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REVIEW

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Diagnostic imaging in lipedema: A systematic review

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Summary

Background: Diagnosing lipedema remains a challenge due to its heterogeneous presentation, co-existing diseases, and the lack of objective diagnostic imaging.

Objective: This systematic review aims to outline the currently available diagnostic imaging methods to characterize lipedema in the legs along with their diagnostic performance.

Methods: PubMed, Embase, Google Scholar, Scopus, and Web of Science were searched. The quality assessment of diagnostic accuracy studies (QUADAS) tool was used for quality assessment.

Results: Thirty-two studies describing a total of 1154 patients with lipedema were included for final analysis. Features for lipedema have been defined using ultrasound (increased subcutaneous adipose tissue), lymphoscintigraphy (slowing of the lymphatic flow and a frequent asymmetry between the lower extremities), computed tomography (symmetrical bilateral soft tissue enlargement without either skin thickening or subcutaneous edema), magnetic resonance imaging (increased subcutaneous adipose tissue), MR lymphangiography (enlarged lymphatic vessels up to a diameter of 2 mm), and dual-energy X-ray absorptiometry (fat mass in the legs adjusted for body mass index (BMI) ≥ 0.46 or fat mass in the legs adjusted for total fat mass ≥ 0.384).

Conclusion: The diagnostic performance of currently available imaging modalities for assessing lipedema is limited. Prospective studies are needed to evaluate and compare the diagnostic performance of each imaging modality. Imaging techniques focusing on the pathogenesis of the disease are needed.

KEYWORDS
adipose tissue, diagnostic imaging, lipedema, lymphatic drainage

1 | INTRODUCTION

Lipedema is a term used for a disproportionate symmetric fat deposition in predominantly the lower extremities of women.[1,2] The diagnosis is based on clinical criteria as proposed by Wold et al.[3]: (a) occurrence almost exclusively in women, (b) bilateral and symmetrical nature with minimal involvement of the feet, (c) minimal pitting edema, (d) pain, tenderness, and (e) persistent swelling of lower extremities despite elevation or weight loss.

Based on distribution, five types and four clinical stages of lipedema have been described.[4–9]

In type I, lipedema fat tissue accumulates around the hips and buttocks (saddle bag phenomena); in type II, accumulation involves the area from hips to knees; and in type III, a hip to ankle phenotype

is observed. Approximately 30% of affected women have an additional involvement of arms (type IV), while it is rare to find fat dominating the calf region only (type V). These regional classifications are developed mainly for therapeutic follow-up purposes and have no pathophysiological basis.

Lipedema can be classified in four clinical stages based on morphological appearance:

- Stage I: Thickening and softening of the subcutis with small nodules; skin is smooth.
- Stage II: Thickening and softening of the subcutis with larger nodules due to increased fibrous tissue; skin texture is uneven ('mattress phenomenon').
- Stage III: Thickening and hardening of the subcutis with large nodules, disfiguring lobules of fat on the inner thighs and inner aspects of the knees/overhanging masses of tissue
- Stage IV: Lipolymphedema.

Clinical diagnosis is not always easy, despite the fact that lipedema is said to be a clinical entity, since mixed forms are frequent.[7] Lipedema, obesity, lymphedema, phlebolymphedema, and lipolymphedema are common causes of lower limb swelling, and the clinical distinction can be difficult.

This distinction is however important since the therapeutic approach will be different.

Currently, there is no consensus about the best imaging technique to assess lipedema.

This systematic review aims to outline the currently available diagnostic imaging methods to characterize lipedema along with their diagnostic performance when available.

2 | MATERIALS AND METHODS

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8]

2.1 | Literature search

For this systematic review, the electronic databases Embase, PubMed, Google Scholar, Scopus, and Web of Science were searched until July 29, 2023, to identify studies that reported on imaging criteria for lipedema along with their diagnostic performance, when available.

Keywords searched were lipedema, diagnostic imaging, ultrasound, lymphoscintigraphy, magnetic resonance imaging (MRI), computed tomography (CT) scan, dual-energy X-ray absorptiometry (DXA), and indocyanine green lymphography (supporting information Appendix).

The search captured review articles, case reports, original research articles, and any other articles relevant to lipedema. Article reference lists were also examined for applicable studies.

2.2 | Inclusion criteria and outcome measures

Studies were eligible if they reported on the following:

- imaging findings/criteria to assess lipedema of the legs
- a minimum number of 5 patients (10 lower extremities) with the clinical diagnosis of lipedema.

Articles in English, German, French, and Spanish were included. Commentaries or discussions, reviews, conference abstracts, case reports covering less than five patients, technical reports, and editorials were excluded.

2.3 | Study selection and data extraction

First, duplicate studies were excluded. Titles and abstracts were screened to assess eligibility. Subsequently, full-text articles of all potentially eligible studies were read to decide if the article met all predefined inclusion criteria. A consensus was reached by the two reviewers in case of discrepancies. In addition, the references of all included studies were manually checked for relevant studies. The Quality Assessment of Diagnostic Accuracy Studies 2 tool was used for quality assessment of the included studies.[9]

From the included studies, the following parameters were extracted: first author, year of publication, study design, sample size, imaging technique, findings in lipedema, and diagnostic accuracy.

3 | RESULTS

3.1 | Study selection

The initial database literature search identified a total of 2777 records, including 82 records from Embase, 67 records from PubMed, 2450 records form Google Scholar, 109 records from Scopus, and 69 records from Web of Science. Of these, 162 duplicate records were excluded. After screening the title and abstracts of 2615 records, 2573 records were excluded according to the inclusion and exclusion criteria. Subsequently, the full text of 39 studies was retrieved and read for eligibility. Three additional studies were found after manually screening the references of the included studies. Finally, **32** studies met the inclusion criteria and were included in this systematic review. The PRISMA flow diagram of the study selection is shown in Figure 1.

3.2 | Study characteristics

Thirty-two studies describing a total of **1154** patients with lipedema were included for final analysis.

Of these, 318 had undergone ultrasound, 446 lymphoscintigraphy, 31 CT scan, 81 MRI/MR lymphangiography, 123 dual-energy X-ray osteodensitometry, and 155 indocyanine green lymphography.

