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ORIGINAL RESEARCH

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Differentiation of lipoedema from bilateral lower limb lymphoedema by imaging assessment of indocyanine green lymphography

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Summary

Lipoedema is characterized by disproportionate painful fat accumulation mostly in the lower limbs. The presence of lymphoedema in lipoedema remains controversial. This study aimed to assess the presence or absence of lymphoedema in the lower limbs of women with lipoedema using indocyanine green (ICG) lymphography. A cross-sectional retrospective study was undertaken in women with a clinical diagnosis of lipoedema whose lower limbs were examined with ICG lymphography. MD Anderson Cancer Center (MDACC) ICG staging was used to determine lymphoedema presence and severity. Patient characteristics, ICG lymphography findings, Stemmer sign, body mass index, waist-to-hip ratio, limb volume and bioimpedance spectroscopy measures were recorded. Forty women with lipoedema underwent ICG lymphography for the lower limbs from January 2018 to July 2022. Thirty-four women (85.0%) were determined by ICG lymphography as MDACC ICG Stage 0 representing normal lymphatics. Of the six women who demonstrated dermal backflow on ICG lymphography, all were determined as ICG Stage 1, four had localized traumatic dermal backflow area at their ankles, one had previously diagnosed with primary lymphoedema and one was classified as lipoedema stage 4. ICG lymphography findings suggested the absence of lymphoedema in a clear majority of women with lower limb lipoedema.

KEYWORDS

lip, lymphatic vessels, oedema, oedemaindocyanine green lymphography

What is already known about this subject?

- Lipoedema is a condition characterized by disproportional symmetrical and painful subcutaneous fat accumulation in women particularly of the lower limbs.

- Diagnosis is difficult as objective laboratory values or medical imaging criteria have not been established.
- There is significant controversy surrounding the presence of lymphoedema in lipoedema.

What this study adds?

- The majority of women with lipoedema had normal lymphatic morphology on examination with indocyanine green lymphography.
- Lymphoedema does not appear to be a common concurrent or associated condition in women with lipoedema.
- Oedema in lipoedema may potentially be orthostatic or associated with increased lower limb adiposity.

1 | INTRODUCTION

Lipoedema was first reported by Allen and Hines in 1940 as a condition affecting almost exclusively women characterized by disproportional subcutaneous fat accumulation of the limbs.[1] The hypertrophic fat tissue can extend from the buttocks to the ankles, and from the upper arm to the wrists. The clinical symptoms of lipoedema include pain in the legs, which increases during the day, tenderness, reported easy bruising and ankle swelling.[2,3] Coupled with a high prevalence of obesity which is consistently reported at up to 80% of the lipoedema population, the diagnosis of 'pure' lipoedema is made more difficult.[4] Lipoedema has been demonstrated to impact patient-reported occupational capacity and health-related quality of life.[5] The genetic background of the condition has not been fully elucidated; however, the phenotype suggests an autosomal-dominant-sex limited with incomplete penetrance hereditary pattern.[6]

Lipoedema has been recognized and was placed on the International Classification of Diseases 11th Revision (ICD11) in 2018 under the section 'EFO2.2LIPOEDEMA Non inflammatory alteration of subcutaneous fat'.[7] Objective diagnosis remains elusive as unequivocal laboratory values or medical imaging criterion have not been established. Lipoedema diagnosis has therefore been based on medical history and physical examination in relation to typical characteristics which includes the complaint of orthostatic oedema.[8,9]

The diagnostic criterion for lipoedema was initially defined by Wold et al. in 1951[10] and modified later by Herbst.[11] However, there has been a significant ongoing controversy and confusion about the presence of lymphoedema in lipoedema.[12] In the current lipoedema staging scale, Stage 4 is named as 'lipo-lymphoedema' and this wording may bring an inaccurate expectation that lymphoedema is a component of lipoedema. Imaging studies with ultrasonography, computed tomography and magnetic resonance imaging have not defined any supportive evidence of subcutaneous oedema in patients with lipoedema[13] nor have they provided specific or pathognomonic findings to discriminate lipoedema.[14] A recent study by Greene and Sudduth used lymphoscintigraphy to investigate abnormal imaging findings on the lower limbs of women with lipoedema and concluded that the risk of lymphoedema in women with lipoedema can be predicted by body mass index (BMI) instead of the lipoedema stage.[15]

