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Ultrasound criteria for lipedema diagnosis

Alexandre Campos Moraes Amato[1,2], Dumitriu Zunino Saucedo[2], Keller da Silva Santos[2] and Daniel Augusto Benitti[3]

Abstract

Background: Lipedema is characterized by the deposition of abnormal fat in the lower and upper limbs bilaterally. It is a disease with high prevalence and genetic characteristics. Non-specific and non-quantified increases in the thickness of the subcutaneous tissue have previously been demonstrated using magnetic resonance imaging and computed tomography.

Objectives: To evaluate the thickness of the dermis and subcutaneous tissue in predetermined areas as a distinguishing feature between individuals with and without lipedema using ultrasound.

Methods: Ultrasound images of 89 female patients were analyzed, including patients undergoing clinical investigation for venous insufficiency or lipedema who underwent ultrasound evaluations at our institution. Patients were divided in two groups: with lipedema clinically diagnosed and those without lipedema. They underwent a common Doppler protocol for venous mapping to assess venous insufficiency associated with the evaluation of dermis and subcutaneous thickness at pre-defined points of the lower limbs.

Results: There were 63 patients with lipedema. Anterior thigh, pre-tibial and lateral aspect of the leg and supra-just medial malleolar region were significantly different. Supra-just medial malleolar region was significantly different with BMI above 25. An optimal cutoff value was calculated for the ultrasound diagnosis of lipedema using thickness of the dermis and subcutaneous tissues.

Conclusions: Studied criteria allow use of simple and reproducible ultrasound cutoff values to diagnose lipedema in the lower limbs. Pre-tibial region thickness measurement, followed by thigh and lateral leg thickness are recommended for the ultrasound diagnosis of lipedema.

Keywords

Varicose veins, ultrasound, lipedema, obesity, lymphedema

Introduction

Lipedema was described in Brazil by Moraes as *lipophilia membralis,* preferential fat deposition in lower limbs.[1] It is characterized by the deposition of abnormal fat in the lower and upper limbs bilaterally, and may be accompanied by complaints of orthostatic edema in women after puberty.[2] The pathophysiology of lipedema is poorly understood; nevertheless it is described as lymphatic compromise in its initial stages,[3] and as frank lymphatic damage in the final stage of lipolympedema.[4] It is a disease with a high prevalence in the population, estimated at 11% of the female population by Földi et al.[5] Lipedema has genetic characteristics[6] and a clear hormonal influence resulting in chronic low-grade inflammatory symptoms.[2] Despite its distinct nature, it is often confused with more commonly diagnosed diseases such as

[1]Chair of Vascular Surgery, University of Santo Amaro, São Paulo, Brazil
[2]Chair of Vascular Surgery, Amato – Institute of Advanced Medicine, São Paulo, Brazil
[3]Department of Vascular Surgery, Medical Valens Center, Campinas, Brazil

Corresponding author:
Alexandre Campos Moraes Amato, Amato - Instituto de Medicina Avançada, Av. Brasil, 2283 - Jardim América - São Paulo CEP 01431.001, Brazil.
Email: dr.alexandre@amato.com.br

obesity, venous insufficiency, and lymphedema,[7,8] all of which have distinct clinical characteristics.

It was previously demonstrated using magnetic resonance imaging[9] and computed tomography that there are non-specific and non-quantified increases in the thickness of the subcutaneous tissue[10] without skin thickening or liquid infiltration in the fat and without muscle edema.[11] The purposes of these previous studies were to differentiate between lymphedema and lipedema. Analysis by Dietzel et al. using dual-energy densitometry reinforced the notion of the disproportionate aspect of fat distribution in the female body; the authors suggested that fat mass in the legs adjusted for BMI was the best index for diagnosing lipedema.[12]

In view of the underdiagnosis of lipedema, and the main clinical characteristic of the disease, characterized by the disproportionate deposition of fat in lower limbs, our primary objective was to measure the thickness of the dermis and subcutaneous tissues in predetermined limb areas so as to differentiate among individuals with and without lipedema on ultrasound using a standard venous evaluation protocol. Our secondary objective was to identify variables that could be useful in future analyses.

