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Comparison of fluid and body composition measures in women with lipoedema, lymphoedema, and control participants

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Summary

Lipoedema is the disproportionate accumulation of adipose tissue in the lower body, often associated with hormonal changes in women. Lipoedema is commonly misdiagnosed as lymphoedema or obesity due to similarities in appearance. The aim of this study is to compare body composition and fluid measures of women with lipoedema, lymphoedema, and matched control participants, to determine differences that may help distinguish between each condition. One hundred and eleven participants aged over 18, who presented with the complaint of leg swelling and underwent indocyanine green lymphography were included in this study. Our analysis showed that the individuals with lymphoedema had a significantly higher overall total body water (*lymphoedema*: 9.6 ± 4.2 L, *lipoedema*: 7.4 ± 2.3 L, *control*: 7.5 ± 1.8 L; $p < .001$) and extracellular fluid (*lymphoedema*: 4.6 ± 1.6, *lipoedema*: 3.4 ± 1.0 L, *control*: 3.5 ± 0.7 L; $p < .001$) in the legs when compared to individuals with lipoedema and matched control participants. Individuals with lipoedema had a significantly higher overall fat mass as a percentage of body weight when compared to individuals with lymphoedema (*lymphoedema*: 33.1% ± 9.5%, *lipoedema*: 39.4% ± 6.5%; $p = .003$). We are unable to distinguish between individuals with lipoedema and control participants, therefore further research needs to be conducted to help reduce misdiagnosis.

KEYWORDS
bioimpedance spectroscopy, body composition, extracellular fluid, lipoedema, lymphoedema

What is already known

- Lipoedema is described as the accumulation of adipose tissue in the bilateral lower legs of women.
- This chronic disease presents symptoms that reduce quality of life.
- Due to similarities in appearance, individuals with lipoedema are commonly misdiagnosed with lymphoedema or obesity.

What this study adds

- Bioimpedance spectroscopy could present a useful clinical diagnostic tool when differentiating lipoedema from lymphoedema.

- Oedema does not appear to be concurrently associated with lipoedema.
- Alone, bioimpedance spectroscopy did not differentiate between participants with lipoedema and control participants matched for body mass index.

1 | INTRODUCTION

Lipoedema is the abnormal painful accumulation of adipose tissue mostly in the lower body, causing a noticeable disproportion between the trunk and lower extremities.[1,2] This chronic condition is typically apparent in women and is often considered a result of hormonal fluctuations.[2] Lipoedema often contributes to psychological and physical problems including anxiety, depression, low self-confidence, heaviness, tension, pain, and tingling, which all reduce the individual's quality of life.[3]

Currently, there is no clear diagnostic criterion for lipoedema. It is usually diagnosed through a physical examination and medical history.[4] Unfortunately, as a result, lipoedema is often incorrectly diagnosed as lymphoedema. Although these conditions present similar characteristics, lymphoedema occurs due to the inadequate functioning of the lymphatic system causing an accumulation of protein-rich fluid in the interstitial space.[3] The lack of lipoedema awareness and the similarities in physical appearance between lipoedema and lymphoedema, contributes to its misdiagnosis. Lipoedema is also commonly misdiagnosed as obesity based on body mass index (BMI) however individuals with lipoedema usually present a normal appearance above their waist but have enlarged and swollen lower limbs.[1] Diagnosis is further confounded often when obesity is concurrent with lipoedema. Improper diagnosis can lead to ineffective treatments and psychological burden on individuals with lipoedema.[5]

Bioimpedance spectroscopy (BIS) measures tissue conductivity in response to a small bioelectrical current allowing for measurements to be calculated on total body, extracellular, and intracellular water.[6] BIS has emerged as one of the most promising techniques to assess fluid status in individuals while also calculating other tissue masses.[7,8] BIS technology is becoming more frequently used for analysing body composition in comparison to dual-energy x-ray absorptiometry (DXA), as DXA equipment is expensive, not portable, and exposes individuals to small amounts of radiation.[9] BIS, however, is a non-invasive method requiring little maintenance, is safe, easy to perform, portable, and relatively inexpensive.[6] BIS is becoming a common clinical measure helping to diagnose conditions such as lymphoedema through its ability to identify accumulation of extracellular fluid (ECF).[10] While there is no current concrete method to diagnose lipoedema, BIS could prove useful in differentiating lipoedema from conditions with similar presentations.

The aim of this study was to investigate potential key differences in body composition and fluid measures that would assist in differentiating lipoedema from lymphoedema and BMI-matched participants. This research may help identify if BIS could be a valid outcome measure for lipoedema diagnosis and aid in monitoring individuals with lipoedema.

2 | METHODS

2.1 | Eligibility criteria

This study is a retrospective analysis where data was collected from participants who underwent Indocyanine green (ICG) lymphography assessment for lower limb swelling at the Australian Lymphoedema Education, Research and Treatment (ALERT) diagnostic and surgical clinics at Macquarie University. Participants with lymphoedema and lipoedema were diagnosed at the ALERT clinic. Initially, participants with lipoedema were selected and then matched for BMI with participants who underwent imaging for chronic or persistent lower limb swelling. Participants had either lymphoedema or neither lipoedema nor lymphoedema confirmed by ICG lymphography. Data from January 2018 to October 2022 was used in this retrospective cross-sectional study. All patients signed a written informed consent before undergoing the ICG procedure. The data included in this study was sourced from electronic medical records and Macquarie University Human Research Ethics Committee granted ethical approval (**52022613944241**). Clinical Innovation and Audit Committee approval was also granted (MQCIAC2022003).