Indocyanine green (ICG) lymphography is an emerging imaging technique used to assess the superficial lymphatics and diagnose lymphoedema by the presence of dermal backflow, which is the reflux of lymph into dermal lymphatics and a specific imaging criterion. ICG lymphography has the advantage of being able to diagnose lymphoedema with higher sensitivity and specificity compared to lymphoscintigraphy.[16] Therefore, we expected that ICG lymphography examination of lower limbs with lipoedema could elucidate the presence of structural changes in the superficial lymphatics if present. The aim of this study was to assess the image findings of ICG lymphography in a cohort of women with a clinical diagnosis of lipoedema to determine the presence and prevalence of lymphoedema in this condition.

2 | METHODS

2.1 | Participants

Clinical data from consenting patients who underwent ICG lymphography from January 2018 to July 2022 were used for this cross-sectional retrospective study. Approval for the use of this data was obtained under Macquarie University Human Research Ethics Application (MQU HREA) Reference Nos: MQCIAC2018017A and 52020107614130.

The clinical diagnosis of lipoedema was made by an experienced rehabilitation specialist prior to ICG lymphography. Diagnosis was confirmed by the primary criteria of symmetrical enlargement of nodular adipose tissue of the lower limbs excluding the feet and the presence of at least two of the secondary criteria: pain or tenderness in the legs; a family history of lipoedema; non-pitting swelling in the legs assessed by firm thumb pressure for 30 s; easy bruising of the legs.[10] In addition to the distribution of disproportionate fat, presence of pitting oedema and Stemmer sign status were noted. The history of bariatric surgery with weight loss and any previous liposuction surgery were recorded. These women were not consecutive attendees as ICG

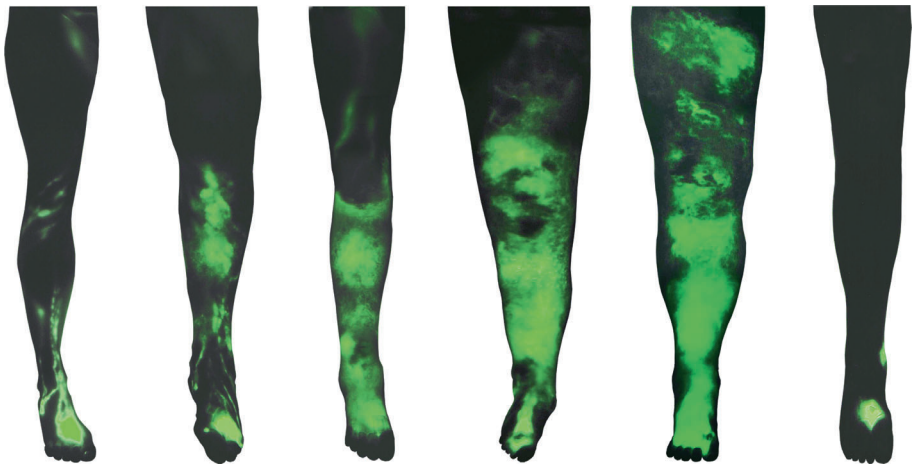

FIGURE 1 MDACC ICG stage: stages 0–5 (from left to right). Stage 0: normal lymphatics, Stage 1: many patent lymphatic vessels with minimal patchy dermal backflow, Stage 2: moderate number of patent lymphatic vessels with segmental dermal backflow, Stage 3: few patent lymphatic vessels with extensive dermal backflow involving the entire leg, Stage 4: no patent lymphatic vessels seen with dermal backflow involving the entire leg with extension to top of the foot and Stage 5: ICG does not move from injection sites. ICG, indocyanine green; MDACC, MD Anderson Cancer Center. Images were reproduced from ref. 22 with permission.

lymphography was not a routine or required investigation but performed as an elective procedure for those who requested further diagnostic clarification.