Methods

Ultrasound images of 89 female patients were analyzed between April 2018 and April 2020 at our institution in the vascular surgery department, using non-probabilistic sampling for convenience. We included patients under clinical investigation for venous insufficiency or lipedema who underwent ultrasound assessment at our institution. Patients under 18 years old, those with venous insufficiency with subcutaneous alterations (C3 to C6), and those who chose not to participate in the study were excluded. Patients with varicose veins (C1 to C2) associated with lipedema were included in the lipedema group, patients without lipedema were included in control group. Distribution of studied population shows an expected unequal proportions of lipedema and control group, for an aimed enrollment ratio of 2:1 for additional safety data (Table 1). There was no significant difference among groups for BMI measurement, height and age. Interval BMI evaluation by showed an unequal proportion of patients when BMI> 25 kg/m^2 between groups. Control group also had a expected higher varicose vein proportion because of the study design.

Diagnosis of lipedema

The patients were evaluated by an examiner experienced in the clinical identification of lipedema. The diagnosis of lipedema remains primarily clinical, using the standardization of pertinent clinical questions from the QuASiL questionnaire[13] associated with the following criteria for classification of the group with the disease: suggestive clinical history in women after puberty; with bilateral symmetrical fat deposit below the hip, sparing of the feet (negative Stemmer sign); non-depressible edema (negative Godet's sign), resistance to elevation of the limbs; painful affected areas that are sensitive to palpation; and increased capillary fragility, with spontaneous bruising.[2,4]

Imaging protocol

The patients underwent the same echo-Doppler protocols for venous mapping to assess venous insufficiency associated with the specific assessment of predefined

Table 1. Characterization of the studied population.

	Lipedema	Control	Total	t-test	Result
n	62	27	89	p=<0.001*	Unequal proportions
BMI (kg/m^2)	30.0±1.4	27.4±1.5	29.3±1.1	p=0.050**	No correlation
Height (cm)	164.37±1.97	166±2.1	164.41±1.92	p=0.749**	No correlation
Varicose veins identified	28 (45.1%)	27 (100%)	55 (61.8%)	p<0.001***	Not independent
20.5 ≤ BMI < 25 kg/m^2	11 (17.7%)	7 (25.9%)	18 (20.22%)	p=0.346*	Equal proportions
25≤ BMI < 30 kg/m^2	24 (38.7%)	12 (44.4%)	36 (40.4%)	p=0.046*	Unequal proportions
BMI ≥ 30 kg/m^2	27 (43.54%)	8 (29.6%)	35 (39.32%)	p=0.001*	Unequal proportions
Age (yr)	46.177 ±3.587	47.963 ±4.467	46.719 ±2.8	p=0.372**	No correlation
Distribution type	1: 10 (16.1%) 2: 17 (27.4%) 3: 35 (56.4%)			p=<0.001***	Unequal proportions
Stage	1:25 (40.3%) 2:15 (24.2%) 3:16 (25.8%) 4:6 (9.6%)			p=0.017***	Unequal proportions

BMI, body mass index; *Z-score; **Spearman rank correlation; ***chi-square.

points (Figures 1 and 2) in ultrasound equipment (Acuson X300, Siemens, Germany), by two examiners blinded to the clinical hypothesis.

All examinations were performed at our institution, following a standard venous ultrasound imaging protocol,[14] using a high frequency linear transducer (7.5 to 13 MHz), focal zone at the point under evaluation, and gain and dynamic gain control adjusted to optimize the obtained image. The measurement of thickness perpendicular to the surface, from the dermis to the subcutaneous transition structure, was included in the venous mapping protocol (Figure 2), using a digital ruler of the body surface until the change from subcutaneous to fascia in four very distinct locations (Figure 1) bilaterally: anterior thigh, pre-tibial, lateral aspect of the leg and supra-just medial malleolar region. At least three measurements were taken at each location. In case of little evident tissue transition, the gain was increased until acceptable visualization. Images were saved on a PACs/DICOM server and reassessed in OsiriX image post-processing software (11.0.3, Pixmeo, Geneva, Switzerland) with confirmation of the measurements.