Participants were included if they were female, aged over 18 years, and diagnosed with either lipoedema, bilateral lower limb lymphoedema, or not diagnosed with either condition. The diagnosis of lymphoedema was confirmed by the presence of dermal backflow (superficial lymphatic congestion) identified on ICG lymphography. Individuals who had dermal backflow in the lipoedema or control group were excluded from the study, as this is indicative of lymphoedema. The lipoedema group presented to the ALERT clinic and was diagnosed as having lipoedema and had ICG lymphography. The reason for undertaking ICG lymphography was to provide to the patient objective lymphatic mapping. This allowed clarification of their condition as many patients had been given a prior diagnosis of or had self-diagnosed lymphoedema. The control group presented with the complaint of leg swelling but did not have characteristics of lipoedema or history of lymphatic injury and were found to have no ICG evidence for the diagnosis of lymphoedema. An ICG may have been performed on a patient to provide objective information to substantiate or confirm a misdiagnosis or personal believe they had a lymphatic cause of the self-report of leg swelling. Individuals who had undergone liposuction surgery, or who had contraindications to BIS such as a pacemaker or implantable device were also excluded. All participants must have had an ICG lymphography assessment on the same day or close to their BIS measurement.

2.2 | Indocyanine green (ICG) lymphography

The ALERT ICG lymphography protocol for the lower limb has been described previously.[11,12] In brief the ICG dye was administered using four injection sites on the circumference of the foot.[12] These injection sites target the four lymphatic groups of the lower leg which include the anteromedial, anterolateral, posterolateral, and posteromedial.[13] Immediately after the injections, lymphatic scanning using the near-infrared camera system (Photodynamic Eye Neo II; Hamamatsu Photonics K.K., Japan) and imaging data was recorded using a digital video recorder (MDR-600HD Ikegami Tsushinki Co., Ltd.). One assessor performed and analysed the lymphatic imaging, which was continuously conducted and completed within an hour.[11,12] Our published protocol[11,12] has ensured the transit of the ICG dye to the drainage areas and a stabilised dermal backflow pattern in the time frame of 60 min. First spontaneous dye movement via the lymphatics was observed before manual lymphatic drainage was performed by an accredited lymphoedema therapist. Only where dermal backflow is present, indicating lymphatic obstruction, is manual lymphatic drainage is applied by a therapist. Where no dermal backflow and normal functioning lymphatic vessels are observed, manual lymphatic drainage is not required and ICG dye is seen at the drainage area such as the inguinal nodal area within the one-hour time frame.

Lymphoedema severity was determined through ICG lymphography and graded from 0 to 5 using the MD Anderson Cancer Center ICG severity scale.[14] Blocked or dysfunctional lymphatic collector vessels cause the retrograde flow of the dye back into the capillaries of the skin, known as dermal backflow.[12] Areas of dermal backflow were marked on a standard body chart using the images taken from the ICG lymphography. The regions of the lower body were examined independently by two researchers to determine the presence of dermal backflow and both legs of each participant were analysed separately for lymphoedema severity.

2.3 | Body composition and fluid measures

Following standard operating procedures, the SOZO® BIS device (ImpediMed, Brisbane, Australia) was used to measure intracellular fluid (ICF) and ECF. It was also used to calculate body composition measures. This device is validated to measure body and fluid composition.[9] Height was measured using a stadiometer recorded to the nearest 0.1 cm (SECA 213, Hamburg, Deutschland) and weight was recorded to the nearest 0.1 kg using electronic scales (SECA 813, Hamburg, Deutschland). Fluid and body composition measures were calculated by the SOZO device using the manufacturer's equations. BMI (weight(kg)/height(m)^2) and fat mass index (FMI) (fat mass(kg)/height(m)^2) were calculated manually.

2.4 | Statistical analysis

Based on our previously analysed BIS data [10] demonstrating a coefficient of variation (CV %) of 0.6 or less, we calculated that 18 participants were required in each group to achieve 80% power at $p = .05$ to detect a difference between the groups. Descriptive analyses were conducted on all three groups. An analysis of variance was conducted on participant characteristics, fluid, and body composition measures using JASP software (Version 0.16.4, Netherlands). If significant differences were observed between groups a Post Hoc test with Tukey's correction for multiple comparisons, was performed. The alpha level of significance was set at $p \leq .05$ and all data was expressed as mean and standard deviations (SD). Cohen's d effect sizes were used to express the magnitude of difference. Greater than or equal to 0.8 was considered a large effect, 0.5 a moderate effect, 0.2 a small effect, and less than 0.2 a trivial effect.[15]

All data were tested for normality through a Q–Q plot and homogeneity of variance was tested through Levene's test for equality of variances. If there was a significant difference in variance, a Welch test was performed to confirm significance between groups. If a significant difference was present between groups and the equality of group variances was compromised a Games–Howell post hoc test was performed with Tukey's correction.

3 | RESULTS

3.1 | Participant characteristics

Forty-one women with lipoedema were assessed with ICG lymphography. Four participants with lipoedema were excluded from the present study, one had contraindications to BIS assessment, one had previous liposuction surgery, and two were diagnosed with lymphoedema concurrent with lipoedema. Therefore, 37 participants with lipoedema were included in this study. Participants with bilateral lymphoedema ($n = 37$) and control participants ($n = 37$) were matched for BMI to individuals with lipoedema.

As presented in Table 1, Lipoedema type and stage varied: Type I ($n = 5$), Type II ($n = 9$), Type III ($n = 22$), Type V ($n = 2$), and Stage 1 ($n = 13$), Stage 2 ($n = 13$), Stage 3 ($n = 10$) and Stage 4 ($n = 1$).