2.2 | Clinical data collection

The Australian Lymphoedema Education, Research and Treatment (ALERT) Clinic specializes in diagnostic assessment and provides management for patients suffering from lymphoedema, lipoedema and chronic oedema. Standardized lipoedema assessment includes history and physical examination by an experienced medical specialist, circumference tape measurement at 4 cm intervals to calculate limb volume using the truncated cone method,[17] BMI and waist and hip circumference measurement to calculate the waist-to-hip ratio. Bioimpedance spectroscopy (BIS) (SOZO® ImpediMed) was used to determine limb extracellular fluid ratio between the ipsilateral lower and upper limbs (L-Dex®) in bilateral lower limbs following standard operating procedures. BIS has been used clinically to diagnose extracellular fluid accumulation and is considered abnormal (or outside normal population range) if an L-Dex® score is greater than 6.5.[18] For the Stemmer sign, the medical specialist pinched the skin above proximal phalanges on the second toes. If the skin could not be pinched and lifted due to increased skin thickness, the Stemmer sign was determined as positive.[19,20] For the pitting test, firm pressure was applied with the thumb to the dorsum of the foot, ankle cuff or shin for 30 s. Pitting oedema was deemed present when an indentation remained after the thumb was lifted.

All patients with a clinical diagnosis of lipoedema were classified by the criteria of limb shape, and skin and tissue characteristics[2,10] (Table S1). Type 4 lipoedema with arm involvement was not classified separately for this study cohort of lower limb lipoedema.

2.3 | The ALERT ICG lymphography imaging protocol

The ALERT ICG lymphography protocol has been previously described for the lower limb.[21,22] In brief, four standardized injections were applied around the foot. These distinct sites were determined by an anatomical study in a cadaver model and enable comprehensive assessment of the four distinct lymphatic pathways of the lower limb.[23] Immediately following injection of the ICG dye, lymphatic imaging commenced using a hand-held near-infrared camera system (PDE Neo II; Hamamatsu Photonics K.K.). Visualized lymphatics were drawn on the patient's skin using a marker pen and imaging data was recorded using a digital video recorder (MDR-600HD: Ikegami Tsushinki Co. Ltd.). Imaging data were collected once the dissemination of ICG had stabilized.[21,22] ICG-guided manual lymphatic drainage (MLD) was required only if dermal backflow was identified to facilitate the transport of ICG dye within the lymphatic system from distal injection sites to proximal drainage regions. Visualized lymphatics were designated into two categories: linear lymphatic vessels were classified as normal; and dermal backflow as a specific diagnostic imaging sign of lymphoedema.[24] The severity of lymphoedema was classified using the MD Anderson Cancer Center (MDACC) ICG staging scale[22,24,25] (Figure 1).

3 | RESULTS

Forty women with lipoedema were included in this retrospective cross-sectional analysis. Thirty-two women underwent bilateral lower limb imaging and eight women, at their request, underwent unilateral lower limb imaging. Therefore, a total of 72 lower limbs were imaged

with ICG lymphography. The characteristics of the participants are summarized in Table 1. The average BMI recorded was 35.1 ± 9.8 with 13 women (33%) with BMI < 30 and 10 women (38%) with BMI > 40. Waist-to-hip ratio below 70%, denoting disproportion of upper to lower body,[26] was evident in only 14.7% of women measured, primarily due to concurrent central obesity with waist measurements >90 cm. Waist-to-hip ratio data was not available for six participants. The percentage volume difference between the lower limbs of 35 (89.7%) of 39 women measured was <5% denoting symmetrical leg volume. Reported onset of lipoedema symptoms was at less than 30 years of age in 82% of the women.

TABLE 1 Participant characteristics.