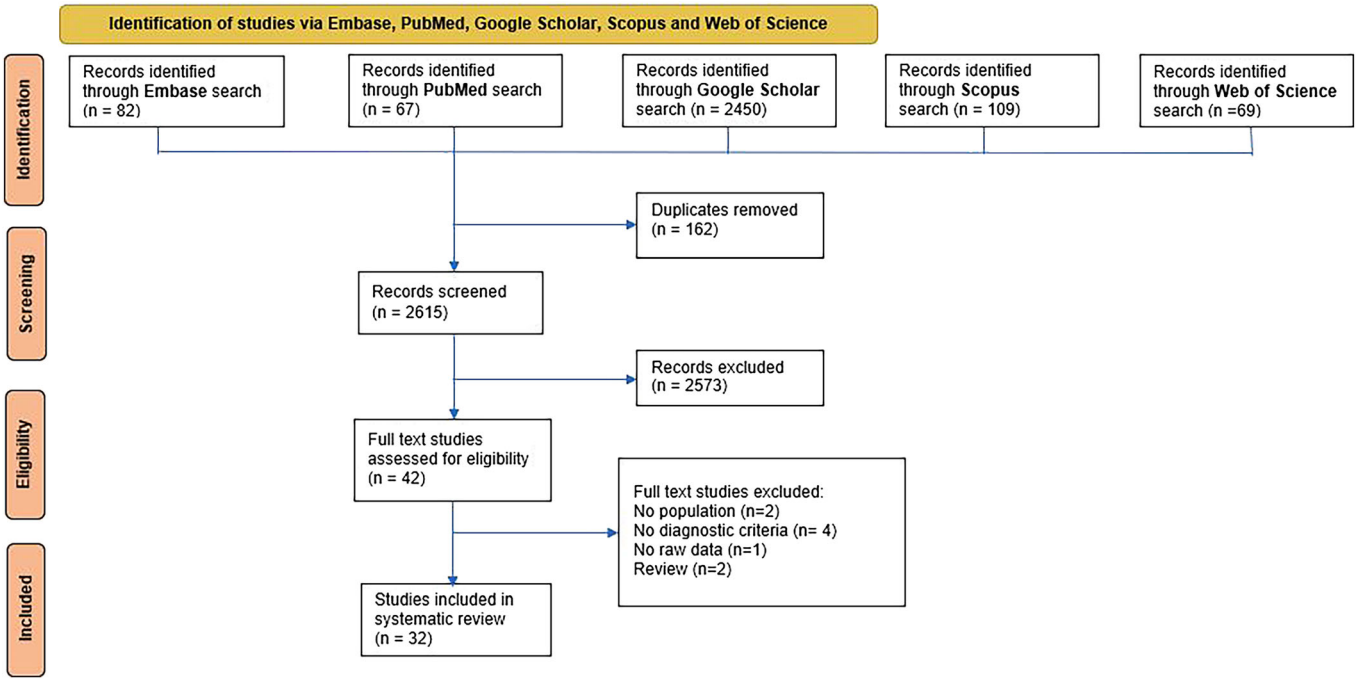

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Quality assessment according to quality assessment of diagnostic accuracy studies (QUADAS) criteria is presented in Table 1. The clinical characteristics used to identify lipedema varied among the studies (Table 2). Characteristics of the imaging studies and their diagnostic findings for lipedema are presented in Tables 3–9.

Seven studies prospectively evaluated ultrasound findings in lipedema (Table 3).[10–16] They all included a control population, which varied from lymphedema and obesity patients to healthy controls. There was variability with regard to the criteria for the clinical diagnosis for lipedema (Table 2). Cutis and subcutis thickness measurements were significantly increased in lipedema as compared with healthy controls. The study of Amato et al.[10] selected 63 patients with varicose veins associated with lipedema and showed excellent performance of ultrasound in measuring the thickness of pretibial subcutaneous fat, with an area under the curve (AUC) of 0.91 and a maximal sensitivity and specificity of 0.79 and 0.96, respectively, for a cutoff of 11.6 mm.

Eleven studies evaluated lymphoscintigraphy findings in lipedema (Table 4).[8,17–26] Six studies included a control population, which consisted of predominantly lymphedema patients or healthy controls.[17–19,24–26] In one study lipedema patients were compared with obese patients.[18] Only four studies used the criteria of Wold et al.[3] for the clinical diagnosis for lipedema (Table 2).[20,22,24,25] A delayed lymphatic transport was observed in five studies[20,23–26] and asymmetry in lymph transport in three studies[20,21,26].

Two studies evaluated CT findings in lipedema (Table 5).[27,28] Monnin et al.[27] used bilateral leg swelling together with a normal lymphoscingram and ultrasound as criteria for diagnosing lipedema, while the criteria were not further specified by Vaughan et al.[28] (Table 2). Both studies found an increased subcutaneous fat characteristic for lipedema.

Eight studies reported on MRI and three studies compared lipedema and lipolymphedema patients.[7,16,29–34] Lohrman and Duewell et al.[7,34] did not specify criteria for diagnosing lipedema. Both MRI and magnetic resonance lymphangiography (MRL) showed an increased subcutaneous fat layer in lipedema,[7,29–34] and MRL showed dilated distal lymphatic vessels (>2 mm) in lipedema in about 40% of cases (Table 6).[30,31,34]

Two studies evaluated DXA findings in lipedema (Table 7).[35,36] They both used criteria from Wold et al. for diagnosing lipedema and added some additional criteria. They both presented cutoff values for identifying lipedema.

Four studies evaluated indocyanine green findings in lipedema (Table 8).[19,37–39]

These studies revealed significant changes in superficial lymph flow in lipedema with slower lymph flow, higher number of abnormal lymphatic vessels, and higher fluorescent intensity in the skin,[19] dilation of lymphatic vessels, intravascular pooling, and greater propulsion rates.[39]

Overall, only three studies reported cutoff values for diagnosing lipedema, and five studies reported the diagnostic accuracy of imaging studies (Table 9).

4 | DISCUSSION

Lipedema is an enigmatic disease, and the clinical distinction between associated diseases like obesity, lymphedema, phlebolymphedema and lipolymphedema can be difficult.

