower extremity swelling. Evaluation for underlying cardiac disease such as heart failure includes brain natriuretic peptide and echocardiography which are occasionally already done before the patient sees you. Similarly, creatinine and creatinine clearance and liver function tests should be reviewed or obtained if renal or hepatic disease is suspected.

Imaging Evaluation

Duplex Ultrasound

Duplex ultrasound (DUS) is the initial imaging test of choice to evaluate leg swelling. DUS should evaluate both the superficial and deep venous systems of the affected extremities. The evaluation should assess for superficial and deep venous reflux, as well as for evidence of prior deep and superficial venous thrombosis.

DUS can also be used to evaluate the abdominal and pelvic vasculature when performed by experienced operators, although it can be limited by extreme obesity and bowel gas.³ The pelvic exam is best performed after a minimum of 6-hour fast (possibly supplemented by oral simethicone pills administered hours before the exam) to minimize bowel gas and motility and optimize visualization of the vasculature. Good-quality exams can reliably visualize the common, internal, and external iliac veins, as well as the inferior vena cava (IVC) and diagnose central venous extrinsic compressions and occlusions. Transabdominal DUS is likely less sensitive to more subtle postthrombotic luminal changes than intravascular ultrasound (IVUS) but functions well as a preliminary evaluation to determine the need for the more invasive imaging. Unlike other noninvasive imaging strategies, ultrasound can also evaluate both anatomy and physiology by assessing for the acceleration of flow typically found in significant stenoses. A velocity in a central venous stenosis that is more than 2.5 times that in a more peripheral vein is frequently used to identify a significant stenosis.⁹ However, there are no accepted evidence-based ultrasound standards for the identification of significant of iliac vein obstruction at this point.

In addition, ultrasound has recently been promoted to distinguish between venous edema and lymphedema based on sonographic tissue characteristics of echogenicity and echo-free space. The study also used ultrasound to distinguish between lymphedema and lipedema, as there was normal dermal thickness and echogenicity with lipedema and in stage II/III lymphedema, increased dermal thickness, and decreased echogenicity.¹⁰

Cross-Sectional Imaging

Contrast-enhanced venous phase computed tomography or magnetic resonance (MR) imaging can also be performed to evaluate the central venous system. Compression may occur from adjacent arterial structures or mass effect from enlarged lymph nodes or tumors. Central venous obstruction may occur from prior thrombosis or hypoplastic or aplastic venous segments, particularly of the IVC. Swelling that is new and rapidly progressive, especially in older patients without other explanation, should raise the possibility of a mass compressing an iliac vein or IVC. Cross-sectional pelvic imaging should be more of a priority in these patients, as opposed to mild, insidiously developing edema in a younger patient. These cross-sectional modalities are probably best utilized after DUS if additional information is needed for diagnosis, as they are substantially more expensive and require contrast in most cases.

Venography and Intravascular Ultrasound

Venography with IVUS is another option for assessing the abdominal and pelvic veins. Venous compressions and stenoses can be diagnosed with more than 85% sensitivity with IVUS.¹¹ While venography and IVUS are invasive diagnostic options, they can be performed in conjunction with intravascular treatment modalities such as venoplasty and stenting. The VIDIO study showed that IVUS and venography

together are more sensitive than venography alone for identifying obstructive iliac lesions, and that IVUS helps in the accurate planning of interventions such as stent placement.¹²

We generally perform these invasive procedures when we are reasonably convinced that a significant compression or occlusion exists based on history and noninvasive imaging and we are likely to proceed with venoplasty and stenting if the lesion is confirmed. Others use IVUS more liberally, performing diagnostic-only invasive studies and discussing the findings with the patient prior to a treatment procedure.

Evidence-based thresholds defining the severity of a stenosis with likelihood for improved clinical outcome after treatment have not been established. Some authors use 50% area reduction compared with an adjacent segment or based on theoretically derived standard diameters (200, 150, and 125 cm² for the common iliac vein, the external iliac vein, and the common femoral vein, respectively) to define a significant lesion.¹³ We support these thresholds for post-thrombotic lesions; however, 66% of normal patients have a stenosis of this degree with no venous complaints.¹⁴ For nonthrombotic lesions, a 70 to 75% area reduction seems more reasonable, although 24% of the normal population has a stenosis to this degree.¹⁴

Lymphatic Imaging

Lymphoscintigraphy is typically performed with Tc-99m sulfur colloid, injected intradermally in the second and third toe webspace. Serial scintigraphic imaging is then performed to evaluate lymph drainage.¹⁰ Newer lymphatic imaging techniques include MR lymphangiography and near-infrared fluorescence imaging (NIRF). NIRF can help stage lymphedema according to the number of lymphatics and rate of propulsions visualized.¹⁰ However, lymphedema is usually a clinical diagnosis and imaging is not typically needed.

Management

Management of lower extremity edema varies with the suspected underlying pathophysiology. Often times, the edema may be multifactorial and therefore management will need to address the various causes. For example, venous and lymphatic disease may coexist, and treatment of both issues may be needed. If history and physical exam suggests a primarily systemic cause of the edema, treatment should be aimed at managing that cause. For the purpose of this article, we will review management of venous and lymphatic etiologies of lower extremity swelling.

