Uncovering Lymphatic Transport Abnormalities in Patients with Primary Lipedema

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Abstract

Background Although lipedema is often clinically distinguished from lymphedema, there is considerable overlap between the two entities. The purpose of this study was to evaluate lymphoscintigraphic findings in patients with lipedema to better characterize lymphatic flow in this patient population.

Methods Patients with lipedema receiving lymphoscintigraphy between January 2015 and October 2017 were included. Patient demographics, clinical characteristics, and lymphoscintigraphic findings were extracted. Klienhan's transport index (TI) was utilized to assess lymphatic flow in patient's lower extremities (LEs).Scores ranged from 0 to 45, with values >10 denoting pathologic lymphatic transport.

Results A total of 19 total patients with lipedema underwent lymphoscintigraphic evaluation. Mean age was 54.8 years and mean body mass index was 35.9 kg/m^2. Severity of lipedema was classified as stage 1 in five patients (26.3%), stage 2 in four patients (21.1%), stage 3 in four patients (21.1%), and stage 4 in six patients (31.6%). The mean TI for all extremities was 12.5; 24 (63.2%) LEs had a pathologic TI, including 7 LEs with stage 1 (29.2%), 3 LEs with stage 2 (12.5%), 6 LEs with stage 3 (25.0%), and 8 LEs with stage 4 lipedema (33.3%). The mean TI was significantly greater for extremities with severe (stage 3/4) lipedema than those with mild or moderate (stage 1/2) lipedema (15.1 vs. 9.7, $p=0.049$). Mean difference in TI scores between each LE for individual patients was 6.43 (standard deviation $+7.96$).

Conclusion Our results suggest that patients with lipedema have impaired lymphatic transport, and more severe lipedema may be associated with greater lymphatic transport abnormalities.

Keywords
- lipedema
- lymphedema
- lymphatic transport abnormalities

Lipedema is an under-recognized chronic disorder characterized by localized adiposity, most often isolated to the lower extremities (LEs). It is found almost exclusively in women and is typically unresponsive to life-style modifications and weight loss.[1] Estimates of the prevalence of lipedema in adult women in the United States have been reported to be as high as 11%.[2] It is clinically distinguished from lymphedema and other disorders that result in swelling of the LEs by its relative sparing of the feet, negative Stemmer's sign, and bilateral involvement. Despite being a relatively common disorder, lipedema is commonly misdiagnosed and an evidence-based theory for its pathophysiology is lacking.[3] Current theories for the pathogenesis of lipedema involve multifactorial mechanisms that include genetics, estrogen influenced adipose deposition, microangiopathy, or lymphangiopathy.[4]

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Although lipedema is often clinically distinguished from lymphedema, there is considerable overlap between the two entities, including the presence of increased interstitial fluid with thickening of the interstitium histologically.[5,6] However, in contrast to lymphedema, the increased interstitial fluid in the early stages of lipedema is thought to be related to secondary lymphatic insult, such as mechanical obstruction of the lymphatic capillaries due to the expansion of adipose tissue, rather than primary defects within the lymphatics themselves. As lipedema progresses to late-stage disease, the development of numerous leaky "microaneurysms" in lymphatic channels has been described and may further contribute to lymphatic dysfunction and the development of lipolymphedema.[7] Previous studies have demonstrated enhanced adipocyte growth in the setting of excess lymphatic fluid.[8] Therefore, the creation of a cycle of robust adipocyte growth and damage to the lymphatic system may contribute to the severity of lipedema as well as to the progressive and accelerating nature of the disease.[4]

The extent to which lipedema ultimately impacts lymphatic transport in the LEs remains unclear. Prior studies examining lymphatic flow in patients with lipedema with lymphoscintigraphy have yielded inconclusive results.[9–11] Quantitative assessment of radiotracer uptake with lipedema has been reported to range from normal to moderately impaired.[9,10] Additionally, subjective visual assessments of lymphatic flow have varied, with one study reporting a similar pattern compared with controls and another study reporting abnormal flow patterns, often with significant asymmetry.[10,11] Studies evaluating lymphatic flow associated with the clinical stage of lipedema are lacking and further add to the confusion. Therefore, the purpose of this study is to evaluate lymphoscintigraphic findings in patients with lipedema to better characterize their lymphatic flow and to determine whether impairments in flow are associated with staging of lipedema severity.