Several diagnostic imaging methods can be used to characterize lipedema. Despite the availability of these imaging methods, they

TABLE 1 Quality assessment of all included studies based on QUADAS-2.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ultrasound							
Amato[10] 2021	High	Low	High	N/A	High	Low	High
Iker[11] 2019	Unclear	Low	Unclear	N/A	Unclear	Low	Unclear
Kasseroll[12] 2019	Low	Low	High	N/A	Low	Low	High
Hirsch[13] 2018	Low	Low	Unclear	N/A	Low	Low	Unclear
Marshall[14] 2011	Low	Low	High	N/A	Low	Low	High
Naouri[15] 2010	Low	Low	High	n/a	Low	Low	High
Dimakakos[16] 1997	High	Unclear	High	N/A	High	Unclear	High
Lymphoscintigram							
Ceylan[17] 2023	Low	Unclear	High	N/A	Low	Unclear	Unclear
Chachaj[18] 2023	Low	Low	High	N/A	Low	High	High
Zaleska[19] 2023	Low	High	Low	N/A	Low	Low	Low
Gould[20] 2020	Low	Low	Low	N/A	Low	Low	Low
Tartaglione[21] 2020	Unclear	Low	Unclear	N/A	Unclear	Low	Unclear
vd Pas[22] 2020	Low	Low	Low	N/A	Low	Low	Low
Forner-Cordeiro[23] 2018	Low	Low	High	N/A	Low	Low	High
Boursier[24] 2004	Low	Low	Low	N/A	Low	Low	Low
Harwood[25] 1996	High	Unclear	Low	N/A	Low	Low	Low
Bilanci[26] 1995	High	Low	High	N/A	High	Low	High
Weissleder[8] 1995	Unclear	Low	Unclear	N/A	Unclear	Low	Unclear
CT							
Monnin[27] 2002	High	High	High	N/A	High	High	High
Vaughan[28] 1990	High	Low	Unclear	N/A	High	Low	Unclear
Magnetic resonance imaging/Magnetic resonance lymphangiography							
Taylor[29] 2023	Low	Low	Low	N/A	Low	Low	Low
Crescenzi[30] 2022	Low	Low	Low	N/A	Low	Low	Low
Cellina[31] 2020	Low	Low	Low	N/A	Low	Low	Low
Crescenzi[32] 2020	Low	Low	Low	N/A	Low	Low	Low
Crescenzi[33] 2018	High	Low	Low	N/A	Low	Low	Low
Lohrman[34] 2009	Unclear	Low	Unclear	N/A	Unclear	Low	Unclear
Dimakakos[16] 1997	High	Unclear	High	N/A	High	Unclear	High
Duewell[7] 1992	Unclear	Low	Unclear	N/A	Unclear	Low	Unclear
Dual-energy X-ray absorptiometry							
Buso[35] 2022	Low	Low	Low	N/A	Low	Low	Low
Dietzel[36] 2015	Low	Low	Low	N/A	Low	Low	Low
Indocyanine green lymphography							
Mackie[37] 2023	Low	High	Low	N/A	Low	High	High
Buso[38] 2022	Low	Low	Low	N/A	Low	Low	Low
Rasmussen[39] 2022	Low	Low	Low	N/A	Low	Low	Low

Note: Quadas-2 indicates the quality assessment of diagnostic accuracy studies.

are not routinely incorporated since lipedema is presumed to be a clinical diagnosis. The diagnostic value of these imaging techniques has therefore not been thoroughly evaluated in the diagnosis of lipedema. To our knowledge, this is the first systematic review to provide an overview of the currently available imaging modalities for lipedema.

TABLE 2 Definition of lipedema in the included studies.

Study	Bilateral symmetric leg swelling	Feet not involved	Pain	Easy bruising	Resistant to weight loss	Minimal pitting oedema	Obesity	Disproportion Upper vs lower extremity
Ultrasound								
Amato[10] 2021	+	+	+	+				
Iker[11] 2019								
Kasseroll[12] 2019			+	+	+			+
Hirsch[13] 2018								
Marshall[14] 2011	+	+	+				+	
Naouri[15] 2010 **≥ 4 criteria**	+		+				+	
Dimakakos[16] 1997	+	+					+	
Lymphoscintigram								
Ceylan[17] 2023								
Chachaj[18] 2023			+	+				+
Zaleska[19] 2023	+				+			
Tartaglione[21] 2020								
vd Pas[22] 2020	+	+	+	+	+	+		
Gould[20] 2019	+	+	+	+	+	+		
Forner-Cordeiro[23] 2018 **≥ 3 criteria**	+	+	+	+				+
Boursier[24] 2004	+	+	+		+	+	+	
Harwood[25] 1996	+	+		+	+	+		
Bilanci[26] 1995	+							
Weissleder[8] 1995								
Computed tomography								
Monnin[27] 2002	+						+	
Vaughan[28] 1990								
Magnetic resonance imaging/MRL								
Taylor[29] 2023	+		+	+		+		
Crescenzi[30] 2022			+	+				
Cellina[31] 2020	+	+	+	+	+	+		
Crescenzi[32] 2020	+	+		+		+		
Crescenzi[33] 2018	+		+	+		+		

TABLE 2 (Continued)

Study	Bilateral symmetric leg swelling	Feet not involved	Pain	Easy bruising	Resistant to weight loss	Minimal pitting oedema	Obesity	Disproportion Upper vs lower extremity
Lohrman[34] 2009								
Dimakakos[16] 1997	+	+					+	
Duewell[7] 1992								
Dual-energy-X-ray absorptiometry								
Buso[35]	+	+	+	+	+	+		+
Dietzel[36]	+	+	+	+	+	+		
Indocyanine green lymphography								
Mackie[37] 2023	+		+	+		+		
Buso[38] 2022	+		+	+	+	+		
Rasmussen[39] 2022								

TABLE 2 (Continued)

Study	Pain/discomfort resistant to elevation of limbs	Increased Sens to touch or limb fatigue	Positive family history of lipedema	Stemmer negative	Godet negative	No lower limb injury	Hypothermia	Hyper-mobility	Normal ultrasound of venous system
Ultrasound									
Amato[10] 2021	+	+		+	+				
Iker[11] 2019									
Kasseroll[12] 2019									
Hirsch[13] 2018									
Marshall[14] 2011									
Naouri[15] 2010 **≥ 4 criteria**			+	+		+			
Dimakakos[16] 1997				+					
Lymphoscintigram									
Ceylan[17] 2023									
Chachaj[18] 2023				+					
Zaleska[19] 2023									
Tartaglione[21] 2020									