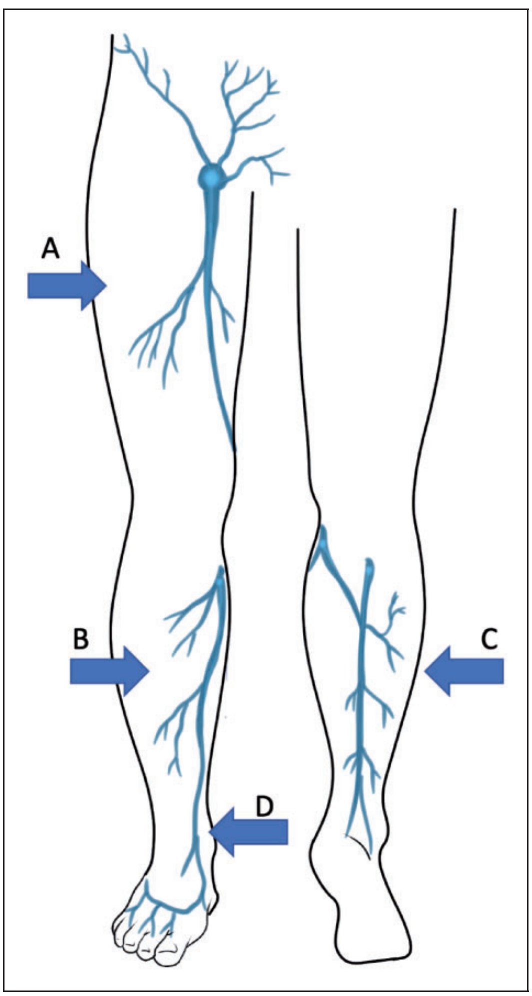

Figure 1. (a) Anterior thigh: midpoint between the iliac crest and the lower patellar border; (b) Pre-tibial: midpoint between anterior tibial tuberosity and medial malleolus; (c) lateral side of the leg: midpoint between lateral malleolus and fibular head; (d) medial supramalleolar.

Statistical analysis

After manual verification of data consistency, descriptive statistical analyses of frequencies was performed using Student's t-test, Spearman rank correlation, Kolmogorov–Smirnov normality test, or Mann–Whitney test. We used the receiver operating characteristic (ROC), considered the best way to quantify accuracy as a positive and negative predictor. An area under the curve (AUC) 1 would be perfect. We assumed 0.9 to 0.99 to be excellent, 0.8 to 0.89 to be good, 0.7 to 0.8 to be moderate, and below 0.7 to be poor. We used the Youden index as the measure of the maximum vertical distance from the equality line to determine the best cutoff value. For the correlations, we assumed a level of statistical significance of 0.05. The software packages used for data analysis were Excel (Microsoft, Redmond, Washington, USA) and Wizard 1.9.40 (Evan Miller, Chicago, IL, USA). This study followed the rules of the National Health Council, referring to resolution 196/96 on research involving human beings, it also followed the declaration of Helsinki and was approved by the Research Ethics Committee.

Results

The sample consisted of 89 patients who were clinically evaluated in a vascular surgery outpatient clinic and underwent venous mapping echocardiography. Mean age was 46 years, with an average body mass index (BMI) of 29.3 kg/m^2. 40.4% had BMI between 25 and 30, followed by 39.3% with BMI between 30 and 46.6, and only 20.2% had BMI between 20.5 and <25 kg/m^2.

The study included 63 patients with lipedema, with the remaining control patients having clinical and echographic pictures suggestive of varicose veins without alteration of lower limb subcutaneous tissue.