Methods

Patients presenting for surgical evaluation of their lipedema between January 2015 and October 2017 were offered lymphoscintigraphy to assess their lymphatic flow and determine if lymphedema surgery may also be beneficial. The protocol and informed consent used for this study were approved by the Institutional Review Board of the home institution, and all research was performed in compliance with the Helsinki doctrine. Informed consent was received by all patients prior to inclusion in this study. Clinical diagnoses of lipedema were assigned according to diagnostic criteria first described by Wold et al.[1] Patients with adiposity or swelling without relative sparing of the feet, Dercum's disease, or other adipose tissue disorders were excluded from this study. Patients with clinical characteristics consistent with lipedema bilaterally but with significant asymmetric enlargement of a given LE were included. Patient demographics, stage of lipedema, and clinical characteristics were extracted for each patient. Stage of lipedema was determined for each patient utilizing a previously reported four-stage system exhibited in ►**Table 1**.[2] The stage was equivalent for both extremities in all patients.

Table 1 Four-stage classification system for describing lipedema

Stage 1	Even skin surface with an enlarged hypodermis
Stage 2	Uneven skin pattern with development of a nodular or mass-like appearance of subcutaneous fat, lipomas, and/or angiolipomas
Stage 3	Large growths of nodular causing severe contour deformity of the thighs and around the knee
Stage 4	Presence of lipolymphedema

Lymphoscintigraphic Technique and Interpretation

Subcutaneous injection of a total of 1.5 mCi per extremity of 99mTc-sulfur colloid was performed under sterile technique between both interdigital web spaces of the first and second toes, bilaterally. Dynamic 1-minute images just above the injection site were obtained for 15 minutes. Subsequently, planar images of the LEs up to the pelvis/abdomen were acquired at 30 minutes and 1 or 1.5 hours following injection. If adequate uptake and visualization of lymphatic vessels and inguinal/parailiac lymph nodes were not observed, additional planar images were acquired at 2 or 3 hours postinjection. Lymphoscintigraphy scans were retrospectively interpreted and scored by a senior nuclear medicine radiology attending who was blinded to all patients' lipedema staging. Scans were visually assessed for the presence of delayed radiotracer uptake/retention in the feet, collateral lymphatic vessels, or dermal backflow. Time of the first planar image demonstrating radiotracer activity in the inguinal lymph nodes, parailiac lymph nodes, and liver was recorded.

For semiquantitative evaluation of lymphatic drainage, we used the numeric transport index (TI) described by Kleinhans et al.[12] By applying this index, we evaluated transport kinetics according to five visually assessed criteria: lymphatic transport kinetics (k), distribution pattern of the radiopharmaceutical (d), time to appearance of lymph nodes (t, minutes), visualization of lymph nodes (n), and visualization of lymph vessels (v). Scores range from 0 to 45, with higher scores indicating greater impairments in flow and TI more than 10 denoting pathologic lymphatic transport. This index has been shown to have a low interuser variability when evaluating lymphedematous or normal limbs in prior studies.[12,13] Lymphatic transport was scored separately for each LE to allow for evaluation of potential asymmetries in lymphatic flow.

Results

A total of 19 patients (38 LEs) with a clinical diagnosis of lipedema received lymphoscintigraphic evaluation and were included in this study. Mean age was 54.8 years (standard deviation [SD] $\pm$ 12.1) and mean body mass index (BMI) was 35.9 kg/m^2 (SD $\pm$ 10.7). No patients had a history of cancer diagnosis, lymph node dissection, or radiation. A total of 10 (52.6%) patients had a history of pelvic or LE surgery, including 3 patients (15.8%) with LE liposuction, 2 patients (10.5%) with hysterectomies, 2 patients (10.5%) with cesarean sections, and

1 (5.3%) with left hip replacement. A total of six patients (31.6%) underwent previous LE vascular procedures consisting of endovascular procedures, sclerotherapy, or venous ablation. Severity of lipedema was classified as stage 1 in five (26.3%) patients, stage 2 in four (21.1%) patients, stage 3 in four (21.1%) patients, and stage 4 in the remaining six (31.6%) patients.

