Tissue Sodium Content is Elevated in the Skin and Subcutaneous Adipose Tissue in Women with Lipedema

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Objective: To test the hypothesis that tissue sodium and adipose content are elevated in patients with lipedema; if confirmed, this could establish precedence for tissue sodium and adipose content representing a discriminatory biomarker for lipedema.

Methods: Participants with lipedema (n = 10) and control (n = 11) volunteers matched for biological sex, age, BMI, and calf circumference were scanned with 3.0-T sodium and conventional proton magnetic resonance imaging (MRI). Standardized tissue sodium content was quantified in the calf skin, subcutaneous adipose tissue (SAT), and muscle. Dixon MRI was employed to quantify tissue fat and water volumes of the calf. Nonparametric statistical tests were applied to compare regional sodium content and fat-to-water volume between groups (significance: two-sided P < 0.05).

Results: Skin (P = 0.01) and SAT (P = 0.04) sodium content were elevated in lipedema (skin: 14.9 ± 2.9 mmol/L; SAT: 11.9 ± 3.1 mmol/L) relative to control participants (skin: 11.9 ± 2.0 mmol/L; SAT: 9.4 ± 1.6 mmol/L). Relative fat-to-water volume in the calf was elevated in lipedema (1.2 ± 0.48 ratio) relative to control participants (0.63 ± 0.26 ratio; P < 0.001). Skin sodium content was directly correlated with fat-to-water volume (Spearman’s rho = 0.54; P = 0.01).

Conclusions: Internal metrics of tissue sodium and adipose content are elevated in patients with lipedema, potentially providing objective imaging-based biomarkers for differentially diagnosing the under-recognized condition of lipedema from obesity.

Introduction

Lipedema is a chronic condition involving excessive and disproportionate adipose tissue deposition in the extremities of females. Importantly, adipose tissue in the legs due to lipedema does not regress in response to typical treatments for obesity, such as diet, exercise, or even bariatric surgery (1). Women with lipedema can appear similar to women with obesity or those with lower extremity lymphedema, and misdiagnosis is common (2). The true prevalence of lipedema is not known, likely because of a lack of awareness of the condition. Despite the availability of clinical criteria, an objective diagnostic test to distinguish lipedema from obesity represents the fundamental unmet need for the field (1,3,4).

Symptoms of lipo-lymphedema in advanced stages of lipedema suggest a role for compromised lymphatic function. Contrast-enhanced imaging of lymphatic vessels in several patients with lipolymphedema revealed dilated and permeable small vasculature throughout the legs (5). Lymphatic vessels drain interstitial fluid and transport large lipoproteins and fatty acids (6), sodium (7), and water from peripheral tissue into the bloodstream. Impaired lymphatic vessel function may reduce clearance of these components

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Volunteer enrollment and inclusion and exclusion criteria

All volunteers provided informed consent in accordance with the Vanderbilt University Institutional Review Board. Female volunteers with lipedema (n = 10; age = 44.0 ± 12.5 years, mean ± standard deviation) were recruited from the Vanderbilt Lymphedema Clinic and an enrollment survey approved by the institutional review board and distributed through social media support groups. All recruited patients were diagnosed with lipedema by a Lymphology Association of North America certified lymphedema physical therapist or qualified physician. Subjects with lipedema additionally underwent a clinical examination to verify that they met all primary criteria and at least one secondary criterion for enrollment (Table 1). Criteria, lipedema stage, and type were adapted from Herbst et al., 2012 (1). Subjects were asked to respond to the visual analogue scale (electronic sliding scale from 0-100) regarding the pain experienced in their legs on a normal day (8). The weight and height of subjects were measured to calculate BMI. The widest girth of each subject’s calf was identified, and calf circumference was measured at this location.

Female control volunteers (n = 11; age = 45.4 ± 12.1 years, mean ± standard deviation) were recruited through the Vanderbilt University Human Imaging Core. Both subjects with lipedema and controls were in a stable condition without active infection or inflammation. Exclusion criteria included evidence of current skin infections or other signs of inflammation and past medical history of hypertension, diabetes, or arthritis in all subjects. Control volunteers were matched for biological sex, age, race, BMI, and calf circumference to participants with lipedema.