Characteristic	Mean ± SD (range)
Age (years)	50.15 ± 13.8 (21–77)
Leg volume difference (%)	3.2 ± 2.6 (0.4–13.3)
Waist-to-hip ratio	0.77 ± 0.06 (0.65–0.87)
BMI	35.1 ± 9.6 (17.5–61.4)
BIS (L-Dex units)	
Left	6.0 ± 4.7 (−1.9 to 19.0)
Right	2.7 ± 3.8 (−4.8 to 13.0)
Age of lipoedema onset	Number (%)
Puberty 10–19 years	17 (44.7)
Young adult 20–30 years	12 (31.6)
Older >40 years	5 (13.2)
Unknown	4 (10.5)
Lipoedema type	Number (%)
Type I	4 (10.0)
Type II	11 (27.5)
Type III	21 (52.5)
Type V	4 (10.0)
Lipoedema stage	Number (%)
Stage 1	14 (35.0)
Stage 2	12 (30.0)
Stage 3	11 (27.5)
Stage 4	2 (5.0)
Undetermined	1 (2.5)

Note: Lipoedema Type IV (arms) not classified.
Abbreviations: BIS, bioimpedance spectroscopy; BMI, body mass index; L-Dex, lymphoedema index; SD, standard deviation; %, percentage.

For ICG lymphography imaging, linear lymphatic vessels and absence of dermal backflow were identified in 63 legs (87.5%) of 34 women (85%), and they were diagnosed as having no lymphoedema (Figure 2, Video S1). All of the women who had no signs of dermal backflow also had a negative Stemmer sign and no pitting oedema. Of this group with no lymphoedema, lipoedema type and stage were various: Type I ($n = 4$), Type II ($n = 10$), Type III ($n = 18$), Type V ($n = 2$) and Stage 1 ($n = 11$), Stage 2 ($n = 12$), Stage 3 ($n = 8$) and Stage 4 ($n = 2$) with one undetermined due to previous liposuction.

There were nine legs in six women with lipoedema who had areas of dermal backflow identified with ICG lymphography. Of these, five legs in four women demonstrated a small area of localized dermal backflow at their ankle or shin and were scored at MDACC ICG Stage 1. We have occasionally observed this type of dermal backflow in normal limbs and therefore these localized dermal backflow areas were considered as traumatic lymphatic damage instead of being representative of lymphoedema. All these women also had negative Stemmer sign. In this group, there were lipoedema Type III ($n = 2$) and Type V ($n = 2$) and lipoedema Stage 1 ($n = 2$) and Stage 3 ($n = 2$). The remaining two women with dermal backflow were diagnosed with lymphoedema (MDACC ICG Stage 1) in bilateral legs. One had a previous diagnosis of bilateral primary lymphoedema on lymphoscintigraphy before onset of lipoedema. The other woman had been previously diagnosed as Stage 4 lipoedema (lipo-lymphoedema). Both women diagnosed with lymphoedema had positive Stemmer sign on clinical examination (Figure 3).

Bioimpedance spectroscopy measurements were in the normal L-Dex® range of −6.5 to +6.5 in 26 of 39 women measured or 61 of 78 legs (78.2%). One woman did not undergo BIS assessment due to having an implanted electrical device. Of the 13 women with an L-Dex® above 6.5, one had a BMI within the normal range, while the remaining 12 had a BMI ranging from 31.9 to 61.4 (mean 41.3 ± 9.7).