The studied groups were independent according to age and BMI, although there was a higher proportion of patients considered to be overweight and obese in the lipedema group (Table 1).

All ultrasound variables (Figures 1 and 2) showed statistically significant differences between the groups studied when not stratified by body mass index classification (Table 2). When reanalyzed using stratification by BMI, only the supramalleolar thickness was not

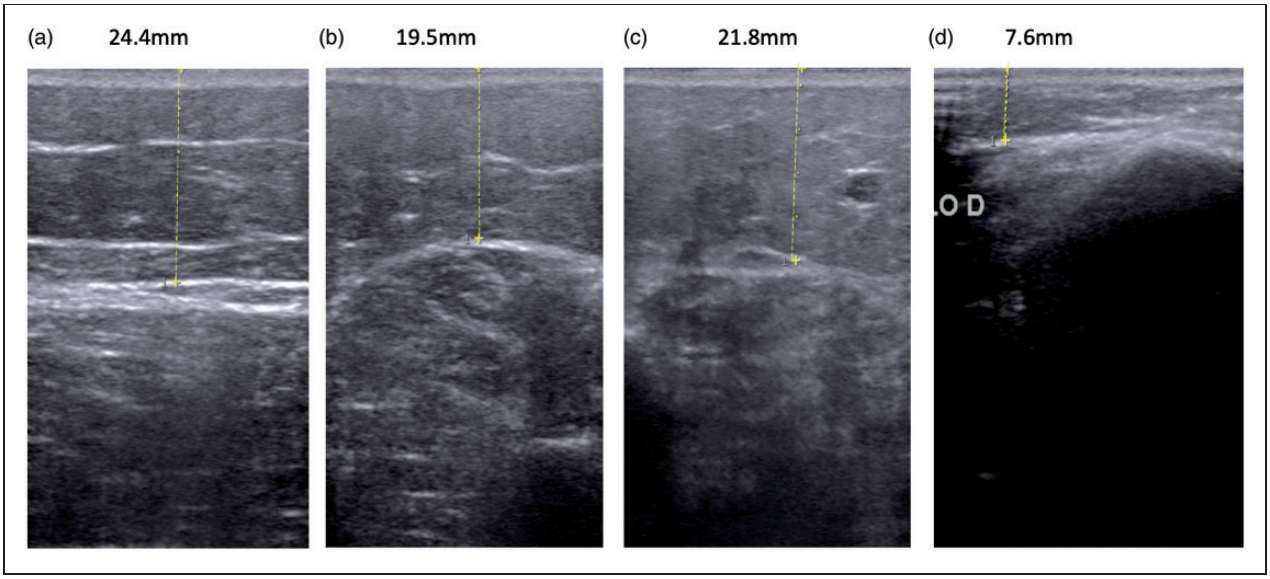

Figure 2. Ultrasound measurements with digital skin and subcutaneous ruler in a patient with clinically diagnosed lipedema. (a) Right thigh; (b) right lateral leg; (c) right pretibial; (d) right malleolus.

Table 2. Comparison between measured values in individuals with and without lipedema, evaluation between groups using Spearman rank correlation.

	Lipedema			Between-group analyses
	(mm)	p**	Control (mm)	p*
Thigh thickness R	20.9 (±0.167)	0.604	12.67 (0.18)	**<0.001**
Thigh thickness L	20.32 (±0.149)		12.38 (±0.151)	**<0.001**
Lateral leg thickness R	12.85 (±0.137)	0.507	6.8 (±0.083)	**<0.001**
Lateral leg thickness L	13.77 (±0.331)		6.4 (±0.078)	**<0.001**
Pre-tibial region thickness R	16.17 (±0.2)	0.819	8.3 (±0.092)	**<0.001**
Pre-tibial region thickness L	16.5 (±0.205)		8.45 (±0.097)	**<0.001**
Supramalleolar thickness R	12.08 (±0.184)	0.828	6.09 (±0.109)	**<0.001**
Supramalleolar thickness L	11.8 (±0.172)		6.6 (±0.12)	**<0.001**

*Bilateral distribution and symmetry were also analyzed bilaterally in patients in the lipedema group using the Student t-test
**R – Right, L – Left.
Boldface for statistically significant values.

statistically significant in the normal weight subgroup (Table 3).