TABLE 1 Lipoedema type and stage.

Characteristics	Number (%)
Lipoedema type	
I	5 (13.5)
II	9 (24)
III	22 (59.5)
V	1 (2.7)
Lipoedema type (mean ± SD)	2.5 ± 0.8
Lipoedema stage	
Stage 1	13 (35.1)
Stage 2	13 (35.1)
Stage 3	10 (27.0)
Stage 4	1 (2.7)
Lipoedema stage (mean ± SD)	2.0 ± 0.9

Note: Lipoedema type IV (arms) not classified.
Abbreviation: SD, standard deviations.

TABLE 2 Participant characteristics for individuals with lymphoedema.

Characteristics	Number (%)
Primary lymphoedema	16 (43.2)
Secondary non-cancer-related lymphoedema	7 (18.9)
Trauma/surgery	2 (5.4
Vascular	2 (5.4)
Unsure	3 (8.1)
Cancer related lymphoedema	11 (29.7)
Gynaecological	10 (27.0)
Genitourinary	1 (2.7)
Mixed primary and secondary lymphoedema	3 (8.1)
MDA stage-left	
1	4 (10.8)
2	22 (59.5)
3	2 (5.4)
4	7 (18.9)
MDA stage-left (mean ± SD)	2.3 ± 0.9
MDA stage-Right	
1	6 (16.2)
2	22 (59.5)
3	2 (5.4)
4	7 (18.9)
Undetermined	1 (2.7)
MDA stage-right (mean ± SD)	2.3 ± 0.9

Abbreviations: MDA, MD Anderson Cancer Center; SD, standard deviations.

Individuals with lymphoedema also had varying MDA stages (Table 2). This study cohort included individuals with lower limb lipoedema therefore Type VI with arm involvement was not classified separately. Lymphoedema was classified as either primary ($n = 16$) or secondary (total $n = 18$, cancer-related lymphoedema $n = 11$, non-cancer related lymphoedema $n = 7$). Between the left and right leg, three individuals had a mix of both primary and secondary lymphoedema.

A comparison of participant characteristics between the three groups are shown in Table 3. The individuals were successfully matched for BMI as there was no significant difference between the three groups ($p = .536$). No difference was present in FMI between the groups ($p = .111$). There was also no significant difference between the groups for height ($p = .723$) and weight ($p = .536$). Age was significantly different between the three groups ($p = .019$). A post hoc test showed that individuals with lymphoedema were older than individuals with lipoedema with a moderate effect size ($p = .025$, $d = 0.63$).

3.2 | Comparison of total body

As shown in Table 4, after a post hoc test individuals with lymphoedema had a significantly greater total body water (TBW) as a percentage of weight ($p = .002$, $d = 0.79$) and fat-free mass (FFM) as a percentage of weight ($p = .002$, $d = 0.79$) than individuals with lipoedema with a moderate effect size. Individuals with lymphoedema had a significantly lower fat mass (FM) as a percentage of weight than individuals with lipoedema with a moderate effect size after a post hoc test ($p = .002$, $d = .79$). A significantly greater skeletal muscle mass (SMM) as a percentage weight ($p = .015$, $d = 0.66$), active tissue mass as a percentage of weight ($p = .002$, $d = 0.82$), and extracellular mass as a percentage of weight ($p = .016$, $d = 0.65$) were present in individuals with lymphoedema when compared to individuals with lipoedema. Protein and mineral as percentage of weight was also significantly greater in individuals with lymphoedema compared to individuals with lipoedema after a post hoc test ($p = .002$, $d = 0.77$), with a moderate effect size. When comparing the hydration index (Hy-Dex) scores individuals with lymphoedema had a significantly greater score than individuals with lipoedema after a post hoc test ($p<.001$, $d = 0.88$), with a large effect size. Although not significantly different, when comparing the Hy-Dex of individuals with lipoedema and control participants a moderate effect size was present ($d = 0.72$). No significant differences were observed between the control participants and individuals with either lipoedema or lymphoedema for any of the overall body composition measures. Moderate effect sizes were observed in ECF as a percentage of TBW ($d = 0.50$) and ICF as a percentage of TBW ($d = 0.50$) when the control participants were compared to individuals with lymphoedema.

3.3 | Comparison of arm composition

The analysis was performed on bilateral arms of 111 individuals therefore 222 limbs were included. As seen in Table 5 there was no significant difference in all measures when comparing the arm composition between individuals with lipoedema, lymphoedema, and control participants. However, when comparing the ECF between individuals with lipoedema and lymphoedema a large effect size was observed ($d = 1.00$). A large effect size was also present when comparing the ECF of individuals with lipoedema and control participants ($d = 1.00$). The remaining effect sizes were small to trivial.

3.4 | Comparison of leg composition

As bilateral legs were assessed, 222 legs were included in this analysis (Table 6). Individuals with lymphoedema had a significantly higher bilateral lymphoedema index (L-Dex) score through a post hoc test when compared to both individuals with lipoedema ($p<.001$, $d = 1.05$) and control participants ($p<.001$, $d = 1.11$) with a large effect size. TBW was significantly greater in individuals with lymphoedema when compared to individuals with lipoedema ($p<.001$, $d = 0.68$) and control participants ($p<.001$, $d = 0.70$) with a moderate effect size. Post hoc testing revealed that the ECF of individuals with lymphoedema was significantly greater than in individuals with lipoedema ($p<.001$, $d = 0.92$) and control participants ($p<.001$, $d = 0.96$), with a large

TABLE 3 Comparison of participant characteristics between individuals with lipoedema, lymphoedema and matched control participants.