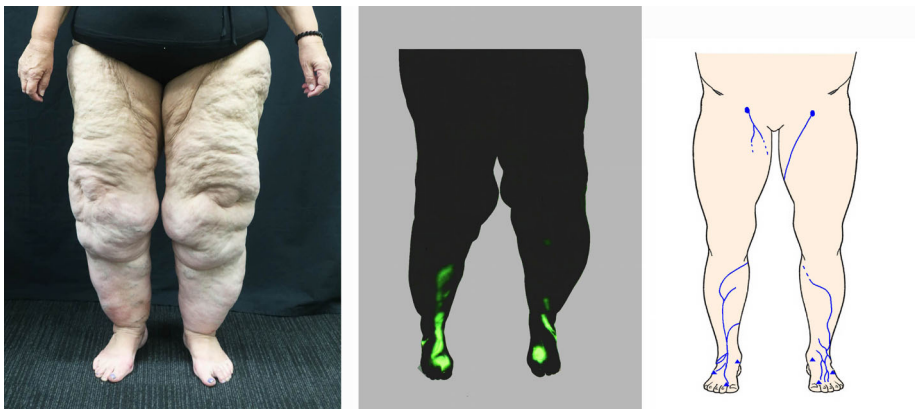

FIGURE 2 ICG image of a woman with lipoedema (Type III, Stage 3, from left; photo, montage of ICG lymphography images and schematic diagram). ICG lymphography demonstrated lymphatic vessels (blue linear vessels) without dermal backflow (MDACC ICG Stage 0). See ICG lymphography video in Video S1. ICG, indocyanine green; MDACC, MD Anderson Cancer Center.

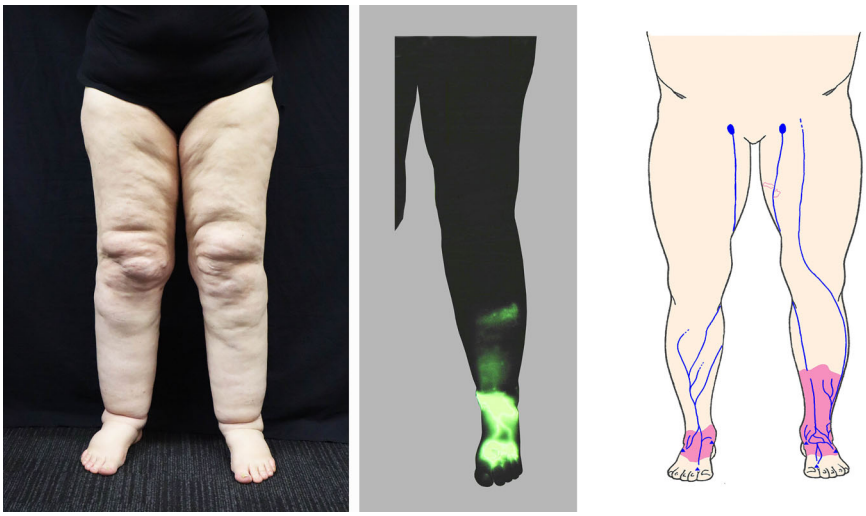

FIGURE 3 ICG lymphography image of a woman with lipoedema and concurrent lymphoedema in the left leg. (Type 3, Stage 4, from left; photo, montage of ICG lymphography images and schematic diagram). ICG lymphography demonstrated dermal backflow (pink shaded areas) in the distal half of the left leg (MDACC ICG Stage 1). ICG, indocyanine green; MDACC, MD Anderson Cancer Center.