The AUCs,[15] which represent the performance of a variable in the diagnosis, were calculated individually for each variable (Table 4). These showed excellent performance in the thickness of the pre-tibial region bilaterally, good accuracy in the lateral leg region and thigh bilaterally and moderate performance in the medial supramalleolar region.

Discussion

The development of therapies for lipedema is hampered primarily by underdiagnosis, mainly due to the absence of a definitive exam that is widely available and easy to perform and interpret; there is also a lack of familiarity among clinicians regarding the diagnostic criteria for lipedema.[16] Lipedema is often confused with lymphedema, physiological disproportion of the body shape, lipohypertrophy, gynecoid obesity,[6] and venous insufficiency. While diagnoses can coexist, early establishment of the initial diagnosis of associated comorbidities often halts the process that would lead to diagnosis of lipedema.

Considering that 49% of women have primary varicose veins,[17] and 11% of women have lipedema, it is not surprising that many women with varicose veins also have lipedema, a fact that contributed to this study. Child et al. reported 39.5% of women with lipedema had concomitant varicose veins and 53% had

Table 3. Comparison between the variables and groups studied highlighted by obesity classification.

	BMI 18.5–24.9			BMI 25–29.9			BMI > 30		
	Lipedema (n=11)	Control (n=7)	p	Lipedema (n=24)	Control (n=12)	p	Lipedema (n=27)	Control (n=8)	p
Age (years)	36.909 (±4.678)	43.286 (±8.704)	0.166	46.667 (±6.25)	53.833 (±7.575)	0.09	49.519 (±5.698)	43.25 (±6.89)	0.269
BMI (kg/cm^2)	23.227 (±0.785)	22.371 (±1.509)	0.269	27.608 (±0.752)	27.517 (±0.657)	0.705	35.004 (±1.726)	31.763 (±1.387)	**0.015**
Thigh thickness R	15.64 (±2.32)	11.13 (±2.68)	**0.010**	20.37 (±2.26)	11.52 (±2.41)	**<0.001**	23.58 (±2.85)	15.56 (±4.54)	**0.003**
Thigh thickness L	15.84 (±2.61)	10.98 (±2.45)	**0.010**	20.33 (±2.18)	11.78 (±2.24)	**<0.001**	22.2 (±2.48)	14.32 (±3.72)	**<0.001**
Lateral leg thickness R	11.48 (±1.8)	7.3 (±2.29)	**0.004**	10.94 (±1.78)	5.77 (±0.8)	**<0.001**	14.5 (±2.58)	7.96 (±2.01)	**<0.001**
Lateral leg thickness L	10.05 (±1.69)	6.85 (±2.12)	**0.021**	14.6 (±8.34)	5.58 (±0.96)	**<0.001**	14.61 (±2.88)	7.3 (±1.79)	**<0.001**
Pre-tibial region thickness R	13.76 (±2.14)	9.27 (±1.81)	**0.003**	13.71 (±1.92)	7.22 (±1.22)	**<0.001**	19.45 (±4.13)	9.21 (±2.16)	**<0.001**
Pre-tibial region thickness L	12.94 (±1.98)	9.47 (±2.12)	**0.029**	14.39 (±2.43)	8.02 (±1.32)	**<0.001**	19.95 (±4.0)	8.32 (±2.58)	**<0.001**
Supramalleolar thickness R	09.62 (±4.53)	8.35 (±3.7)	0.773	10.19 (±2.29)	5.57 (±1.08)	**0.005**	14.97 (±3.27)	5.19 (±2.15)	**<0.001**
Supramalleolar thickness L	10.06 (±3.69)	7.38 (±3.62)	0.410	10.54 (±2.45)	6.04 (±1.51)	**0.006**	13.7 (±3.09)	6.86 (±3.05)	**0.006**