Multimodal MRI acquisition

All volunteers were scanned using 3.0-T MRI (Philips Achieva; Philips Healthcare, Best, The Netherlands). The leg with the widest calf girth was used for imaging if asymmetry presented. The calf was then centered over four standard sodium solutions (aqueous sodium chloride in the physiologic range of tissue sodium content from 10-40 mmol/L; Figure 1A-1B) embedded in a platform on which the calf was allowed to rest for 10 minutes before the acquisition of the sodium image. Sodium imaging of the calf was implemented using a quadrature knee coil tuned for sodium signal reception (Rapid Biomedical GmbH, Rimpar, Germany). A three-dimensional gradient-echo sequence was employed: field of view = 192 × 192 mm², acquired matrix size = 64 × 64, and slice thickness = 30 mm. A repetition time (TR) and echo time (TE) of 130/0.99 milliseconds was chosen to reduce error from residual T1 signal effects; this is the shortest TR required to measure tissue sodium content with a relative error of less than 5% compared with longer acquisitions that allow full recovery. The sodium image acquisition time was approximately 15 minutes.

Proton images were acquired during the same scan session without moving the subject by using the body coil for reception. The Dixon method was performed to separate the proton signal from fat and water tissue-species in the same acquisition and provided fat-weighted and water-weighted images in the identical field of view as the sodium image (TR = 200 milliseconds; TE₁ = 1.15 milliseconds; TE₂ = 2.30 milliseconds; matrix size = 192 × 192; in-plane spatial resolution = 1 × 1 mm²; six slices each 5-mm thick). The total scan time required for proton imaging was approximately 4 minutes.

Image segmentation and analysis

Mean signal intensity was measured in each standard solution in order to calibrate the magnitude sodium signal intensity to known sodium concentrations on a per-voxel basis for each subject (Figure 1C). A quantitative sodium map was calculated and interpolated to match the matrix size of the Dixon images for each subject (Figure 1D).

Regions of interest (ROIs) were segmented on the central slice of the Dixon water-weighted image, including the outer and inner borders of the skin and the total muscle. The skin region was further segmented as the posterior semiperimeter of the skin because the anterior surface of the lower leg tapers along the slice dimension. The SAT region was defined as the area between the skin and the total muscle. Voxels in bone and blood vessels were removed from analyses. Figure 2A-2C depicts sample Dixon fat- and water-weighted images and segmented ROIs.

The circumference of the calf was measured as the perimeter of the skin in units of centimeters. The area of SAT was normalized by
calf circumference to provide a relative measure of the amount of SAT in units of millimeters in the leg.

The total adipose tissue volume in the leg was calculated by using an automated segmentation routine. A threshold was applied to the central Dixon fat-weighted images based on a k-means clustering algorithm (k-means function in MATLAB R2015a; MathWorks, Natick, Massachusetts) assuming two compartments: fat and water. The ratio of the number of voxels in fat tissue (Figure 2D) to the number of voxels in water tissue (Figure 2E) was taken as the fat/water volume ratio.
water volume ratio (see Figure 2F). This measure accounts for the presence of adipose from all tissues in the calf including intramuscular adipose and the volume of the muscle.

**Statistical testing**

The primary statistical objective of this study was to determine whether tissue sodium content was significantly different in each ROI in patients with lipedema compared with controls matched for biological sex, age, race, BMI, and calf circumference. To evaluate this objective, mean sodium content was measured from the skin, SAT, and muscle ROIs, and standard deviations within each cohort were calculated. Group differences between tissue sodium were tested by using a nonparametric Mann-Whitney \(U\) test with two-sided \(P < 0.05\) required for significance. Values are reported as group mean \(\pm\) standard deviation, and the group range reflects minimum and maximum values. Group differences between age, race, BMI, and calf circumference were also tested with the same criteria to ensure participants were well matched between groups for these parameters. As an exploratory analysis, we analyzed the subgroup of participants with lipedema that were early stage (stages 1 or 2) and compared their imaging values with the subgroup of control volunteers who were matched for biological sex, age, race, BMI, and calf circumference to this patient group. The assessments of these two subgroups were similar to the overall group assessments and were performed to evaluate whether the MRI protocol has potential to discriminate between early stage lipedema and controls.

A secondary statistical objective was to determine whether adipose content in the calf was significantly higher in participants with lipedema compared with controls matched for biological sex, age, race, BMI, and calf circumference. Two measures of adipose content were evaluated, including (1) SAT area normalized by calf circumference and (2) total fat/water volume in the calf. Group differences between normalized SAT area and fat/water volume were tested by using a nonparametric Mann-Whitney test \(U\) with two-sided \(P < 0.05\) required for significance.