TABLE 2 (Continued)

Study	Pain/discomfort resistant to elevation of limbs	Increased Sens to touch or limb fatigue	Positive family history of lipedema	Stemmer negative	Godet negative	No lower limb injury	Hypothermia	Hyper-mobility	Normal ultrasound of venous system
vd Pas[22] 2020									
Gould[20] 2019									
Forner-Cordeiro[23] 2018 **≥ 3 criteria**				+					
Boursier[24] 2004	+		+						
Harwood[25] 1996	+								
Bilanci[26] 1995				+			+		
Weissleder[8] 1995				+					
Computed tomography									
Monnin[27] 2002									+
Vaughan[28] 1990									
Magnetic resonance imaging/MRL									
Taylor[29] 2023			+	+				+	
Crescenzi[30] 2022			+					+	
Cellina[31] 2020									
Crescenzi[32] 2020			+	+				+	
Crescenzi[33] 2018			+	+				+	
Lohrman[34] 2009									
Dimakakos[16] 1997				+					
Duewell[7] 1992									
Dual-energy-X-ray absorptiometry									
Buso[35]	+	+							
Dietzel[36]	+								
Indocyanine green lymphography									
Mackie[37] 2023			+						
Buso[38] 2022									
Rasmussen[39] 2022									

TABLE 3 Ultrasound studies reporting on lipedema findings.

Study	Study design	Population		Mean age (years)		Criteria for lipedema	Duration of disease (years)	BMI		Cutis + subcut thickness measurements (mm)	Cut off for lipedema
		Lipedema	Control	Lip	Control			Lipedema	Control		
Amato[10] 2021	P	63 patients with varicose veins associated with lipedema	27 controls	46.2 ± 3.6	48 ± 4.5	See Table 1	NR	30.0 ± 1.4	27.4 ± 1.5	Thigh Lip 20.9, C 12.7 Lateral leg Lip 13.8, C 6.4 Pretibial Lip 16.5, C 8.4	**Thigh ≥ 17.9** **Pretibial ≥ 11.6** **Lat leg ≥ 8.4**
Iker [11] 2019	P	12 stages I and II	10 Lymph 8 HC	41.8 (24–69)	Lymph 63.1 (21–83) HC 58.1 (21–80)	ISL stages I and II not further specified	NR	24.6	Lymph 24.2 HC 23.3	Lip thigh 28.7 Lymph 24.2 HC 13.5	-
Kasseroll[12] 2019	P	69	12 HC	37 ± 12.4	46.3 ± 12.4	See Table 1	NR	27.9 ± 5.6	31.3 ± 6.0	-	-
Hirsch[13] 2018	P	136	42 LH 30 obesity 36 HC	39.3 ± 12.7	LH 42.9 ± 12.2 Ob 41.1 ± 11.7 HC 50.9 ± 17.7	NS	NR	29.8 ± 6.7	LH 30.7 ± 7.5 Ob 46.0 ± 10.1 HC 22.4 ± 3.2	5–8 cm above med malleolus Lip 22 ± 8 LH 19 ± 7 Obesity 27 ± 9 HC 10 ± 4	-
Marshall[14] 2011	P	24	38 HC	40.7 ± 11.7	45.8 ± 12.9	F, symmetric, leg enlargement w/o feet, resistant adiposity, pain	NR	27.7 ± 3.7	23.5 ± 2.7	Above medial malleolus Lip 16.5 ± 4.1 HC 11.2 ± 2.9	**≥ 16 mm**
Naouri [15] 2010	P	8 females	16 lymph 8 healthy	NR	NR	Swollen legs and ≥ 4 clinical criteria; see Table 1	NR	NR	NR	-	-
Dimakakos[16] 1997	P	6 females	10 lymph, 5M, 5F - 2 stage I - 5 stage II - 3 stage III	53.3 (18–64)	39.2 (20–66)	Overweight, stemmer sign negative feet free of edema	4–50	NR	NR	Thigh: Lip 24.5 ± 12.5 Lymph 12.9 ± 4.1	-

Abbreviations: C, control; H, healthy; HC, healthy control; LH, lipohypertrophy; Lip, lipedema; Lymph, lymphedema; NR, not reported; NS, not specified; Ob, obesity; P, prospective.

TABLE 4 Lymphoscintigraphy studies reporting on lipedema findings.

Study	Study design	Population		Mean age (range)		Criteria for lipedema	BMI	
		Lipedema	Control	Lipedema	Control		Lipedema	Control
Ceylan[17] 2023	R	34	40 lymph	31.25 (29.24–33.46)		NS	-	-
Chachaj[18] 2023	P	51 43.1% stage I 45.1% stage II 11.8% stage III	31 obese	43.3 ± 13.6	44.7 ± 13.5	See Table 1	31.8 ± 8.2	36.0 ± 7.2
Zaleska[19] 2023	P	34	23 HC	47.7 ± 13.9	48 ± 18.5	See Table 1	31.2	29.7
Gould[20] 2020	P	19 - 5 stage I - 4 stage II - 4 stage III - 6 stage IV	-	54.8 ± 12	-	Wold et al.	35.9 ± 10.7	-
Tartaglione[21] 2020	P	54	-	46 ± 19	-	NS	32.3 (21.7–58.5)	-
vd Pas[22] 2020	P	117	-	40.9 (21–64)	-	Wold et al.	-	-
Forner-Cordeiro[23] 2018	P	83 - 33 stage I - 21 stage II - 23 stage III - 6 stage IV 11 type 2 62 type 3 9 type 4 1 type 5	-	49.7 (18–80)	-	See Table 1	29.9 (28.4–31.3)	-
Boursier[24] 2004	P	15	15 lymph, 12F,3M	31.5 ± 15	28.7 ± 12.6	Wold et al.	35.1 ± 9	23.4 ± 3
Harwood[25] 1996	P?	10	12 HC 35 lymph			NS	-	-
Bilanci[26] 1995	P	12	5 lymph 5 controls	37	37	Symmetric swelling, hypothermia of skin, Stemmer -, plantar positioning alterations	-	-
Weissleder[8] 1995	R	17	-	-	-	Stemmer negative	-	-

Abbreviations: P, prospective, R, retrospective; lymph, lymphedema; HC, healthy control; lip, lipedema; F, female; M, male; NS, not specified; NR, not reported, LV, lymphatic vessel.
TI, transport index (< 10 minutes is considered normal). TI more than 10 denoting pathologic lymphatic transport, DCF, distal collateral flow.