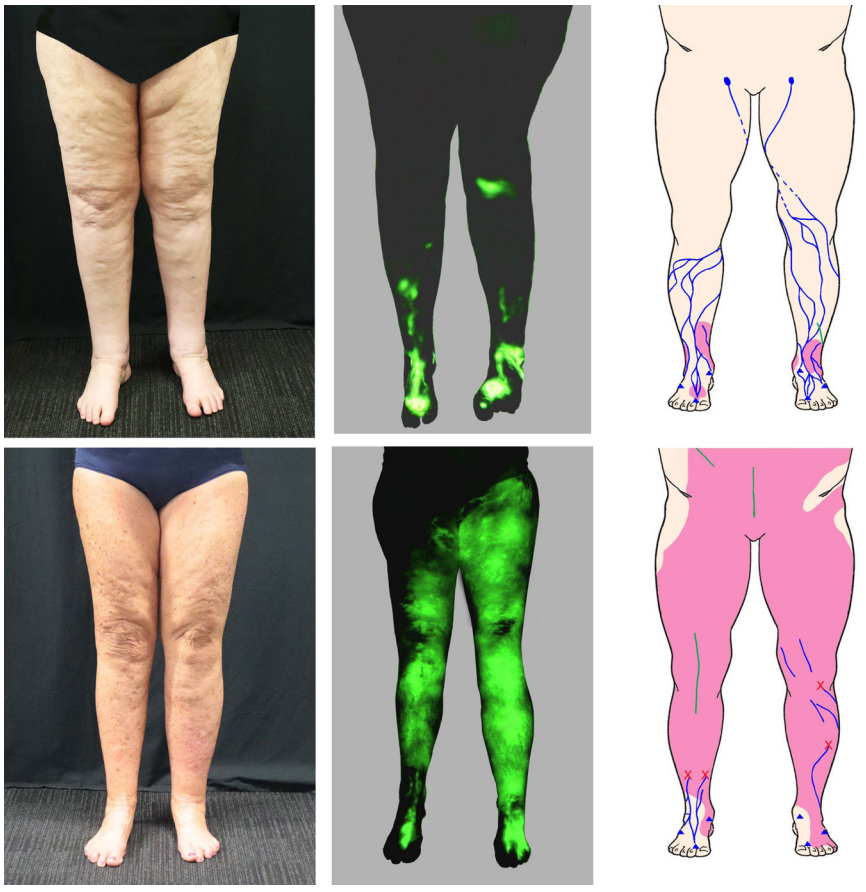

FIGURE 4 ICG lymphography in a woman with lipoedema (top row, Type V, Stage 3; right leg: MDACC ICG Stage 1, left leg: MDACC ICG Stage 1) and a woman with bilateral lymphoedema from our archival data (bottom row, right leg: MDACC ICG Stage 3, left leg: MDACC ICG Stage 4). From left: photo, montage of ICG lymphography images and schematic diagram (blue: lymphatic vessel, red: dermal backflow, green: surgical scar, triangle: ICG injection site, X: obstruction site). Leg shapes were almost identical between the two women. ICG lymphography demonstrated localized dermal backflow with no major structural changes in the superficial lymphatics in lipoedema (top row). In lymphoedema, extensive dermal backflow covered almost the entire legs (bottom row). ICG, indocyanine green; MDACC, MD Anderson Cancer Center. See ICG lymphography video for top row in Video S2 and for bottom row in Video S3.

4 | DISCUSSION

The aim of this study was to use the standardized ALERT ICG lymphography protocol to assess the presence of lymphoedema in a cohort of women with a clinical diagnosis of lipoedema. The results of this study showed that 85% of women presenting with a clinical diagnosis of lipoedema had linear lymphatic vessels and no evidence of dermal backflow (Figure 2, Videos S1 and S2). Localized dermal backflow at the ankle and shin was identified in a small number of women ($n = 4$). However, these images were unlikely to be determined as diagnostic signs of lymphoedema, rather they were considered as minor lymphatic damage associated with past local injury. These findings also supported our contention that the volume increase in the lower limbs was not pathologically caused by lymphoedema.

Only two of the 40 women included in this study were diagnosed with lymphoedema by ICG lymphography. Of these two, one had a background of previously diagnosed primary lymphoedema before lipoedema onset with an ICG lymphography pattern of primary