A third statistical objective was to determine whether tissue sodium content was associated with normalized SAT area or fat/water volume in the calf. To evaluate this objective, a two-sided nonparametric Spearman correlation test was applied, and Spearman’s rho and significance level \((P < 0.05)\) were determined between each study measure over all participants \((n = 21)\).

**Results**

**Volunteer demographics**

Table 2 summarizes the clinical features of patients with lipedema. The age at the onset of symptoms was coincident within 3 years of either menarche or pregnancy in all cases. All patients confirmed that symptomatology did not respond noticeably to diet or exercise. Those participants who received liposuction or gastric bypass surgery were imaged at least 1 year following surgery.
Those who received gastric bypass surgery reported less change in their lower body compared with upper body volume following the procedure.

Table 3 summarizes the demographic information of participants with lipedema (n = 10; percent female = 100%; race: nine Caucasian, one Black; age = 44.0 ± 12.5 years; age range = 17-61 years; BMI = 33.0 ± 7.6 kg/m²; BMI range = 21.3-48.9 kg/m²; widest calf circumference = 44.1 ± 5.5 cm; widest calf circumference range = 36.8-56.5 cm). Control volunteers (n = 11; percent female = 100%; race: nine Caucasian, two Black; age = 45.4 ± 12.1 years; age range = 33-65 years; BMI = 30.6 ± 4.5 kg/m²; BMI range = 23.8-38.6 kg/m²; widest calf circumference = 41.2 ± 3.4 cm; widest calf circumference range = 37.2-46.9 cm) were matched for biological sex (P = 1.00), age (P = 0.99), race (P = 0.99), BMI (P = 0.56), and calf circumference (P = 0.32) to participants with lipedema.

Tissue sodium content and adipose composition

Calf tissue sodium content was significantly elevated in patients with lipedema compared with controls in the skin (14.9 ± 2.9 mmol/L vs. 11.9 ± 2.0 mmol/L; P = 0.01; Figure 3A) and SAT (11.9 ± 3.1 mmol/L vs. 9.4 ± 1.6 mmol/L; P = 0.04). Sodium content trended higher in

![Figure 3](https://example.com/figure3.png)

**Figure 3** Group results of (A) tissue sodium content (mmol/L) in the skin, SAT, and muscle regions; (B) SAT area (mm²) normalized by calf circumference (mm) has units of millimeters; and (C) tissue composition in terms of fat/water volume (ratio). (D–F) These trends and significant differences in the skin and SAT are observed in a subset of patients with early stages of lipedema (stages 1 or 2). Significant group differences (*P < 0.05, two-sided) were determined by a Mann-Whitney U test.
Participants with lipedema demonstrated larger normalized SAT area (13.4 ± 4.7 mm vs. 8.7 ± 3.8 mm; \( P = 0.02 \); Figure 3B) and a greater fat/water volume compared with controls (1.2 ± 0.48 ratio vs. 0.63 ± 0.26 ratio; \( P < 0.01 \); Figure 3C).

A subgroup of patients with early stage lipedema (stages 1 or 2; \( n = 7 \); age = 38.4 ± 10.4 years; BMI = 29.8 ± 5.4 kg/m\(^2\); calf circumference = 42.2 ± 3.2 cm; race: seven Caucasian) and a matched subgroup of female controls (\( n = 7 \); age = 41.1 ± 6.1 years; BMI = 29.9 ± 4.2 kg/m\(^2\); calf circumference = 41.1 ± 3.1 cm; race: seven Caucasian) were taken from this study’s volunteers. Sodium was significantly elevated in the skin (13.8 ± 1.9 mmol/L vs. 11.4 ± 1.3 mmol/L; \( P = 0.04 \); Figure 3D) and SAT (11.2 ± 2.7 mmol/L vs. 8.8 ± 1.5 mmol/L; \( P = 0.03 \)) of participants with early stage lipedema relative to matched controls. The normalized SAT area was not significantly different between participants with early stage lipedema and matched controls (8.8 ± 4.7 mm vs. 11.7 ± 3.4 mm; \( P = 0.21 \); Figure 3E). Fat/water volume was significantly elevated in patients with early stage lipedema (1.1 ± 0.32 ratio vs. 0.65 ± 0.29 ratio; \( P = 0.04 \); Figure 3F).