TABLE 4 (Continued)

Study	Asymmetry in lymph transport	Delayed uptake	Disturbed inguinal uptake	Alterations	TI <10	Mean TI (range)
Ceylan[17] 2023	-	-	-	DCF 28/34 lip 7/40 lymph	-	-
Chachaj[18] 2023	NR	NR	0%	Minor 76.5% lip 93.5% obesity Moderate 37.3% 51.6%	NR	NR
Zaleska[19] 2023	NR	NR	NR	>3 LV calf 56% lip 13% HC 47% dilated LV 26% tortuous LV in Lip vs 4.3% and 0% in HC	-	-
Gould[20] 2020	Yes	36.8	5%	-	36.8%	stages I and II: 9.7 (SD 5.6) stages III andIV: 15.1 (SD 9.7)
Tartaglione[21] 2020	Yes	NR	7.5%	Tortuous course + coll flow 75% Collaterals or popliteal uptake 49%	38.9%	9 (3–16)
vd Pas[22] 2020	-	NR	R leg 60.3% Left leg 64.7%	-	NR	NR
Forner-Cordeiro[23] 2018	NR	47%	NR	-	NR	NR
Boursier[24] 2004	-	Yes	1/15		NR	NR
Harwood[25] 1996	-	Yes	NR		NR	NR
Bilanci[26] 1995	Yes	Yes	NR		NR	NR
Weissleder[8] 1995	NR	NR	8.8%		70.6%	NR

Abbreviations: P, prospective, R, retrospective; lymph, lymphedema; HC, healthy control; lip, lipedema; F, female; M, male; NS, not specified; NR, not reported, LV, lymphatic vessel.
TI, transport index (< 10 minutes is considered normal). TI more than 10 denoting pathologic lymphatic transport, DCF, distal collateral flow.

TABLE 5 CT scan studies reporting on lipedema findings.

Author	Study design	Population		Mean age	BMI	Criteria for lipedema	Findings in lipedema
		Lipedema	Control group				
Monnin[27] 2002	P	20	44 Lymph 12 DVT 34 normal	NR	NR	Bilateral leg swelling with normal LSG and US	Increased sc fat without either skin thickening or sc edema
Vaughan[28] 1990	R	11	9 Lymph, 5F, 4 M	NR	NR	NS	Increased sc fat

Abbreviations: CT, computed tomography; DVT, deep venous thrombosis; LSG, lymphoscintigram; lymph, lymphedema; NR, not reported; NS, not specified; P, prospective, R, retrospective; sc, subcutaneous; US, ultrasound.

As lipedema is often misdiagnosed with lymphedema and to exclude any damage to the lymphatic vessels, diagnostic tests performed in lymphedema are being used in lipedema. The imaging techniques primarily focus on quantitative measurements and visual assessment of the subcutaneous fat and the lymphatic system. However, diagnostic imaging modalities that adequately capture qualitative factors specific to the pathogenesis of lipedema (extracellular matrix remodeling, inflammation, fibrosis) are lacking.

4.1 | Ultrasound

High-frequency ultrasonography is a noninvasive cost-effective tool that can be used to evaluate the skin and subcutaneous thickness and echogenicity. However, it is highly operator dependent, and it cannot visualize the individual lymphatics. It can be of great value to distinguish lipedema from lymphedema.[11,15,16] Lymphedema is associated with increased skin thickness and dermal hypoechogenicity, while lipedema is associated with increased thickness and hypoechogenicity of the subcutaneous adipose tissue in the limb.

Marshall and Schwahn-Schreiber[40] proposed an ultrasound-based classification of lipedema severity, measuring the thickness of the dermis and subcutaneous tissue 6 to 8 cm above the medial malleolus as follows: 12–15 mm, low grade lipedema; 15–20 mm, moderate lipedema; >20 mm, clear lipedema; and >30 mm, pronounced lipedema. In a population of 24 women with lipedema, they found the median thickness of the subcutis and cutis to be 16 mm versus 11 mm in women without lipedema.

Amato et al.[10] proposed measurements of subcutaneous tissue thickness, using a high-frequency linear transducer, at predefined zones of the limbs, considering the existence of different distributions of lipedema in the lower extremities. For the diagnosis of lipedema, a cutoff value of 11.7 mm for pretibial region thickness measurements was suggested (sensitivity 79%, specificity 96%), followed by a cutoff value of 17.9 mm for thigh (sensitivity 67%, specificity 94%) and a cutoff of 8.4 mm for lateral leg thickness (sensitivity 78%, specificity 84%).[10]

Ultrasonography can be performed in very overweight subjects, unlike CT or MRI, where there are weight and size limitations based on the machine.

4.2 | Lymphoscintigraphy

Lymphoscintigraphy represents the current gold standard in the evaluation of the lymphatic pathways. It is helpful to exclude lymphatic dysfunction when assessing leg edema or enlargement.

Radioactive nanocolloid is injected intradermally into web spaces of the feet. Tracer uptake into the lymphatic tissue is followed with sequential gamma imaging in rest and after movement. In patients with abnormal lymphatic function, stasis of dye in the foot or reflux of dye into the tissues of the extremity can be observed.

Lymphoscintigraphy provides low spatial and temporal resolution to accurately outline the internal anatomy of the lymphatic vessels.[41–45] Furthermore, the long acquisition times make it uncomfortable for the patients. The colloid binding tracer is very specific for the lymphatic system.[44]

Patients with lipedema will usually show normal lymphatic flow and uptake but may be slower overall compared with that of normal individuals.[20,22,25,46–48] A recent prospective study involving 83 women with a diagnosis of lipedema demonstrated the presence of abnormal lymphoscintigraphy findings (light to moderate delay in transportation and asymmetric distribution) in 47% of the patient population.[23]

More severe lipedema may be associated with greater lymphatic transport abnormalities.[20] A frequent asymmetry between the lower extremities is noticed in the lymphoscintigraphic findings in contrast to the bilateral clinical presentation of the disease.[49] Depending on the pattern of the adipocyte tissue expansion in each limb, different degrees of lymphatic transport abnormalities may be observed. Interestingly, Van de Pas et al.[22] found a symmetrical lymphatic function after liposuction. Weissleder et al.[8] proposed that lymphoscintigraphy should be performed in lipedema to prove or exclude damage of the lymphatics and before liposuction to exclude a lymph drainage abnormality.

