Editorial

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Lymphedema and lipedema: More than a swollen limb?

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Commentary on: Aday et al. National survey of patient symptoms and therapies among 707 women with a lipedema phenotype in the United States. *Vasc Med* 2024; 29: 36–41; and Khalid et al. Venous thromboembolic outcomes in patients with lymphedema and lipedema: an analysis from the National Inpatient Sample. *Vasc Med* 2024; 29: 42–47.

The focus of the approach to lymphedema and lipedema has traditionally been on peripheral manifestations in the limbs (e.g., swelling); however, there is a growing appreciation of the potential concomitant systemic manifestations of both disease states. Two articles in this issue of *Vascular Medicine* by Aday et al.[1] and Khalid et al.[2] explore the potential clinical implications and manifestations of lymphedema and lipedema beyond their well-appreciated peripheral features.

There is debate regarding the interaction between lymphatic function and lipedema. Some consider lipedema a lymphatic disease, though others believe there is little overlap between the two. There are conflicting data regarding lymphatic function in the setting of lipedema as assessed on imaging studies.[3,4] Platelet factor 4 was identified as a potential biomarker for both lymphedema and lipedema, suggesting some overlap in underlying pathophysiology.[5] Assessment of capillaries from skin and fat biopsies demonstrated that obese patients with lipedema had increased lymphatic vessel area compared to obese controls.[6] It remains to be determined how much lymphatic dysfunction contributes to the development of lipedema, rather than as a consequence of lipedema or concomitant obesity, particularly at a later stage. There is evidence of an increased inflammatory state associated with both, which could have systemic implications.[7] A single-center study demonstrated increased disease inter-relationship and a higher rate of comorbidities in patients with both lipedema and lymphedema compared to controls.[8]

In their article, Aday and colleagues offer a unique perspective of the clinical features of lipedema via a patient survey.[1] Responses from over 700 women with self-reported lipedema were compared to 216 controls. Beyond edema, symptoms and signs of easy bruising, joint hypermobility, varicose veins, flu-like symptoms, and fatigue were more frequent in the lipedema group. Such features have been noted by others in the past, but this study demonstrates high rates in a large cohort of women. These findings support the hypothesis that lipedema is not just an adipose deposition disorder, but a connective tissue disorder with associated microvascular and neuronal dysfunction.[9]

In their analysis, Khalid and colleagues utilized the National Inpatient Sample (NIS) to evaluate the association of venous thromboembolism (VTE) with lymphedema and lipedema in a population of patients with obesity, demonstrating that both are independently associated with VTE.[2] The authors note the potential of an associated increased inflammatory state or increased immobility that could lead to an elevated risk of VTE in this patient population.

The authors of both studies are commended for their efforts to investigate these poorly understood disease processes; however, interpretation of their results must be in the context of the limitations, which reflect the limitations and available options to study these diseases, specifically lipedema.

Despite estimates that lipedema may be present in millions of women in the United States, there remains no standardized diagnostic criteria for this disease and disagreement persists among experts.[9,10] In a recent consensus statement for the standard of care of lipedema, diagnostic considerations are proposed, many of which are nonspecific and have overlap with a variety of other disease processes.[9] Another consensus statement states that pain is a requirement for the diagnosis, or otherwise the process should be categorized as lipohypertrophy rather than lipedema.[10] Undoubtedly, there is overlap between patients who have a pathologic process of lipedema with traditional

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obesity and the normal variation in body shape, which can make it difficult to diagnose. The survey findings reported by Aday et al. highlight this challenge, as less than half of patients were diagnosed with lipedema by a physician.[1] This demonstrates both the poor recognition of lipedema by physicians and the difficulty in diagnosing a disease process with a wide spectrum of presentations and no clear diagnostic criteria. It is possible that a large proportion of patients who were self-diagnosed as having lipedema did not have what many clinical experts would consider lipedema. Additionally, there is potential for selection bias as those who chose to fill out the survey may have more advanced disease, skewing the rates of symptoms to be higher.

In the study by Aday and colleagues, the average body mass index (BMI) of patients with lipedema was nearly 41 kg/m^2 compared to only 27 kg/m^2 in the control group. Though the authors performed an analysis adjusting for obesity, given the overlap in symptoms of edema, altered gait, and chronic venous disease among those with obesity, it is difficult to fully assess how much lipedema versus obesity alone contributed to the differences between groups. An interesting follow-up study of patients with obesity but without lipedema would be interesting to further determine the relationship of these symptoms to lipedema specifically.

The study by Khalid et al. also has limitations, many of which the authors note.[2] Utilization of administrative claims databases offers a unique opportunity to analyze a large cohort of patients, but this approach is limited by the availability and accuracy of billing codes used for specific patients and disease states. There is no International Classification of Disease (ICD) code for lipedema, thus the authors utilized surrogate codes of 'lipomatosis, not elsewhere classified' and 'edema, unspecified'. Though these billing codes are recommended for patients with lipedema, a code of 'edema' in an inpatient population is quite nonspecific. There is a wide range of potential contributors to edema, including obesity itself, which was a requirement for inclusion. The analysis does not report how many of the 50,645 patients analyzed as having lipedema had an associated billing code of the more specific lipomatosis versus the code of edema.

Though all patients included in the analysis were obese, comparison of weight or BMI is not available in the NIS database. It is plausible that those with lymphedema or lipedema had more severe obesity, which could contribute to elevated VTE risk. Given the clear relationship of a BMI greater than 50 and development of lymphedema, the lymphedema group could represent those with more extreme obesity.[11] It would be interesting to evaluate the association of VTE in both lymphedema and lipedema in the nonobese population to further delineate how much of the associated risk is attributed to lymphedema and lipedema rather than potential differences in severity of obesity.

Both studies are important and add to our current understanding of lymphedema and lipedema; however, the limitations highlight how much more there is to learn about these diseases. There is critical need for greater physician awareness, improved diagnostic criteria, and specific billing codes (i.e., for lipedema) to allow for more optimal investigation and a greater understanding in the hope of improving outcomes for patients with these conditions.

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