Delayed uptake with notable retention of radiotracer in the feet was observed in 14 LEs (36.8%). A total of 13 (34.2%) LEs had evidence of collateral lymphatic vessels, and 8 LEs (21.1%) demonstrated some degree of dermal backflow. Multiple inguinal lymph nodes were visualized in 36 (94.7%) LEs, with visualization occurring before or at the time of planar images taken at the 1- or 1.5-hour mark following colloid injection in 35 (92.1%) LEs. Parailiac lymph node visualization occurred in 35 (92.1%) LEs and hepatic activity was noted in 16 patients (84.2%). A single patient with stage 3 lipedema and a history of bilateral outer thigh liposuction required 3 hours for inguinal lymph node visualization to occur in both LEs. Only one inguinal lymph node and no parailiac lymph nodes were visualized in her left LE, and an absence of hepatic activity was noted 3 hours following colloid injection.

Semiquantitative analysis revealed a mean TI of 12.5 (SD $\pm$ 8.39). A total of 14 LEs (36.8%) had nonpathologic lymphatic transport (TI $<$ 10). Of these, eight LEs (five patients) were classified as stages 1 and 2 lipedema and six LEs (four patients) had stages 3 and 4 lipedema (►**Fig. 1**). The remaining 24 LEs (63.2%) had pathologic lymphatic transport (TI $\geq$ 10) consisting of 10 LEs with stages 1 and 2 lipedema and 14 LEs with stages 3 and 4 lipedema (►**Fig. 2**). Asymmetries in lymphatic transport were commonly observed in patients with pathologic or nonpathologic TI. Mean differences in TI scores between each LE in patients was 6.43 (SD $\pm$ 7.96), with nine (47.4%) patients having differences of five or more between legs. Four patients (21.1%) were considered to have pathologic lymphatic transport observed in one LE and normal lymphatic transport in the contralateral LE, including two patients with clinical stage 4 lipedema, one with stage 2 lipedema and one with stage 1 lipedema (►**Fig. 3**). The mean TI for each lipedema stage was 10.4 (SD $\pm$ 5.7) for stage 1, 8.9 (SD $\pm$ 5.7) for stage 2, 15.4 (SD $\pm$ 9.1) for stage 3, and 14.9 (SD $\pm$ 10.5) for stage 4 with no statistically significant difference between the groups ($p = 0.270$). The mean TI for mild to moderate stage lipedema LEs (stages 1 and 2) was 9.7 (SD $\pm$ 5.6), while the mean TI for severe stage lipedema LEs (stages 3 and 4) was 15.1 (SD $\pm$ 9.7). This difference was found to be statistically significant ($p = 0.049$). Pearson's correlation analysis demonstrated no significant association between BMI and TI of all LEs, $r(32) = 0.287$, $p = 0.099$ (►**Fig. 4**).

Discussion

In this study, we found impaired lymphatic transport in patients diagnosed with lipedema. Beyond having a pathological TI, many LEs had other recognizable alterations of lymphatic transport, including collateral pathways and dermal backflow. Although there was no significant differences in TI between the various lipedema stages, patients with severe lipedema (stages 3 and 4) were found to have significantly worse lymphatic transport overall than patients with mild or moderate lipedema (stages 1 and 2), suggesting a possible relationship between severity of lipedema and impairment of the lymphatic system. Additionally, the absence of a correlation between BMI and TI may provide insight into the multifactorial etiology of this complicated disease process.

Other studies have similarly shown that advanced cases of lipedema can lead to lymphatic abnormalities, possibly due to lipedema-induced microangiopathy causing extrusion of plasma proteins, fluid accumulation in the pericellular space,