Chachaj et al.[18] demonstrated similar lymphoscintigraphic alterations (e.g., additional lymphatic vessels and popliteal lymph nodes, indicating an overload of the lymphatic system rather than insufficiency), within lower limbs of women with lipedema and obesity. Therefore, lymphoscintigraphy is not a diagnostic tool to distinguish lipedema from obesity.

TABLE 6 MRI/MRL scan studies reporting on lipedema findings.

Author	Study design	Imaging	Population		Mean age (range) in years		BMI	
			Lip	C	Lip	C	Lip	C
Taylor[29] 2023	P	MRI	15	13 HC	43.2 ± 10	42.2 ± 13.5	30.3 ± 4.3	28.8 ± 4.6
Crescenzi[30] 2022	P	MRL	14 3 stage I 10 stage II, 1 stage III	12 LL 8 lymph 14 HC	41.9 ± 10.7	LL44.5 ± 9.8 Lymph 54 ± 6.4 HC 42.8 ± 13.2	30.5 ± 4.5	LL 30.3 ± 4.3 Lymph 28.3 ± 6.3 HC 28.8 ± 4.4
Cellina[31] 2020	P	MRL	11 8 stage I 3 stage II	11 LL	33.2 ± 7	39 ± 12	31.2 ± 1.1	31.4 ± 1.2
Crescenzi[32] 2020	P	MRI	15 3 stage I 8 stage II 4 stage III	14 HC	43.2 ± 10	42.8 ± 13.2	30.3 ± 4.4	28.8 ± 4.4
Crescenzi[33] 2018	P	MRI	10	11 HC	44.0 ± 12.5	45.4 ± 12.1	30.6 ± 4.5	33.0 ± 7.6
Lohrman[34] 2009	P	MRL	5	8 LL	39 (12–71)		NR	NR
Dimakakos[16] 1997	P	MRI + US	6	12 HC: 3 M, 9F	53.5 (18–64)	36.8 (25–58)	NR	NR
Duewell[7] 1992	P	MRI	5	5 lymph: 4F, 1 M 4 PE: 3F, 1 M	47	36 lymph	29.5	28 lymph

Abbreviations: C, control; F, female; HC, healthy control; Lip, lipedema, LL, lipolymphedema; Lymph, lymphedema; M, male; NR, not reported; NS, not specified; P, prospective; PE, phlebedema; SAT, subcutaneous adipose tissue.

TABLE 6 (Continued)

Author	Duration of swelling		Criteria for lipedema	Increased subcutaneous fat		Dilated distal lymphatic vessels (>2 mm)		High signal intensity areas	
	Lip	C		Lip	C	Lip	C	Lip	C
Taylor[29] 2023	NR	NR	See Table 1	SAT 7.52 ± 2.30 ml	SAT 4.47 ± 1.88 ml				
Crescenzi[30] 2022	NR	NR	See Table 1	7.06 ± 2.35 ml	LL 5.75 ± 2.18 ml Lymph 4.84 ± 2.39 ml HC 3.97 ± 1.75 ml	36%	33% LL 88% lymph	36% focal 36% diffuse	LL 42% focal 33% diffuse lymph 62% focal 38% diffuse
Cellina[31] 2020	13.3 ± 7.4	14.5 ± 5.9	Wold et al.	11/11 (100%)	11/11 (100%)	2/11 (36.3%)	10/11 (90.9%)	0/11 (0%)	11/11 (100%)
Crescenzi[32] 2020	NR	NR	See Table 1	SAT calf 6.85 ± 2.30 mm^2 Fat/water ratio 1.03 ± 0.37	SAT calf 3.97 ± 1.75 mm^2 Fat/water ratio 0.56 ± 0.21	NR	NR	Skin sodium 16.3 ± 2.6 Muscle sodium 20.3 ± 3.0	Skin sodium 14.4 ± 2.2 Muscle sodium 18.3 ± 1.7
Crescenzi[33] 2018	NR	NR	See Table 1	SAT calf 11.9 ± 3.1 mmol/L Fat/water ratio 1.2 ± 0.48	SAT calf 9.4 ± 1.6 mmol/L Fat/water ratio 0.63 ± 0.26			Skin sodium 14.9 ± 2.9 mmol/L	Skin sodium 11.9 ± 2.0 mmol/L
Lohrman[34] 2009	NR	NR	NS	10/10 (100%)	16/16 (100%)	4/10 (40%)	8/16 (50%)	0/10 (0%)	16/16 (100%)
Dimakakos[16] 1997	NR	NR	Overweight Stemmer-feet free of edema	Yes	NR	NR	NR	NR	NR
Duewell[7] 1992	NR	NR	NS	Yes	NR	NR	NR	NR	NR

Abbreviations: C, control; F, female; HC, healthy control; Lip, lipedema, LL, lipolymphedema; Lymph, lymphedema; M, male; NR, not reported; NS, not specified; P, prospective; PE, phlebedema; SAT, subcutaneous adipose tissue.

TABLE 7 DXA findings in lipedema.

Author	Study design	Population		Mean age		BMI		Criteria for lipedema	DXA criteria for lipedema
		Lipedema	Control group	Lipedema	Control	Lipedema	Control		
Buso[35]	R	74 3 type I 11 type II 29 type III 31 type IV 14 stage I 39 stage II 19 stage III 2 stage IV	148	40 ± 12	41 ± 12	31.3 ± 8.9	30.7 ± 6.8	See Table 1	Legs FM/total FM ≥ 0.384 Sensitivity 0.95 Specificity 0.73
Dietzel[36]	P	49	78	Reported per BMI				See Table 1	Legs FM/BMI ≥ 0.46 Sensitivity 0.87 Specificity 0.68

Abbreviations: BMI, body mass index; DXA, dual-energy X-ray absorptiometry; FM, fat mass; P, prospective, R, retrospective.