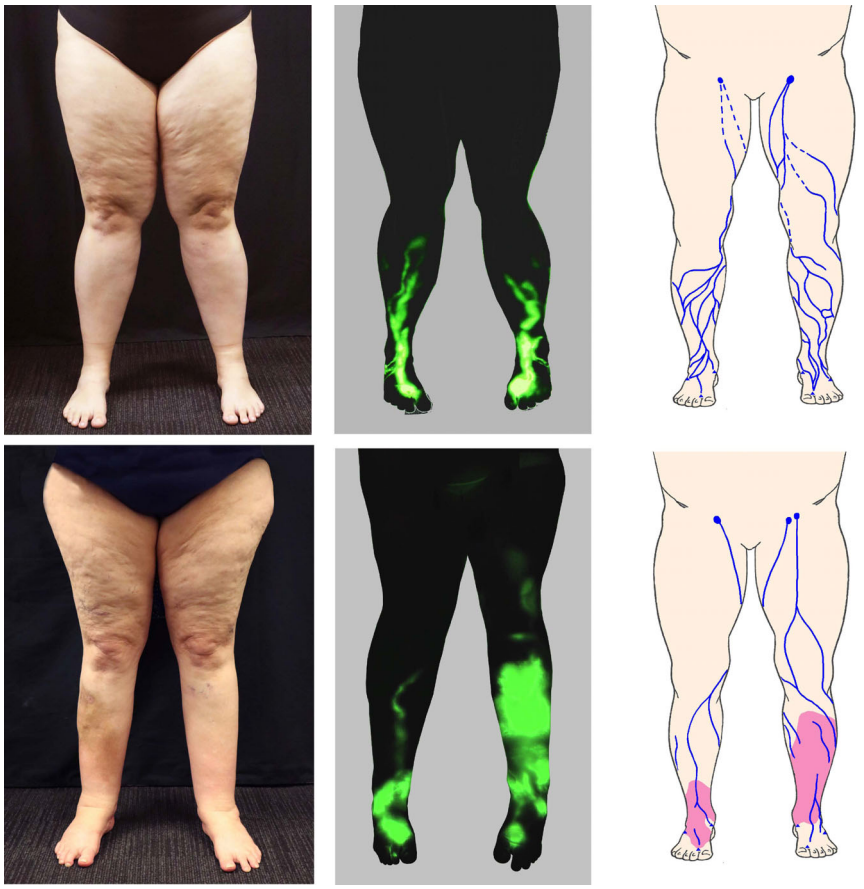

FIGURE 5 ICG lymphography image of a woman with lipoedema (top row, Type 2, Stage 3; right leg: MDACC ICG Stage 0, left leg: MDACC ICG Stage 0) and a woman with bilateral lymphoedema from our archival data (bottom row, right leg: MDACC ICG Stage 1, left leg: MDACC ICG Stage 3). From left: photo, montage of ICG lymphography images and schematic diagram (blue: lymphatic vessel, red: dermal backflow, triangle: ICG injection site). Leg shapes were very similar between the two women. ICG lymphography demonstrated no dermal backflow in lipoedema (top row). Dermal backflow areas were identified in lymphoedema (bottom row). ICG, indocyanine green; MDACC, MD Anderson Cancer Center.

lymphoedema evident. Therefore, only one of the 40 women with lipoedema (2.5%) had ICG lymphography evidence that might be suggestive of lipoedema-associated lymphoedema (Figure 3). However, the BMI for this individual was in the obese class 2 range. As the risk of lymphatic dysfunction increases with an elevated BMI,[27] it could be that the lymphoedema in this case was associated with elevated BMI which would then classify as obesity-related lymphoedema. Therefore, these two women may be considered as having concurrent conditions of lipoedema and lymphoedema rather than lymphoedema linked to lipoedema.

In the present study, BIS L-Dex® scores above 6.5 suggesting increased extracellular fluid accumulation were recorded for 13 of the 39 women measured (33%). However, 12 (92%) women with elevated L-Dex® scores had a BMI within the obese class 1 to class 3 ranges. Previous research has demonstrated an expansion of extracellular fluid in women with obesity compared with nonobese women.[28] Therefore, the elevated BIS L-Dex® scores observed in some women in the present study could potentially be due to obesity-related expansion of extracellular fluid rather than lymphoedema. Furthermore, orthostatic oedema may be primarily associated with lipoedema[1,10] and also may develop due to venous hypertension secondary to obesity, and the valvular incompetence of varicose veins which is commonly associated with lipoedema.[29] This orthostatic oedema which may also be recorded as an increased BIS L-Dex® score, can nevertheless be uncomfortable and cause heaviness similar to lymphoedema and typically responds well to management techniques such as compression, manual lymphatic drainage or sequential intermittent pneumatic compression pump use.