Measures	Lipoedema	Lymphoedema	Control	*p*-value
Age (years)	**49.6 ± 12.2**[a]	***58.7 ± 16.7***	**50.9 ± 15.2**	**.019**
Height (cm)	163.2 ± 5.5	163.7 ± 6.3	162.6 ± 6.6	.723
Weight (kg)	90.8 ± 23.5	85.3 ± 22.4	86.7 ± 19.8	.526
BMI kg/m^2	34.2 ± 9.1	31.9 ± 8.8	33.0 ± 8.1	0.536
FMI kg/m	13.9 ± 5.5	11.2 ± 5.8	12.3 ± 5.2	.111

Note: Data shown as mean ± standard deviations. **Bold:** Significant change between the groups ($p < .05$).
Italics: Moderate or large effect size between groups.
Abbreviations: BMI, body mass index; cm, centimetre; FMI, fat-mass index; kg, kilogram; kg/m, kilograms per metre; kg/m^2, kilograms per square metre.
[a]Post hoc test significantly different from lymphoedema group.

TABLE 4 Comparison of overall body composition between individuals with lipoedema, lymphoedema and matched control participants.

Measures	Lipoedema	Lymphoedema	Control	*p*-value
TBW (L)	39.6 ± 7.8	40.6 ± 7.3	39.8 ± 6.1	.799
TBW % weight	**44.4 ± 4.8**[a]	***49.0 ± 6.9***	**46.8 ± 5.0**	**.003**
ECF (L)	17.4 ± 3.2	18.5 ± 3.3	17.5 ± 2.5	.449
ECF % TBW	44.2 ± 1.9	45.0 ± 1.9	44.1 ± 1.7	.103
ICF (L)	22.1 ± 4.7	22.4 ± 4.1	22.3 ± 3.8	.967
ICF % TBW	55.8 ± 1.9	55.0 ± 1.9	*55.9 ± 1.7*	.103
FFM (kg)	54.0 ± 10.7	55.5 ± 10.0	54.4 ± 8.4	.795
FFM % weight	**60.6 ± 6.5**[a]	***66.9 ± 9.5***	**63.9 ± 6.8**	**.003**
FM (kg)	36.8 ± 14.2	29.8 ± 14.7	32.3 ± 13.1	.094
FM % weight	***39.4 ± 6.5***[a]	**33.1 ± 9.5**	**36.1 ± 6.8**	**.003**
SMM (kg)	20.6 ± 3.3	21.8 ± 3.8	21.2 ± 2.8	.302
SMM % weight	**23.5 ± 4.1**[a]	***26.6 ± 6.0***	**25.1 ± 4.1**	**.021**
BMR (cal/day)	1519.7 ± 246.4	1421.2 ± 249.8	1467.8 ± 213.6	.208
ATM (kg)	29.4 ± 7.5	30.0 ± 6.7	29.7 ± 5.9	.927
ATM % weight	**32.6 ± 3.3**[a]	***35.9 ± 4.8***	**34.6 ± 3.7**	**.002**
ECM (kg)	24.6 ± 3.9	25.5 ± 3.4	24.7 ± 2.6	.419
ECM % weight	**28.1 ± 4.4**[a]	***31.0 ± 5.2***	**29.3 ± 4.0**	**.021**
Protein and mineral (kg)	14.5 ± 2.9	14.9 ± 2.7	14.6 ± 2.2	.782
Protein and mineral % weight	**16.2 ± 1.8**[a]	***17.9 ± 2.6***	**17.1 ± 1.8**	**.003**
Hy-Dex	**−4.3 ± 16.8**[a]	***11.2 ± 18.5***	***2.7 ± 13.5***	**<.001**
Phase angle (degrees)	4.9 ± 0.7	4.6 ± 0.7	4.9 ± 0.6	.126

Note: Data shown as mean ± standard deviations. **Bold:** Significant change between the groups ($p < .05$).
Italics: Moderate or large effect size between groups.
Abbreviations: ATM, active tissue mass; BMR, basal metabolic rate; cal/day, calories per day; ECF, extracellular fluid; ECM, extracellular mass; FM, fat mass; FFM, fat-free mass; Hy-Dex, hydration index; ICF, intracellular fluid; kg, kilogram; L, litre; SMM, skeletal muscle mass; TBW, total body water.
[a]Post hoc test significantly different from lymphoedema group.

effect size. The ECF as a percentage of TBW was significantly greater in individuals with lymphoedema when compared to individuals with lipoedema ($p = .032$, $d = 0.42$) after a post hoc test. Individuals with lymphoedema had a significantly greater ICF through a post hoc test compared to individuals with lipoedema ($p = .015$, $d = 0.47$) and control participants ($p = .010$, $d = 0.51$). Through a post hoc test individuals with lymphoedema had a significantly lower ICF as a percentage of TBW ($p = .032$, $d = .42$) and phase angle ($p = .009$, $d = 0.48$) when compared to individuals with lipoedema, with a small effect size. Individuals with lymphoedema had a significantly greater lean soft tissue (LST) when compared to individuals with lipoedema ($p<.001$, $d = 0.66$) and control participants ($p<.001$, $d = 0.70$) through a post hoc test presenting a moderate effect size. There was no significant difference for any of the leg composition parameters between individuals with lipoedema and control participants, with trivial effect sizes.

TABLE 5 Comparison of arm composition between individuals with lipoedema, lymphoedema, and matched control participants.