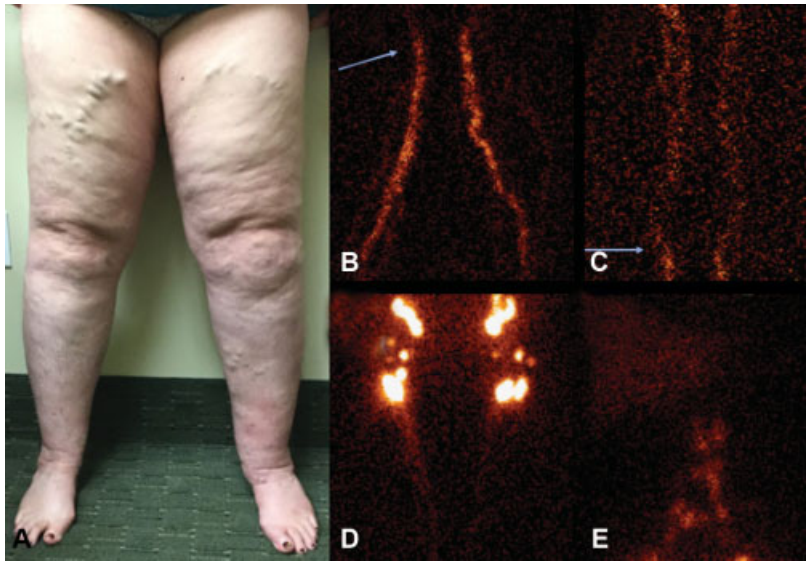

Fig. 1 (**A**) A 47-year-old woman with long-standing stage 3 lipedema. Planar images taken at 1 hour postcolloid injection at the level of the (**B**) anterior tibia, (**C**) anterior femur, (**D**) anterior pelvis, and (**E**) anterior abdomen (arrows indicating the level of the right knee). Uptake of colloid was demonstrated and the main calf lymphatic channels were well delineated with no collateral vessels identified bilaterally. Distinct iliac and retroperitoneal nodes and adequate hepatic activity were observed at 1 hour. Transport index was scored as 6.2 for both the right and left lower extremities.

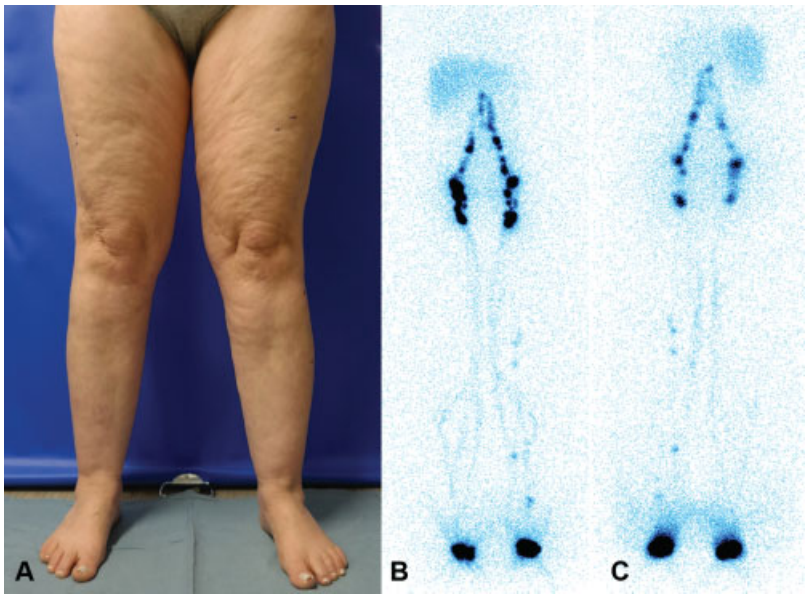

Fig. 2 (**A**) A 57-year-old woman with stage 2 lipedema. (**B**) Anterior planar image and (**C**) posterior planar image of the lower extremities taken 1.5 hours following injection of colloid demonstrating moderate retention in the bilateral feet and poor delineation of the main calf lymphatic vessels, with the presence of significant collateral lymphatic flow. Adequate visualization of the iliac and retroperitoneal nodes with hepatic activity was observed at 1.5 hours. Transport index was scored as 15.6 for both the right and left lower extremities.