All values are expressed as mean ± standard deviation. Thicknesses are presented in mm. Variables were evaluated using Spearman's rank correlation.
Boldface for statistically significant values.

telangiectasias and reticulae.[6] Our population of patients with lipedema had varicose veins in 45.1% of cases. In addition, many symptoms of lipedema mimic venous symptoms, including the feeling of heaviness and swelling in the legs. The vast majority of patients with lipedema are subject to undergoing venous echocardiography at some point in their lives.

The simplification of the diagnosis of obesity using BMI as a criterion, which disregards the distribution of body composition and clinical symptoms, can exacerbate the underdiagnosis of lipedema; after all, after obesity has been defined, why proceed with the diagnosis of lipedema? The definition of a single clinical diagnosis that explains all the patient's symptoms may be more elegant; however, it is not always correct and often prevents implementation of optimal therapy; this is because there are treatment measures aimed at lipedema that provide a greater probability of success. The literature makes it clear that 50% of patients with lipedema are also overweight or obese.[7,18,19] We found that 81% of the group with lipedema could be considered overweight or obese when evaluated using BMI only, regardless of body disproportion. We must identify better methods of diagnosing overweight and obesity in patients with lipedema.

The dermis thickness evaluated using high definition ultrasound (20 MHz) for non-vascular use proved to be excellent for differentiating between lipedema and lymphedema or controls previously, and suggested the hypothesis of the crenulated junction between dermis and hypodermis transition as a possible marker of lipedema, as well as unclear lower junction between dermis and hypodermis as a marker of lymphedema[20]; however, the characteristics of the dermis were not able to differentiate lipedema from normal individuals, and use of the high-definition transducer is not standard in leg echo Doppler protocols. In a previous work using ultrasound, Iker et al. showed that the differentiation between lipedema and lymphedema using ultrasound was relatively easy, with the analysis of skin thickness and hypoechogenicity of the subcutaneous ankle fat.[21] We know that the dermal thickness is different in patients with lymphedema due to associated dermal and subdermal lymphatic changes; in addition, changes such as hypostasis and changes in the water balance and fatty components can occur. In other words, the echographic aspects of the dermis and fat differ between lipedema and lymphedema. In this same study, the lower echogenicity of lipidemic fat was demonstrated when compared to normal individuals, in addition to suggesting an increase in the thickness of the subcutaneous tissue in lipedema, but without applicability or definition of clinical criteria. Considering the clinical difficulties in differentiating between lipedema, lymphedema, and normal

Table 4. Area under the curve (AUC) and best cutoff obtained by the characteristic of receiver operation (ROC) for independent analysis of BMI.

	Area under the curve (AUC)	AUC assessment	p	Optimal cutoff value (mm)	Optimal cutoff sensitivity	Optimal cutoff specificity	Maximum specificity cutoff value (mm)
Thigh thickness R	0.8699	Good	**<0.001**	19.5	0.67	0.92	24.2
Thigh thickness L	0.8926	Good	**<0.001**	17.9	0.67	0.92	20.8
Lateral leg thickness R	0.8894	Good	**<0.001**	8.9	0.78	0.84	12.2
Lateral leg thickness L	0.8891	Good	**<0.001**	8.4	0.76	0.80	10.6
Pre-tibial region thickness R	0.9079	Excellent	**<0.001**	11.6	0.79	0.96	12.9
Pre-tibial region thickness L	0.9092	Excellent	**<0.001**	11.8	0.77	0.92	14
Supramalleolar thickness R	0.7888	Moderate	**<0.001**	7.1	0.77	0.73	12.2
Supramalleolar thickness L	0.7670	Moderate	**<0.001**	7.0	0.67	0.61	12.6

Best cutoff was estimated by the Youden index (J = sensitivity + specificity-1), and optimal cutoff was adjusted to match contralateral measurement considering the symmetry of the lipedema, clinical applicability of the measurement and likelihood ratio. Sensitivity and specificity were obtained in the optimal cutoff. The optimal cutoff value shows the best distinctive statistical power between cases and controls, while the maximum specificity cutoff shows the limit measurement value for a specificity of 1.
Boldface for statistically significant values.