Measures	Lipoedema	Lymphoedema	Control	*p*-value
TBW (L)	1.8 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	.426
ECF (L)	0.8 ± 0.1	*0.9 ± 0.1*	*0.9 ± 0.1*	.340
ECF % TBW	46.8 ± 2.1	47.2 ± 2.1	46.9 ± 1.7	.433
ICF (L)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	.529
ICF % TBW	53.2 ± 2.1	52.8 ± 2.1	53.1 ± 1.7	.433
LST (kg)	2.3 ± 0.4	2.4 ± 0.3	2.4 ± 0.4	.392
SMM (kg)	1.9 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	.058
Phase angle (degrees)	4.8 ± 0.6	4.8 ± 0.7	4.9 ± 0.5	.549

Note: Data shown as mean ± standard deviations. Italics: Moderate or large effect size between groups.
Abbreviations: ECF, extracellular fluid; ICF, intracellular fluid; kg, kilogram; L, litre; LST, lean soft tissue; SMM, skeletal muscle mass; TBW, total body water.

TABLE 6 Comparison of leg composition between individuals with lipoedema, lymphoedema and matched control participants.

Measures	Lipoedema	Lymphoedema	Control	*p*-value
Bilateral L-Dex	**4.0 ± 4.9[a]**	***12.6 ± 11.6***	***3.8 ± 4.3[a]***	**<.001**
TBW (L)	**7.4 ± 2.3[a]**	***9.6 ± 4.2***	***7.5 ± 1.8[a]***	**<.001**
ECF (L)	**3.4 ± 1.0[a]**	***4.6 ± 1.6***	***3.5 ± 0.7[a]***	**<.001**
ECF % TBW	**46.9 ± 3.3[a]**	**48.7 ± 5.3**	**47.3 ± 3.1**	**.041**
ICF (L)	**4.0 ± 1.5[a]**	**5.0 ± 2.8**	***4.0 ± 1.1[a]***	**.011**
ICF % TBW	**53.1 ± 3.3[a]**	**51.3 ± 5.3**	**52.7 ± 3.1**	**.041**
LST (kg)	**9.6 ± 3.1[a]**	***12.4 ± 5.4***	***9.7 ± 2.3[a]***	**<.001**
SMM (kg)	6.9 ± 1.6	6.9 ± 2.0	6.7 ± 1.3	.540
Phase Angle (degrees)	**5.6 ± 0.9[a]**	**5.0 ± 1.6**	**5.5 ± 0.9**	**.013**

Note: Data shown as mean ± standard deviations. **Bold:** Significant change between the groups (p <.05).
Italics: Moderate or large effect size between groups.
Abbreviations: ECF, extracellular fluid; ICF, intracellular fluid; kg, kilogram; L, litre; LST, lean soft tissue; SMM, skeletal muscle mass; TBW, total body water.
[a]Post hoc test significantly different from lymphoedema group.

4 | DISCUSSION

BIS technology used in this study aimed to identify fluid and body composition characteristics that distinguish individuals with lipoedema from individuals who have lymphoedema or control participants. We believe this study has helped to highlight the functionality of BIS measures in the diagnosis and monitoring of individuals living with lipoedema and lymphoedema. This study has identified clear differences in fluid and body composition measures between the three groups which could be advantageous for clinical diagnosis.

Lymphoedema is the accumulation of protein-rich fluid in the interstitium caused by impaired lymphatic drainage[16] resulting in swelling, inflammation, and tissue fibrosis.[16] In our study, leg ECF and TBW were greater in the individuals with lymphoedema compared to both individuals with lipoedema and control participants. This finding correlates with the literature as in the early stages of lymphoedema lymph accumulates,[10,17,18] therefore justifying the increase in ECF and TBW. Unlike lymphoedema, the presence of oedema in individuals with lipoedema is currently under debate. Oedema occurs when an excessive volume of fluid accumulates either within the cells or in the interstitial space.[19,20] This can be detrimental to tissue function as oedema increases diffusion distance for oxygen and other nutrients, compromising cellular metabolism.[19,20] Our study showed no evidence of increased TBW or ECF in individuals with lipoedema compared to the control participants suggesting the absence of oedema. Similarly, a study by Monnin-Delhom et al.[21] evaluated computed tomography imaging to distinguish between deep venous thrombosis, lymphoedema, and lipoedema. They found no patterns of oedema through computed tomography, ultrasound, or magnetic resonance imaging (MRI) for individuals with lipoedema, however, computed tomography did find oedema in 95% of individuals with lymphoedema and 42% of individuals with deep venous thrombosis. It is also interesting to note that in the current study, individuals with lipoedema did not show a difference in TBW or ECF in their arms when compared to individuals with lower limb lymphoedema however differences were presented in the legs. As our study focused on bilateral leg lymphoedema we would expect to see an increase in fluid levels in the legs only. This study showed that there was no increased oedema present outside the affected area of individuals with lipoedema or lymphoedema. This highlights that both oedema and clinically evident pitting oedema is not a feature of lipoedema.