4.3 | CT scan

CT is a noninvasive imaging study that can be used to evaluate patients with enlarged extremities. As with ultrasonography, the affected skin and the subcutaneous tissue layers can be imaged. Lipedema patients present with homogeneous enlargement of the soft tissues without skin thickening, subcutaneous edema, or muscle hypertrophy.

Monnin et al. showed excellent performance of CT for diagnosing lipedema with a sensitivity of 100% and a specificity of 95%. However, diagnostic cutoff values were not presented in their study. CT is fast and can help to differentiate different causes of leg edema. Radiation exposure is, however, a major drawback. Furthermore, there is a table weight limit (205 kg), with a maximum width restriction of 60 cm. Also, lymphatics cannot be visualized.

4.4 | MR imaging

MRI and its modified form, MRL, are valuable to evaluate the lymphatic circulation when lymphatic involvement is unclear.

MR imaging provides a superior quality of soft tissue imaging, giving information about the distribution of fluids and the degree of fibrosis in the subcutaneous fat.[16] Duewell et al.[7] indicated that MRI can show diffuse fatty hypertrophy in patients with lipedema.

Lipedema is characterized by an increased layer of subcutaneous fat without changes in signal intensity between T-2 and T-1 weighted images, confirming that the tissue does not contain excess fluid.[7,16] Crescenzi et al. demonstrated elevated tissue sodium by multinuclear MRI in patients with lipedema.[32,33]

A drawback of MRI is the weight limit of the machine (180 kg), with a maximum restriction width of 60 cm. Furthermore, claustrophobia is an exclusion criterium.

4.5 | MR lymphangiography

MRL requires injection of a contrast agent (gadolinium) into the skin of the forefoot in order to evaluate the lymphatic circulation. MRL is an accurate minimally invasive imaging modality with a high resolution to delineate pathologically modified lymphatic pathways. It is useful to distinguish lipedema from lymphedema.

If the extent of lymphatic involvement is unclear at the initial clinical examination or requires a better definition for optimal therapeutic planning, MRL can identify the anatomic and physiological derangements of the lymphatic system.[42–44,50,51]

MR lymphangiography can further characterize pure lipedema by an increased layer of subcutaneous fat in the leg, with a maximum mean diameter (measured from the cutis to the epifascial facia) of 4.4 cm at the level of the lower leg and 7.7 cm at the level of the upper leg. Enlarged lymphatic vessels up to a diameter of 2 mm were found, indicating a subclinical status of lymphostasis, while enlarged lymphatic vessels were revealed up to a diameter of 3 mm in patients with lipolymphedema.[42]

Noninjection MR lymphangiography, through heavily T2-weighted and fat-suppressed sequences, is able to evaluate the subcutaneous soft tissues to delineate the presence, severity, and extent of lymphedema, as well as associated soft-tissue changes such as adipose deposition and fibrosis avoiding the need of contrast media injection.[52] It may have an important role in differentiating lipedema

TABLE 8 ICG Lymphography studies reporting on lipedema findings.

Study	Study design	Population		Mean age (range)		Criteria for lipedema	BMI	
		Lipedema	Control	Lipedema	Control		Lip	C
Mackie[37] 2023	R	40 14 stage I 12 stage II 11 stage III 2 stage IV	-	50.1 ± 13.8	-	See Table 1	35.1 ± 9.6	
Zaleska[19] 2023	P	50 - 6 stage I - 29 stage II - 15 stage III	50 HC	47.7 ± 13.9	48 ± 18.5	See Table 1	31.2	29.7
Buso[38] 2022	R	45 10 stage I 22 stage II 13 stage III	-	39 ± 10.5	-	See Table 1	27.4 (25.6–32.7)	-
Rasmussen[39] 2022	P	20 8 stage I 11 stage II 1 stage III	9 HC	40.5 (23–48)	43 (30–58)	NR	29.3 (21.4–36.0)	30.3 (23.5–37.6)

Abbreviations: BMI, body mass index; C, control; HC, healthy control; Lip, lipedema, LV, lymphatic vessels; NR, not reported; $T10^{I}$, distance (cm) covered by dye at 10 min; $T25^{I}$, distance (cm) covered by dye at 25 min.

TABLE 8 (Continued)

Study	Slower flow of ICG dyed lymph	LV in lower calf	>3 visualized LV	Abnormal LV	Fluorescent intensity
Mackie[37] 2023	NR	NR	NR	87.5% no dermal backflow	NR
Zaleska[19] 2023	Yes Upper calf level reached by 8% lip vs 56% control	5 (83.3%) stage I, 21 (72.4%) stage II 5 (33.3%) stage III	Higher number in lipedema vs controls	Lower calf foggy 54% Dilated 62% vs *14% in control* Confluent 12% Upper calf 23% foggy 25% dilated 2% lazy 7% intermittent 6% dilated	Higher in lipedema
Buso[38] 2022	$T10^{I} = 0.46$ $T25^{I} = 0.79$	NR	NR	NR	NR
Rasmussen[39] 2022	NR	NR	NR	98% abnormal: Segmented, Tortuous dilated vessels, interstitial accumulation No Dermal backflow	Active lymphatic pumping higher pumping rates (events/min) stage 1: 1.4 stage 2: 1.4 stage 3: 1.8 HC 0.4 events/min

Abbreviations: BMI, body mass index; C, control; HC, healthy control; Lip, lipedema, LV, lymphatic vessels; NR, not reported; $T10^{I}$, distance (cm) covered by dye at 10 min; $T25^{I}$, distance (cm) covered by dye at 25 min.

TABLE 9 Studies reporting the diagnostic accuracy of imaging studies for lipedema.