Skin sodium content correlated significantly with SAT sodium content (Spearman’s rho = 0.66; \( P = 0.001 \)) and with muscle sodium content (Spearman’s rho = 0.75; \( P < 0.001 \)). The normalized SAT area was significantly correlated with fat/water volume (Spearman’s rho = 0.92; \( P < 0.001 \)), and each correlated with BMI (Spearman’s rho = 0.54; \( P = 0.01 \); and Spearman’s rho = 0.58, \( P = 0.006 \), respectively). Only sodium content in the skin was significantly correlated with the fat/water volume (Spearman’s rho = 0.54; \( P = 0.01 \)).

Case examples of sodium content maps and corresponding anatomical Dixon fat-weighted images are presented in Figure 4 from patients with stage 1 and stage 4 lipedema alongside control females with similar age, race, BMI, calf circumference, and normalized SAT area.

**Discussion**

Because of a lack of clinical awareness of lipedema, and the difficulty in differentiating the source of leg swelling, patients with lipedema currently suffer from a delay in diagnosis and mismanagement for years or even decades (9). One major unmet clinical need in lipedema management rests with the lack of a diagnostic test capable of objectively reporting internal differences in the tissue composition and function in women with lipedema versus women with obesity. Such a diagnostic test would be important for understanding lipedema etiology and also for establishing precedent for lipedema as a distinct condition from obesity. In this study, we applied clinically accessible sodium MRI methodologies followed by adipose tissue composition analysis to test the hypothesis that adipose accumulation would be uniquely accompanied by sodium accumulation in women with lipedema compared with female controls. The primary findings were that tissue sodium content was significantly elevated in the skin and SAT in patients with lipedema compared with female controls matched for age, race, BMI, and calf circumference as well as in a subset of patients with early stage lipedema compared with a subset of matched controls. We additionally measured significantly elevated adipose content of the legs in women with lipedema, which correlated significantly with the skin sodium content among all participants. These findings provide evidence in support of a distinct etiology of lipedema that can be measured by
Skin sodium accumulation is an emerging hallmark of inflammatory diseases and cardiovascular risk factors. Tissue sodium is elevated in patients with hypertension (10), systemic sclerosis (11), infection (12), or insulin resistance (13), and it was recently correlated with left ventricular hypertrophy in chronic kidney disease (14). We have shown here that skin sodium is elevated in women with lipedema who are normotensive and without diabetes or heart disease. Though women with lipedema do not have an increased prevalence of diabetes compared with the population of women in the United States (15,16), further research is needed to investigate the impact of other vascular or metabolic disorders on the sodium levels in patients with lipedema who are already at higher risk for storing sodium in their skin and SAT. A differential diagnosis may be achieved with a combination of clinical tests or a multimodal imaging protocol such as the methods we employed for this study. Furthermore, the emerging role of elevated peripheral sodium in many prominent diseases underscores the need to develop robust tools for quantifying tissue sodium content as well as treatment strategies capable of modifying sodium in specific tissues.

Elevated tissue sodium content was also measured in the SAT, including in the subset of participants with early stage lipedema. Sodium was not observed in the SAT of women with similar BMI and calf circumference. In this preliminary study, we were not able to address mechanistic hypotheses; however, we were intrigued by the fact that lipedema features macrophage infiltration in the SAT (15). Inflammatory-induced macrophages are also present in abdominal adipose tissue deposits in persons with metabolic syndrome (17), which is similarly characterized by adipose volume growth at the inflamed site. In an earlier study, we showed that inflammation was associated with increased skin sodium storage (12); here, we have presented evidence that adipose deposition is significantly correlated with local sodium accumulation in a clinical population. Further studies should investigate the variation in sodium levels in patients at their sites with the greatest and fewest adipose deposits throughout the body and whether local adipose deposition is regionally dependent on sodium accumulation. In particular, the function of salt-sensing macrophages in the regulation of tissue volume and metabolism (18) is likely significant to lipedema pathophysiology. MRI-based tissue sodium and adipose volume measures have the potential to serve as noninvasive clinical biomarkers of inflammatory pathways in adipose tissue.