In contrast to lymphoedema, lipoedema is the accumulation of abnormal fat in the bilateral lower legs, often considered to be due to hormonal changes.[22] Through BIS analysis we found that the percentage of overall FM was significantly greater in individuals with lipoedema compared to individuals with lymphoedema. This is as expected due to the abnormal accumulation of adipose tissue. However, as the BIS technology only provides calculations for overall FM, it was unable to differentiate between individuals with lipoedema and control participants in our study. As fat accumulates in the lower body of individuals with lipoedema, their upper bodies generally remain disproportionate and free of excessive fat accumulation. Whereas in BMI-matched individuals, fat accumulation is not restricted to the lower body which could explain the similar overall FM results. Therefore, although the BIS could be successful in differentiating between lipoedema and lymphoedema, differences in BIS body composition measures between individuals with lipoedema and BMI-matched individuals were not apparent. It would be interesting to see if there was a distinct difference in lower body FM between individuals who have lipoedema and individuals matched for BMI. Two current studies by Di Renzo et al.[23,24] investigated body composition differences between participants with lipoedema and control participants using a DXA scan. Both studies found significantly greater FM (kg and %) in the legs of individuals with lipoedema. However, neither study matched participants for BMI and in the study by Di Renzo et al.[24] individuals with lipoedema had a larger BMI compared to the control group. It is, therefore, hard to conclude that the larger FM in the legs observed in their study was a result of lipoedema, as it could be the result of a larger overall BMI. However, in the current study matching participants based on BMI alone poses difficulties. The increased ECF seen in individuals with lymphoedema elevates their BMI. While matching participants based on BMI, a lower FM is evident in individuals with lymphoedema when compared to individuals with lipoedema. Although BIS can detect ECF accumulation in lymphoedema, it does not measure segmental FM, therefore we are unable to determine if FM is different in the legs of individuals with lipoedema compared to individuals with lymphoedema and BMI-matched individuals. Further research should be conducted to examine the leg FM of individuals with lipoedema and controls matched for BMI. This would help to determine whether these segmental measures are useful in the diagnosis of lipoedema.

Muscle mass has not been well-researched in individuals with lipoedema. The recent studies by Di Renzo et al.[23,24] using DXA also reported a significantly larger lean mass in individuals with lipoedema when compared to control participants. The DXA measures lean soft tissue which is largely comprised of water.[25] Older adults have an increased ECF to ICF ratio and as the DXA cannot distinguish water within the intracellular space from extracellular water, cellular muscle atrophy is masked.[25] In our study individuals with lipoedema had a lower age when compared to both individuals with lymphoedema and control participants. We expect this due to lipoedema being caused by the onset of hormonal changes such as puberty or pregnancy.[26] Although we matched for BMI, age influences SMM resulting in the involuntary loss of SMM and strength as we age.[27] As individuals with lymphoedema were significantly older than individuals with lipoedema it would be anticipated for them to have a lower SMM. However, the SMM % was higher in individuals with lymphoedema compared to individuals with lipoedema. Initially, individuals with lymphoedema were advised not to exercise as it was considered unsafe.[28] However recent research has indicated that exercise-induced weight loss can reduce the effects of lymphoedema by improving circulation, helping to remove the lymph out of the affected area and decrease swelling.[28] An 8-week home-based progressive resistance exercise programme by Gautam et al.[29] showed significant reductions in the circumference and volume of the affected upper limb in patients with lymphoedema post-breast cancer. As recent literature supports the positive effect of exercise for lymphoedema it is likely that many of the individuals with lymphoedema in our study were encouraged to exercise.[30] As several factors influence SMM it is hard to make accurate conclusions on the differences observed between the groups in our study. A study by van Esch-Smeenge et al.[31] found that individuals with lipoedema had a clinically relevant lower exercise endurance capacity through a 6-min walk test and a significantly lower quadriceps muscle strength when compared to individuals with obesity. Similarly, through MRI, Crescenzi et al.[32] observed an elevated intramuscular adipose tissue and reduced muscle size in women with lipoedema when compared with BMI-matched participants. These studies highlight the need for further investigation into muscle mass and exercise capacity of individuals with lipoedema. In our study, inclusion of physical activity questionnaires and age-related adjustments may have helped explain the differences in SMM observed between the groups.

Imaging techniques including computed tomography and MRI have been used in research involving lipoedema and lymphoedema to assess body composition, however these techniques are not suitable for routine clinical practice.[18] Lymphoedema diagnosis presents difficulties as there is not one assessment with the required specificity and sensitivity. Most assessments are indirect and are focused on abnormal limb size through circumferential measures or by water displacement.[18] BIS is a promising body composition assessment tool that is becoming noticed for its advantageous measures that help to identify early lymphoedema as part of a post-cancer lymphoedema surveillance. It uses the flow of a small electrical current passing through the body, measuring its impedance.[18] The impedance magnitude is inversely proportional to the volume of fluid in the tissues.[18] The BIS produces a L-Dex score which measures the difference in volume between limbs.[17] Early lymphoedema is indicated through a change of +6.5 L-Dex units from baseline, through a lineralized and scaled ratio.[10,17] The L-Dex scale is based on the mean and two SD.[10,17] The leg L-Dex scores were greater for individuals with lymphoedema (12.6 ± 11.6) when compared to both individuals with lipoedema (4.0 ± 4.9) and control participants (3.8 ± 4.3). This highlights that L-Dex scores through a standing BIS device can potentially differentiate lymphoedema from lipoedema and BMI-matched participants. BIS presents a valuable tool in lymphoedema diagnosis and monitoring and it has previously been reported as an effective measurement to predict lymphoedema onset in the arm, through ECF and subclinical changes in ECF.[10] BIS alone could not be used to

differentiate between these three conditions potentially due in part to its inability to measure FM of individual limbs. Segmental analyses can be performed through a DXA scan. DXA scans are considered a reference method in clinical research, measuring FM, FFM, and bone mineral density.[33] However, DXA cannot differentiate or estimate ECF or ICF,[25] therefore, a combination of these technologies could potentially be useful when analysing the body composition of individuals with lymphoedema, lipoedema, and participants matched for BMI.