Although there was normal lymphatic morphology found on ICG lymphography for the majority of women in the present study, the functional capacity of normal lymphatics can be overloaded particularly in situations of increased peripheral venous stasis, reduced physical activity and obesity.[30] Lymphoedema is however assessed clinically by the presence of persistent pitting oedema and skin thickening and confirmed objectively by the presence of dermal backflow identified with ICG lymphography (Figures 4 and 5, Videos S2 and S3). These findings were not evident in the women with lipoedema in the present study, except for the two women diagnosed with lymphoedema who both demonstrated a positive Stemmer sign and pitting oedema in the foot (Figure 3). This provides support for the use of these two simple clinical signs in the diagnostic examination for women presenting with lipoedema.

The lymphatic vessels could not always be continuously tracked through the lower limbs during the ICG lymphography examination due to increasing depth of the overlying adipose tissue, however, normal vessels in the foot and ankle were clearly visualized (Figure 2, Video S1). At the popliteal region and inguinal region where there was less overlying adipose tissue, normal lymphatic vessels and lymph nodes were identified in the majority of women in this study. This is

consistent with previous research using ICG lymphography which also demonstrated no major lymphatic structural changes or dermal backflow in women with lipoedema.[31,32] In addition, spatial resolution of ICG lymphography rapidly deteriorates below the skin, which skews measurement of lymphatic vessel geometry or assessment of vessel dilation. Therefore, although the lymphatic vessels may seem dilated when they were deep to overlying adipose tissue, this was not considered to represent abnormal dilated lymphatic vessels[33] but rather were due to a known optical scatter property of ICG lymphography.[34]

The pathophysiology of lipoedema remains unclear. The putative causes include altered adipogenesis, microangiopathy, and disturbed lymphatic microcirculation. No specific biomarkers have yet been established, and diagnosis is currently made predominantly on clinical grounds.[13] It is frequently difficult distinguishing obesity or gynoid body habitus from lipoedema due to concurrent or overlaying clinical features. Many women with lipoedema mistakenly interpret swelling to be attributed to lymphoedema or at least a lymphatic insufficiency, or misinterpret oedema or fluid accumulation to be their main cause of increasing leg volume. The conservative treatment for lipoedema, often by therapists trained in lymphoedema management, is frequently undertaken as oedema management. This adds further to the controversy surrounding lymphoedema and lipoedema by conceptualizing a primary or concurrent underlying lymphatic abnormality causing oedema in lipoedema. This is not always due to the patients' interpretation of internet or informal information but is directly espoused by some surgeons undertaking liposuction and some therapists treating lipoedema as a lymphatic condition.[35]

The advantage of this study is that it proposes a potential objective imaging guideline to differentiate lipoedema from lymphoedema, with a subsequent translation to therapeutic management. The current limitation may be the cost of the ICG lymphography examination without a medical code for health-care benefits. This can result in selection of participants desirous of the investigation to demonstrate lymphatic compromise. There was ethical dilemma in recommending such an investigation very likely to provide normal lymphatic imaging and therefore not satisfying the participants' expectation.

5 | CONCLUSIONS

Women with lipoedema of the lower limbs and negative Stemmer sign on examination predominantly demonstrated normal lymphatic morphology when imaged by a standardized ICG lymphography procedure for lower limb assessment. Our findings suggest that lymphoedema should not be expected as a common concurrent or associated condition in women with lipoedema. The results of the current study also support the Stemmer sign as a simple and useful clinical examination sign of lymphoedema.

AUTHOR CONTRIBUTIONS

Helen Mackie: Conceptualization; data collection; formal analysis; writing – original draft; writing – review and editing. **Belinda Thompson**: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Hiroo Suami**: Conceptualization; data collection; formal analysis; images and medical illustrations; writing – review and editing. **Asha Heydon-White**: Data collection; writing – original draft; writing – review and editing. **Robbie Blackwell**: Data collection; writing – review and editing. **Fiona Tisdall Blake**: Data collection; writing – review and editing. **Louise A. Koelmeyer**: Conceptualization; project administration; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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