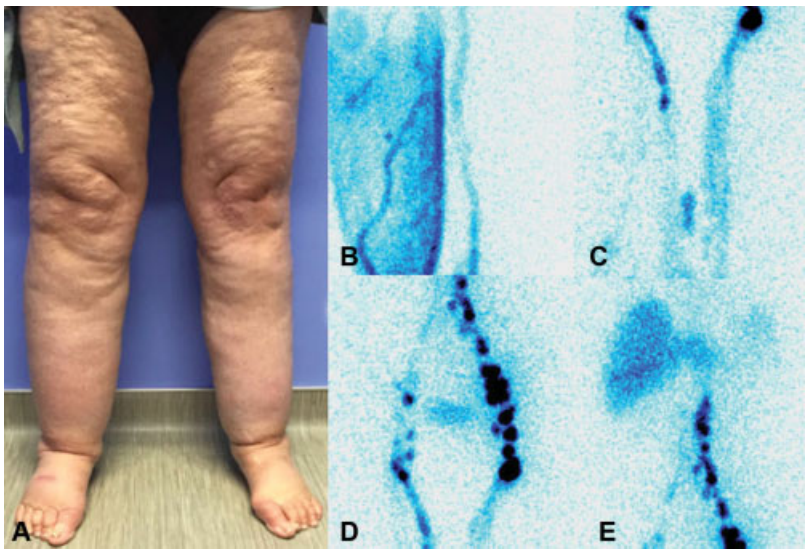

Fig. 3 (**A**) A 71-year-old woman with stage 4 lipedema and notable asymmetric enlargement and pitting edema more severe in the right lower extremity. Planar images taken at 3 hours postcolloid injection at the level of the (**B**) anterior tibia, (**C**) anterior femur, (**D**) anterior pelvis, and (**E**) anterior abdomen. Significant collateral lymphatic flow and dermal backflow were observed in the right lower extremity up to the level of the knee. Transport index was scored as 23.2 and 7.4 for the right and left lower extremities, respectively.

and dilation of the prelymphatic drainage system.[14,15] Previous studies have utilized fluorescence microlymphography to demonstrate pathological changes in lymphatic vessels, including the development of microlymphatic aneurysms, in the skin of areas affected by lipedema.[7,11] Bilancini et al (1995) demonstrated that patients with lipedema have abnormal lymphoscintigraphic profiles and slower lymphatic flow,[11] and a recent prospective study involving 83 women with a diagnosis of lipedema demonstrated the presence of abnormal lymphoscintigraphy findings in 47% of the patient population.[16] While the results of our study support that lymphatic abnormalities may accompany lipedema, our findings are unique in showing that severity of lipedema may be associated with increased impairment of lymphatic transport. It has been suggested that as lipedema progresses, the pressure of fat cells on lymph collectors causes circulatory disturbances at the superficial layers.[17] In prolonged cases of lipedema, the lymphatic vasculature loses its ability to perform their function leading to impaired lymphatic transport and accumulation of lymphatic fluid.[17]

Many patients had differences in TIs between LEs, suggesting that they exhibit differences in the severity of lymphatic disease between limbs. Other studies have similarly identified asymmetric lymphatic transport patterns in patients with

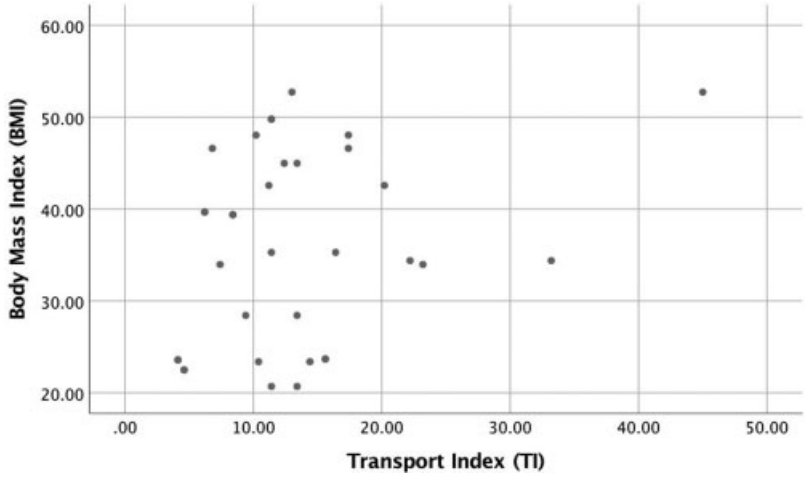

Fig. 4 Pearson's correlation analysis between body mass index and transport index of all lower extremities.

clinical lipedema.[11] Although patients with extreme differences between limbs may be more likely to seek and be offered treatment, this finding nonetheless highlights that patients presenting with lipedema in clinical practice may demonstrate asymmetric patterns of lymphatic transport. For example, two patients in our series had clinically identical stage 4 lipedema bilaterally, but had significant transport delay in only one limb. Another patient with bilateral stage 1 lipedema had significant clinical enlargement and lymphatic transport delay in 1 extremity alone.