Our research provided some clear differences between individuals with lymphoedema and individuals with lipoedema, however failed to provide distinctive differences between individuals with lipoedema and control participants. The use of only BIS technology to analysis body composition measures between individuals with lipoedema, lymphoedema, and a control participants is a limitation that is evident in this study. Although it had favourable measures for identifying lymphoedema, BIS lacked the ability to distinguish between individuals with lipoedema and control participants. If other forms of body composition were assessed, we may have been able to identify more diagnostic factors separating individuals with lipoedema from the control participants. BIS does have the ability to measure segmental muscle mass of individuals however it is not able to determine segmental FM. Further research into segmental FM and muscle mass may help to identify distinguishable differences between lipoedema and BMI-matched individuals, while strengthening the differences between individuals with lymphoedema and lipoedema. Individuals with lymphoedema showed a significantly larger SMM. As this was a retrospective study, we did not have records of how much physical activity each individual performed. This could explain why individuals with lymphoedema had a higher SMM when compared to individuals with lipoedema. BMI matching could also be an influencing factor, as individuals with lymphoedema may have an elevated BMI due to additional ECF rather than FM. Further investigation into muscle mass between individuals with lipoedema, lymphoedema, and control participants could uncover distinguishable aspects for not only for diagnosis but disease management.

5 | CONCLUSION

Lipoedema, lymphoedema, and obesity are chronic conditions that impact an individual's quality of life. Lipoedema is often misdiagnosed causing prolonged ineffective and costly treatments, decreasing the individual's ability to manage their condition effectively. This misdiagnosis is contributed to by a lack of awareness of lipoedema and the absence of clear diagnostic criteria. This study aimed to identify distinct differences in body composition and ECF measures that would assist in distinguishing lipoedema from lymphoedema and a control group. We identified differences in leg ECF % and overall TBW % between individuals with lipoedema and lymphoedema. Leg ECF, TBW, and bilateral L-Dex measures were also greater in individuals with lymphoedema when compared to either individuals with lipoedema or control participants. These results aligned with current lymphoedema literature. ECF as an objective measure of tissue oedema showed no difference between individuals with lipoedema and control participants confirmed by ICG to not have lymphoedema, whereas increased ECF was characteristic of lymphoedema. Elevated lower limb ECF as an indicator of oedema is not found in lipoedema. Individuals with lipoedema had a larger FM % when compared to individuals with lymphoedema. This could be due to the lack of specificity in limb FM measures and that BMI was artificially elevated in individuals with lymphoedema due to the accumulation of ECF. There were no differences in FM when individuals with lipoedema were compared to control participants. Although this study shows promising findings and highlights the potential effectiveness of the BIS technology in lymphoedema diagnosis, further investigation must be conducted on muscle mass and segmental FM between individuals with lipoedema, lymphoedema, and a control group.

AUTHOR CONTRIBUTIONS

All authors helped in the development of the idea and design of the study. Participant data was assessed and allocated into groups by both Rhiannon Stellmaker and Belinda Thompson. Rhiannon Stellmaker conducted the data analysis and wrote the first draft of the manuscript. The manuscript was edited and revised by Belinda Thompson, Helen Mackie, and Louise Koelmeyer. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare that there are no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Okhovat JP, Alavi A. Lipedema: A Review of the Literature. *Int J Low Extrem Wounds*. 2015;14(3):262-267. doi:10.1177/1534734614554284
2. Reich-Schupke S, Schmeller W, Brauer WJ, et al. S1 guidelines: Lipedema. *J Dtsch Dermatol Ges*. 2017;15(7):758-767. doi:10.1111/ddg.13036
3. Duygu E, Bakar Y, Keser I. An important tool in lymphedema management: validation of Turkish version of the patient benefit index-lymphedema. *Lymphat Res Biol*. 2020;18(1):49-55. doi:10.1089/lrb.2018.0036
4. Macdonald JM, Sims N, Mayrovitz HN. Lymphedema, lipedema, and the open wound: the role of compression therapy. *Surg Clin North Am*. 2003;83(3):639-658. doi:10.1016/s0039-6109(02)00201-3