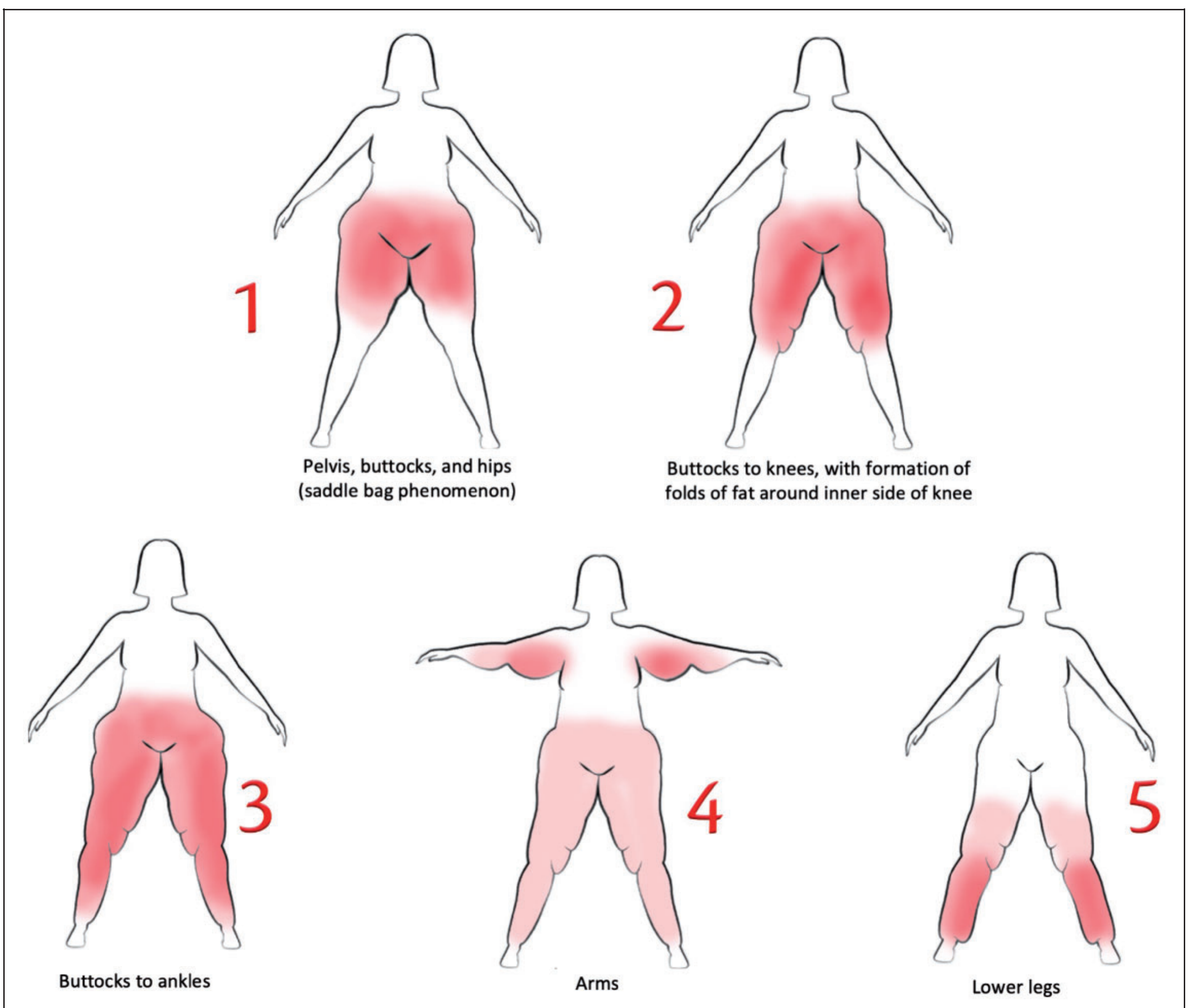

Figure 3. Classification of lipedema by body distribution.