Venous Etiologies

For many patients with mild edema of venous origin with mild or no symptoms, conservative care is the appropriate therapy. This includes avoiding long periods of sitting and standing, frequent ambulation and exercise, maintaining bodyweight close to ideal body mass index (BMI), and graduated compression stockings (GCSs). There is theoretical value in eliminating the edema, which contains potent inflammatory inducing proteins as a means to protect the

lymphatics, skin, and subcutaneous tissues from irreversible damage in all patients. While there are no data to support that use of GCS prevents the complications of chronic edema, biopsy data demonstrate a reduction in tissue inflammation after their use.¹⁵

For patients in whom the edema is symptomatic, affecting quality of life and not effectively managed with conservative care, the treatment of lower extremity edema of venous etiology depends on the location and type of venous pathology. In patients with IVC or iliac vein compression/obstruction, the focus is on treating the obstruction. In patients with nonthrombotic and postthrombotic iliac vein occlusion, treatment is usually venoplasty and stenting when technically feasible. Primary stent patency rates in the literature have been quoted at around 90 to 100% in nonthrombotic patients and 74 to 89% for postthrombotic patients.^{13,16} It is important to share with patients that it is difficult to predict the degree of edema improvement following ilio caval stenting. Systematic reviews have found rates of relief from swelling following treatment ranging from 66 to 89%.¹³ An explanation for some of these partial or complete failures relates to secondary lymphedema that results from longstanding edema as well as the selection of patients in whom the edema was not venous in etiology in the first place.

In patients with mild edema and symptoms thought to be secondary to superficial venous reflux, conservative management with GCSs is the mainstay treatment. For many patients with venous edema from saphenous reflux, the edema is mild and usually associated with other signs and symptoms of venous disease. Significant edema and saphenous reflux, without other signs and symptoms, should prompt a thorough search for an alternative cause for the swelling. In patients in whom conservative care of saphenous reflux is inadequate, with or without other associated symptoms as an indication for treatment, thermal and nonthermal ablation modalities are recommended. Edema is very rarely caused by nonsaphenous superficial venous reflux. Deep venous reflux alone can cause severe lower extremity edema and in most cases is managed with conservative care alone. In severe cases of deep vein reflux associated with venous ulcers, transposition of an axillary vein segment into the popliteal position, deep vein ligation, or investigational prosthetic valves may be considered.

As mentioned with iliac vein stenting, it is important to frankly discuss the fact that edema associated with superficial venous reflux may not improve. A recent study of patient-reported outcomes following endovenous laser ablation (EVLA) for saphenous vein reflux showed that 75.8% of patients reported reduced or resolved swelling following the procedure.¹⁷ Of note, performance of microphlebectomy for varicose veins with the EVLA was predictive of high patient satisfaction with regard to edema resolution.¹⁷

As mentioned, after saphenous ablation, longstanding true venous edema may not improve or improve only slightly. Edema in these cases begins as venous edema, but over time it leads to long-term destruction of lymphatic channels and function, with progression to secondary superimposed

phlebolymphe'dema. Therefore, the swelling is no longer reversible with the treatment of the venous condition alone.⁴

Lymphatic Etiologies

Lymphedema is a chronic condition which may be primary or secondary in nature and often overlaps/coexists with underlying venous disorders. Primary lymphedema is related to congenital abnormalities in the lymphatic channels (aplasia or hypoplasia) resulting in accumulation of excess fluid and impaired lymphatic drainage in the affected limb. Secondary lymphedema is more common, and in Western societies it occurs secondary to chronic venous disease, prior to surgery or radiation therapy for malignancy and trauma.

Lymphedema treatment is primarily aimed at management of the symptoms and preventing complications, as there is no definitive cure. The mainstays of treatment include compression and complete decongestive therapy including manual lymphatic drainage.⁸ Certified lymphedema therapists are experts in utilizing these strategies, as well as skin care, exercise therapy, and creating custom elastic and inelastic compression garments for patients as indicated. There is no general consensus as to whether stiff or elastic compression is best; however, patient compliance is critical. The use of Velcro-based inelastic compression has been demonstrated to be equivalent to many other forms of compression for both lymphedema and the treatment of venous leg ulcers.¹⁸ Intermittent pneumatic compression has been shown to significantly improve quality of life affecting symptoms and decrease limb girth, in particular reducing the incidence and overall cost of cellulitic complications.¹⁹

Lymphovenous anastomosis and lymph node transfers are operations which have been demonstrated to help women with upper extremity lymphedema after axillary lymph node dissection. These procedures have been anecdotally used to treat primary and benign causes of secondary lower extremity lymphedema; however, there are no data at this point to demonstrate their effectiveness and durability in these populations.

Obesity can cause functional iliac vein and IVC obstruction leading to lower extremity edema; therefore, if obesity is suspected to be a primary and secondary factor, medical and surgical treatments are strongly recommended. In patients with morbid obesity (BMI > 40) and nonthrombotic iliac vein obstruction, bariatric surgery may be preferable, as symptom response to treatment has been shown to be inferior in these patients.²⁰

Conclusion

Diagnosis and evaluation of lower extremity swelling requires a careful history, physical, laboratory, and imaging workup. The differential is broad and often the etiology is multifactorial. Treatment of lower extremity swelling is aimed at the disease process(es) which caused it. With venous etiologies of lower extremity swelling, conservative treatment usually involves GCSs, weight loss, and increased activity, which help many patients, especially with milder

edema. In refractory cases, intervention targeted at the area of venous pathology is often required. Treating underlying venous compressions and thromboses in the deep veins and superficial venous insufficiency often improves symptomatic lower extremity swelling in patients refractory to conservative care. However, longstanding venous edema, either from reflux or obstruction, can be difficult to eliminate, as it often is complicated by secondary phlebolymphe-
 dema. Lymphedema management most commonly includes compression and manual lymphatic drainage therapy, is best provided in conjunction with a certified lymphedema therapist, and should be offered to patients with venous edema that does not resolve after adequate therapy.

Conflict of Interest

None declared.

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