Our findings also revealed a trend for higher sodium throughout the muscle of participants with lipedema. Additionally, we measured significantly higher fat/water volume in the calf of lipedema patients, indicating both elevated intramuscular adipose tissue and reduced muscle size. Though elevated sodium has also been observed throughout the muscle in the case of anaerobic exercise (19), local muscle injuries (20), or essential hypertension with increasing age (10,21), lipedema is the first condition in which we have observed both increased muscle sodium and adipose content. This suggests that myopathy may be a clinical feature of lipedema, which is consistent with the frequently reported symptom of chronic fatigue. Our findings are in line with a recent report of significantly reduced muscle strength bilaterally in the legs of women with lipedema compared with women who have obesity (22).

Mechanisms related to lymphatic dysfunction may underlie tissue sodium and adipose accumulation in patients with lipedema. The accumulation of sodium in the interstitium is consistent with impaired lymphatic capillary clearance function (7,23). Reduced lymphatic processing capacity is also consistent with clinical symptoms of lymphedema that occur in advanced stages of lipedema. The relationship between lymphatic function and tissue sodium storage remains to be evaluated in vivo, although these studies may be possible with the emergence of lymphatic imaging modalities, including indocyanine green near-infrared imaging (24,25) and magnetic resonance lymphangiography (26,27,30). Noninvasive lymphangiography approaches (26,27), which exploit contrast derived from the long magnetic resonance relaxation times of lymphatic fluid relative to other tissues, may have particular relevance in this field, as they can be performed in 10 minutes or less and without exogenous contrast agents, thereby making them ideal candidates for surveillance imaging or evaluating therapy responses. Therefore, one logical extension of the current study is to evaluate the relationship between tissue sodium content and lymphatic function in the lower extremities of patients affected by secondary lymphedema or lipedema.

One practical limitation of this study is the restriction of waist circumference and limb circumference by the MRI gantry bore and coil size, respectively. Participants in this study were limited to BMI < 40 kg/m² and calf circumference < 60 cm. This limitation likely limits patients with more advanced stages of lipedema given the size constraints of a 3.0-T MRI. However, patients with less severe stages of lipedema also demonstrated elevated sodium in the skin and SAT as exemplified here in case examples and subgroup analyses. Tissue sodium content may, therefore, be useful to distinguish lipedema from obesity prior to clinically observable features, such as SAT volume or leg girth. The order of pathological events cannot be determined from this initial cross-sectional study. Note that participants with lipedema and the control group were not identically matched for the number of participants in each group, and, rather, group size was determined after matching for the following five demographic parameters: biological sex, age, race, BMI, and calf circumference.

Though our lipedema cohort was representative of a lipedema cohort in the general population, this study included patients with lipedema who had undergone a variety of prior treatments, including complete decongestive therapy, liposuction, and gastric bypass surgery. All surgical procedures had occurred more than 1 year prior to enrollment in this study. In a meta-analysis, we evaluated whether the trends for tissue sodium content were different in these subjects; however, we found no trend for a difference in tissue sodium content in these participants compared with the other participants. The effect of complete decongestive therapy or surgical intervention on tissue sodium or adipose content was beyond the scope of this study, and future imaging studies are needed to investigate the impact of conservative or surgical interventions on tissue composition in patients with lipedema definitively.

The acquisition of sodium MRI requires specialized multinuclear scanner capabilities and specialized coils tuned to the sodium resonance. Though not as common as proton resonant hardware, this hardware is commercially available and actively used at many medical centers in the United States. The imaging approach we have employed is both standardized and noninvasive, and it has the
potential to become more widely utilized because of a growing need for clinical methods that can evaluate sodium at the tissue level (29).

Conclusion
In this study, we quantified tissue sodium and adipose content by using a multimodal clinical MRI protocol in women with lipedema. We measured significantly elevated sodium in the skin and SAT and significantly higher fat/water volume in patients with lipedema. The accumulation of tissue sodium and adipose content indicates reduced vascular clearance or increased deposition and inflammation in the pathophysiology of lipedema. Furthermore, tissue sodium accumulation may provide a functional link between the disrupted microenvironment of the tissue and proinflammatory immune cell polarization in patients with lipedema. These findings underscore the potential relevance of tissue sodium as a molecular biomarker of tissues affected by lipedema. Along with MRI-based adipose volume quantitation in the leg, sodium MRI has the potential to provide an important noninvasive differential diagnosis of lipedema from obesity.

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