Figure 4. Location of the lipedema evaluation points. (a) Thigh; (b) pre-tibial; (c) lateral leg; (d) medial malleolus; (e) anteromedial region of proximal leg with typical fat deposition for possible future investigation.

individuals, ultrasound proved to be of great value in diagnostic investigation.

Marshall and Schwahn-Schreiber suggested possible difference between skin and subcutaneous with ultrasound measurement in 62 women with and without lipedema.[22] They 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 to 15 mm, lipohyperplasia or mild lipedema; 15 to 20 mm, moderate lipedema; > 20 mm, indisputable lipedema; and > 30 mm, severe lipedema. They also suggested that normal people measure 2.1 mm at that point. However, although this location has not been reevaluated in our study, we extended the Marshall assessment to other areas, because we considered the existence of different distributions of lipedema (Figure 3), covering the assessment of types 1 (Point A), 2 (Point B), 3 (Points A–D), and 5 (Points B and D); type 4, in the upper limbs, rarely presents in isolation.

Analyzing the best cutoff values using the Youden index, regardless of BMI, we obtained the best clinical applicability values (Table 4), which established the best cutoff values for the clinical diagnosis of lipedema using ultrasound. The disadvantage of the Youden index is the inability to differentiate between sensitivity and specificity, and this was clearly apparent in the measurement of the left supramalleolar thickness, where the best cutoff would be 10.8 mm with sensitivity of 0.52 and specificity of 0.92. We chose to adjust optimal cutoff value Table 4 considering the symmetrical bilaterality of lipedema and approximating the cutoff value of the left leg and the right leg, aiming at better clinical applicability of the values. We also showed that the skin and subcutaneous thickness were significantly different between patients with and without lipedema, regardless of BMI, with no need for correction of values by BMI. Bilateral assessment helped to confirm limb symmetry typical of lipedema.

When evaluating the echographic images of the subcutaneous tissue, we noticed that the clinical complaint of edema in the lower limbs was more closely correlated with the clinical description of the patient, who often finds the word "edema" the way to describe the sensation in the limbs, rather than with the presence of interstitial fluid in subcutaneous tissue clearly present in lymphedema. Possibly the sensation of tension and swelling described is associated with inflammatory symptoms of lipedema[2] or with the disturbance in the distribution of fat and water suggested by Iker et al.[21]

Based on our results (Table 4), we suggest a cutoff of 11.7mm for pre-tibial region thickness measurements, with better accuracy, followed by a cut off of 17.9mm for thigh and a cutoff of 8.4mm for lateral leg thickness for the diagnosis of lipedema.

As the study developed, we identified easy-to-obtain ultrasound variables that can help differentiate between lipedema and normal individuals and can be studied in the future, such as the typical fat deposition in the anteromedial region of the proximal leg, close to the tendon insertion of anserine bursa (Figure 4(e)), the lateral peri-malleolar region and the pain referred to the maneuvers to assess venous reflux.

Conclusion

We established clinical applicability criteria with simple and reproducible ultrasound cutoff values for the diagnosis of lipedema in the lower limbs. We suggest pre-tibial region thickness measurements, with better accuracy, followed by thigh and lateral leg thickness for the diagnosis of lipedema.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The institution ethics committee approved this study (REC number: 202008).

Guarantor

ACMA.

Contributorship

ACMA, DZS, KSS and DAG researched literature and conceived the study. ACMA was involved in protocol development, gaining ethical approval, patient recruitment and data analysis. ACMA wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iD

Alexandre Campos Moraes Amato https://orcid.org/0000-0003-4008-4029

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