5. Naouri M, Samimi M, Atlan M, et al. High-resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. *Br J Dermatol*. 2010;163(2):296-301. doi:10.1111/j.1365-2133.2010.09810.x
6. Earthman C, Traughber D, Dobratz J, Howell W. Bioimpedance spectroscopy for clinical assessment of fluid distribution and body cell mass. *Nutr Clin Pract*. 2007;22(4):389-405. doi:10.1177/0115426507022004389
7. Khin EE, Elmaghrabi AY, Alvarado LA, Modem V, Quigley R. Fluid balance assessment in pediatric hemodialysis patients by using whole-body bioimpedance spectroscopy (WB-BIS). *Pediatr Nephrol*. 2022;37(10):2449-2456. doi:10.1007/s00467-022-05469-6
8. Lane MT, Doernte LA, Spears AM, Bean RM, Moon JR. Relationships between dual-energy x-ray absorptiometry bone mineral content and bone mineral density and standing and sitting bioimpedance spectroscopy variables in healthy men and women. *FASEB J*. 2018;32(S1):768.10. doi:10.1096/fasebj.2018.32.1_supplement.768.10
9. Esco MR, Fedewa MV, Freeborn TJ, et al. Agreement between supine and standing bioimpedance spectroscopy devices and dual-energy x-ray absorptiometry for body composition determination. *Clin Physiol Funct Imaging*. 2019;39(5):355-361. doi:10.1111/cpf.12585
10. Koelmeyer LA, Ward LC, Dean C, Boyages J. Body positional effects on bioimpedance spectroscopy measurements for lymphedema assessment of the arm. *Lymphat Res Biol*. 2020;18(5):464-473. doi:10.1089/lrb.2019.0067
11. Koelmeyer LA, Thompson BM, Mackie H, et al. Personalizing conservative lymphedema management using indocyanine green-guided manual lymphatic drainage. *Lymphat Res Biol*. 2021;19(1):56-65. doi:10.1089/lrb.2020.0090
12. Suami H, Thompson B, Mackie H, et al. A new indocyanine green fluorescence lymphography protocol for diagnostic assessment of lower limb lymphoedema. *J Plast Reconstr Aesthet Surg*. 2022;75(11):3946-3955. doi:10.1016/j.bjps.2022.08.017
13. Shinaoka A, Koshimune S, Suami H, et al. Lower-limb lymphatic drainage pathways and lymph nodes: a ct lymphangiography cadaver study. *Radiology*. 2020;294(1):223-229. doi:10.1148/radiol.2019191169
14. Nguyen AT, Suami H, Hanasono MM, Womack VA, Wong FC, Chang EI. Long-term outcomes of the minimally invasive free vascularized omental lymphatic flap for the treatment of lymphedema. *J Surg Oncol*. 2017;115(1):84-89. doi:10.1002/jso.24379
15. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Erlbaum Associates; 1988.
16. Lyons O, Modarai B. Lymphoedema. *Surgery*. 2019;37(2):81-87. doi:10.1016/j.mpsur.2018.12.004
17. Ward LC. Bioelectrical Impedance Spectrometry for the Assessment of Lymphoedema: Principles and Practice. In: Greene A, Slavin S, Brorson H, eds. 1st ed. Springer; 2015:123-132.
18. Ward LC, Czerniec S, Kilbreath SL. Quantitative bioimpedance spectroscopy for the assessment of lymphoedema. *Breast Cancer Res Treat*. 2009;117(3):541-547. doi:10.1007/s10549-008-0258-0
19. Scallan J, Huxley VH, Korthuis RJ. Capillary fluid exchange: regulation, functions, and pathology. *Integrated Systems Physiology: from Molecule to Function to Disease*. Morgan & Claypool Life Sciences; 2010.
20. Tiwary SK. *Approach To Lower Limb Oedema*. Springer; 2022.
21. Monnin-Delhom ED, Gallix BP, Achard C, Bruel JM, Janbon C. High resolution unenhanced computed tomography in patients with swollen legs. *Lymphology*. 2002;35(3):121-128.
22. Amato ACM, Amato FCM, Amato JLS, Benitti DA. Lipedema prevalence and risk factors in Brazil. *J Vasc Bras*. 2022;21:e20210198. doi:10.1590/1677-5449.202101982
23. Di Renzo L, Cinelli G, Romano L, et al. Potential effects of a modified mediterranean diet on body composition in lipoedema. *Nutrients*. 2021;13(2):358. doi:10.3390/nu13020358
24. Di Renzo L, Gualtieri P, Alwardat N, et al. The role of IL-6 gene polymorphisms in the risk of lipedema. *Eur Rev Med Pharmacol Sci*. 2020;24(6):3236-3244. doi:10.26355/eurrev_202003_20690
25. Kuchnia AJ, Yamada Y, Teigen L, Krueger D, Binkley N, Schoeller D. Combination of DXA and BIS body composition measurements is highly correlated with physical function-an approach to improve muscle mass assessment. *Arch Osteoporos*. 2018;13(1):97. doi:10.1007/s11657-018-0508-7
26. Reich-Schupke S, Altmeyer P, Stucker M. Thick legs—not always lipedema. *J Dtsch Dermatol Ges*. 2013;11(3):225-233. doi:10.1111/ddg.12024
27. Walston JD. Sarcopenia in older adults. *Curr Opin Rheumatol*. 2012;24(6):623-627. doi:10.1097/BOR.0b013e328358d59b
28. Morris C, Wonders KY. Concise review on the safety of exercise on symptoms of lymphedema. *World J Clin Oncol*. 2015;6(4):43-44. doi:10.5306/wjco.v6.i4.43
29. Gautam AP, Maiya AG, Vidyasagar MS. Effect of home-based exercise program on lymphedema and quality of life in female postmastectomy patients: pre-post intervention study. *J Rehabil Res Dev*. 2011;48(10):1261-1268. doi:10.1682/jrrd.2010.05.0089
30. Hayes SC, Singh B, Reul-Hirche H, et al. The effect of exercise for the prevention and treatment of cancer-related lymphedema: a systematic review with meta-analysis. *Med Sci Sports Exerc*. 2022;54(8):1389-1399. doi:10.1249/MSS.0000000000002918
31. van Esch-Smeenge J, Damstra RJ, Hendrickx AA. Muscle strength and functional exercise capacity in patients with lipoedema and obesity: a comparative study. *J Lymphoedema*. 2017;12(1):27-31.
32. Crescenzi R, Marton A, Donahue PMC, et al. Tissue sodium content is elevated in the skin and subcutaneous adipose tissue in women with lipedema. *Obesity*. 2018;26(2):310-317. doi:10.1002/oby.22090
33. Achamrah N, Colange G, Delay J, et al. Comparison of body composition assessment by DXA and BIA according to the body mass index: a retrospective study on 3655 measures. *PLoS One*. 2018;13(7):e0200465. doi:10.1371/journal.pone.0200465

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