Author	Imaging	Optimal cutoff value (mm) for diagnosing lipedema	AUC	Sensitivity	Specificity
Amato[10] 2021	Ultrasound	Thigh thickness ≥17.9 mm	0.89	0.67	0.92
		Pretibial thickness ≥11.7 mm	0.91	0.79	0.96
		Lat leg thickness ≥8.4 mm	0.89	0.76	0.80
Ceylan[17] 2023	LSG	Distal collateral flow No cutoff values	NR	0.80	0.80
Buso[35] 2022	DXA	Legs FM/total FM ≥ 0.384	0.90	0.95	0.73
Dietzel [36] 2015	DXA	Legs fat mass per BMI (kg m ^{2}) ≥ 0.46	0.82	0.87	0.68
Monnin [27] 2002	CT	Symmetrical bilateral soft tissue enlargement without either skin thickening or sc edema. No cutoff values	NR	1.0	0.95

Abbreviations: AUC, area under the curve; BMI, body mass index; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; FM, fat mass; LSG, lymphoscintigram; NR, not reported.

from lymphedema and in evaluating mixed forms of lipedema such as lipolymphedema and lipophlebolymphedema.

MRL is free of radiation and depicts deeper lymphatic channels with higher resolution. It evaluates the lymphatic system in a morphological and functional way. However, venous contamination could be a major obstacle in image interpretation. Furthermore, MRL is costly and potentially patient-unfriendly, because the acquisition time is approximately 1 h and 15 min.[52] The intracutaneous injection of gadolinium is still off-label and can cause patient discomfort and local reactions.[31]

4.6 | DXA

DXA, measuring regional body composition, provides quantification and distribution information about total and regional fat, lean, and bone mass, thus representing a useful tool for diagnosis, staging, and follow-up of lipedema patients.[36]

Dietzel et al. found that fat mass in the legs adjusted for BMI is the best index for diagnosing lipedema, with a cutoff value of 0.46 (sensitivity 87%, specificity was 68%).[36] However, BMI analysis may be misleading since it considers total weight without considering regional fat distribution, which is a hallmark of lipedema.[35] Buso et al. therefore optimized diagnostic efficacy by dividing the amount of leg fat mass by total fat mass and presented this index with a cutoff value of 0.383 (sensitivity 95%, specificity of 73%).[35]

Body composition measurement with DXA is an attractive option because of the available data, its noninvasive character, low price, and very low radiation exposure (< 10 lSv for a whole-body DXA scan) compared with CT or MRI scan.[53] Furthermore, it is a fast exam, and results can be obtained for the whole body or by region of interest.[54] It allows a precise analysis of three components via a whole-body scan: the total body fat mass, the total body lean mass, and the bone mineral content.

The disadvantage is that DXA cannot differentiate between water and fat component.

4.7 | Indocyanine green lymphography

Indocyanine green lymphography is an emerging imaging technique that allows for the visualization of superficial individual lymphatic vessels along the limb, observation of the rate of formation and drainage of tissue fluid/lymph, and places of fluid accumulation in the subcutaneous tissue (on the depths of 15–20 mm) in real time. About 80% of lymph in the limb travels through superficial lymphatic vessels, which are specifically explored by ICG.[55]

ICG lymphography has the advantage of being able to diagnose lymphedema with higher sensitivity and specificity compared with lymphoscintigraphy.[56] In lipedema patients, significant changes in superficial lymph flow were revealed, for example, slower lymph flow, higher number of abnormal lymphatic vessels and higher fluorescent intensity in the skin,[19] dilation of lymphatic vessels, intravascular pooling, and greater propulsion rates,[39] suggesting overloading of functional capacity of the lymphatic vessels, leading to a constantly increased accumulation of lymph in the interstitial space. However, major lymphatic structural changes or dermal backflow are absent in women with lipedema.[38,39]

Up to date, none of the imaging patterns found in lipedema patients are pathognomonic for the disease. Our pooled analysis, based on **32** studies, including **1154** patients, showed that there is no consensus about the best imaging technique to assess lipedema. Despite the availability of different imaging methods, none of these tools have been yet validated or implemented in clinical practice since lipedema is presumed to be a clinical diagnosis.

Only 4 out of the 32 studies included in this review presented data on the diagnostic performance for lipedema.[10,35,36,57] Although many studies have been performed on lymphoscintigraphy in

lipedema, none of them reported on diagnostic accuracy in these patients.

This study has several limitations: The QUADAS assessment showed that most of the included studies had multiple biases based on patient selection and reference standard (Table 1). Despite the internationally recognized criteria of Wold et al. for diagnosing lipedema, these were not systematically used in all studies for patient selection. Several studies presented modifications based on the existing criteria or used different criteria. Furthermore, there are no data in the literature regarding the ROC curves, sensitivity, and specificity of the clinical criteria used to diagnose lipedema, while this has been the gold standard for decades. It is thus difficult to compare a diagnostic imaging test with this gold standard, which introduces further bias.

The types and stages of lipedema were often not specified in the studies included. From the literature, it is clear that types I to III are the most frequent forms. The severity of the disease is presumed to influence the imaging findings. This could, however, not be objectified in this review since these data were often lacking in the original studies. Based on the results presented, no conclusions can be drawn on these subsets of patients.

The number of patients in the studies presented was often low, and a healthy comparison group was not always included. The population was often compared with lymphedema patients, in an attempt to differentiate these two disorders. This, however, makes it difficult to draw firm conclusions on criteria specific for lipedema. Another limitation of this systematic review is the heterogeneity between the included studies.

4.8 | Perspectives

Diagnostic imaging modalities that capture qualitative factors specific to the pathogenesis of lipedema are needed. Lipedema appears to manifest in dilated lymphatic vessels, and enhanced lymphatic pumping is observed, potentially in response to inflammatory adipose tissue. Additional studies, including assays of inflammatory markers, may reveal molecular differences in the onset of lipedema and lymphedema. These studies could also include MR lymphangiography with molecular MRI metrics of adipose tissue composition including sodium, which has previously demonstrated sensitivity for lipedema. Prospective studies incorporating these imaging techniques are needed to guide further treatment decisions, especially when clinical distinction from other diseases is difficult or when diagnosis co-exist. Strictly defined selection criteria for lipedema are important. A classification (of type and grade) should also be included in future studies together with a follow-up.

5 | CONCLUSION

The diagnostic performance of currently available imaging modalities is limited in providing accurate information about the presence of lipedema and qualitative factors specific to the pathogenesis of lipedema are lacking. Based on the proposed criteria of the currently available imaging modalities, prospective studies are needed to evaluate and compare the diagnostic performance of each imaging modality. Imaging techniques focusing on the pathogenesis of the disease are needed.

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SUPPORTING INFORMATION

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