One explanation for the asymmetrical profile of lymphatic transport may incorporate the theory of how injury to the lymphatics can occur with lipedema as a corollary to the pathophysiology in obesity.[18] Obesity models demonstrate a pattern of lymphatic obstruction from fat overgrowth, which leads to injury, inflammation, and further lymphatic blockage.[18,19] The lymphatic transport system subsequently becomes overloaded and cannot accommodate flow in the setting of obesity.[19] A similar mechanism may occur in lipedema, resulting in concomitant findings of both lymphatic pathology and expansion of adipose tissue.[20] Depending on the pattern of the adipocyte tissue expansion in each limb, different degrees of lymphatic transport abnormalities may be observed. Further study is needed to identify causative factors behind differences in disease expression between patients.

Despite variations in disease severity, patients with lymphedema would greatly benefit from treatments that provide return of function to the lymphatics while improving the aesthetic appearance of the LEs. Although various conservative approaches exist, patients with severe lymphedema who have previously failed conservative management may additionally benefit from surgical intervention. These surgical management options for lipedema include liposuction, the most commonly performed treatment, and debulking surgery, often used in more complicated and advanced cases.[21] However, a variety of treatment modalities tailored to correcting lymphatic transport abnormalities may be performed as adjuncts to traditional lipedema surgery, and have been shown to improve patient's quality of life in patients with lymphedema.[22–26] A combination of lymphovenous anastomosis and debulking surgery, for example, has been performed at our institution and can offer improvement in physiologic drainage of excessive lymphatic fluid and removal of excess adipose tissue, respectively. Combining these techniques may reduce the cellular and metabolic load on the lymphatic system while adding capacity to the system of lymphatic transport by bypassing the native routes of lymphatic flow and increasing the drainage of the limb. Removal of lymphatic fluid may in turn decrease adipogenesis, as lymphatic fluid has been shown to upregulate adipose generation and differentiation.[27–29]

Importantly, identifying which patients should be screened with lymphoscintigraphy for lymphatic transport abnormalities remains challenging; however, our results suggest that the staging system for lipedema severity may be helpful in identifying patients who may require close clinical monitoring to uncover underlying lymphedema. Therefore, it may be useful to perform lymphoscintigraphy on patients with obvious clinical signs and symptoms suggestive of severe lipedema,although our results also demonstrate significant lymphedema in patients with mild to moderate lipedema as well. Because of this, clinical evaluations of patients with mild to moderate disease should include in-depth assessment of other genetic, hormonal, and surgical factors that could help suggest the presence of underlying lymphatic abnormalities in these patients with less severe lipedema. Despite this discrepancy, lipedema staging can provide value by confirming and localizing lymphatic transport abnormalities to one or both extremities and can help determine which patient will require combined management of both lipedema and impaired lymphatic transport. Further investigation of clinical signs for identifying patients with possible underlying lymphatic transport abnormalities, and of surgical modalities for the combined treatment of lymphedema and lipedema, will be necessary to determine the ideal management for these conditions.

Although this is the largest study of its kind, our study size may have limited the ability to uncover a significant difference in TI between the various lipedema stages. Despite this, our results demonstrated a statistically significant difference between patient with mild to moderate lipedema (stages 1 and 2) and those with severe lipedema (stages 3 and 4)

suggesting these variables may be correlated but require studies with greater power to definitely draw a conclusion.

Conclusion

This study suggests that although there was no significant difference between TI and lipedema stage, lipedema patients with severe disease often have clinically relevant lymphatic disease and lipedema staging may be correlated with lymphatic transport abnormalities in these patients. Therefore, patients with lipedema should be staged based on clinical exam and disease severity to provide close monitoring to uncover any underlying comorbid lymphatic transport abnormalities which may be present. Improved understanding of the relationship between lipedema and lymphatic transport may lead to the determination of optimal diagnostic and treatment algorithms for these patients.

Note
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Conflict of Interest
None declared.

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