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ORIGINAL ARTICLE
MISCELLANEOUS

International ultrasound protocol for the diagnostic evaluation of lipedema: anatomical, fascial and microvascular criteria

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ABSTRACT

Background: Lipedema is a chronic disorder of adipose and loose connective tissue characterized by a symmetrical and disproportionate fat distribution, predominantly affecting women. Despite increasing recognition, the lack of a standardized and reproducible imaging protocol limits objective diagnosis, differentiation from related conditions, and comparability across centers. Ultrasonography represents an accessible and versatile tool for evaluating subcutaneous tissue, fascial structures, and microcirculation in lipedema.

Methods: We developed an international, multidisciplinary, expert-based ultrasound protocol using a structured methodological framework. The protocol integrates standardized anatomical measurement points for the lower limbs (A-D) and upper limbs (1-6), quantitative assessment of subcutaneous thickness using validated cutoff values, qualitative evaluation of tissue architecture, and systematic analysis of superficial and deep fasciae. High-sensitivity Doppler techniques, including Micro Flow Imaging, were incorporated to assess microvascular patterns. Histological correlations were derived from previously published data from the authors' group, supporting the interpretation of microvascular and structural findings. The protocol was constructed through integration of current literature and expert clinical experience from a multidisciplinary international group. A structured worksheet was designed to support standardized clinical and imaging data collection.

Results: The proposed protocol enables consistent identification of lipedema-related ultrasonographic features, including increased subcutaneous thickness, septal disorganization, nodularity, fascial thickening, reduced fascial gliding, and low-resistance microvascular flow. The use of standardized measurement points

and cutoff values enhances reproducibility and supports differentiation from lymphedema, edema, obesity, and lipohypertrophy. By integrating quantitative, qualitative, and functional parameters, the protocol addresses current limitations of purely qualitative ultrasound classifications. The worksheet and cartographic approach allow systematic bilateral documentation and facilitate multicenter comparability.

Conclusions: This international ultrasound protocol provides a comprehensive and standardized approach for the diagnostic assessment of lipedema, integrating subcutaneous, fascial, and microvascular parameters. It should be interpreted as an expert-informed framework intended to improve diagnostic consistency and to support future prospective validation studies. Its application may improve diagnostic accuracy, promote multicenter research, and support longitudinal monitoring and therapeutic decision-making.

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Key words: Lipedema; Ultrasonography; Subcutaneous fat; Fascia; Microcirculation; Ultrasonography, Doppler.

Introduction

Lipedema is a chronic disorder of loose connective tissue that predominantly affects women and is characterized by a disproportionate distribution of adipose tissue in the lower limbs and, in many cases, also in the upper limbs. This accumulation occurs symmetrically, frequently sparing the hands and feet, and is associated with pain, a sensation of heaviness, hypersensitivity to touch, functional lymphatic dysfunction, and functional limitation. In addition to volume increase, the tissue exhibits nodular and fibrotic characteristics, with typical worsening during periods of hormonal change, such as puberty, pregnancy, and menopause, as well as during phases of weight gain and changes in body contour.[1]

Currently, lipedema is recognized as a disease of adipose tissue and loose connective tissue, affecting almost exclusively women, in which the subcutaneous adipose tissue of the buttocks, hips, and extremities becomes fibrotic and painful, significantly impacting quality of life.[2] This tissue is relatively resistant to diet, physical exercise, and, in many cases, even bariatric surgery, which contributes to underdiagnosis, misattribution to simple obesity, and delays in the implementation of specific therapies. Recent guidelines, such as the Standard of care for lipedema in the United States, describe this condition as a disease of the extracellular matrix and loose adipose tissue, characterized by chronic low-grade inflammation, tissue remodeling, and microvascular and fascial involvement.[1]

In parallel, histological and imaging studies reinforce that lipedema is not merely a "fat hypertrophy," but rather a complex disorder involving adipocytes, extracellular matrix, microvasculature, the superficial lymphatic system, and, increasingly, the fascial system (superficial and deep fascia).[3] Changes in subcutaneous thickness, lobular architecture, fascial structures, and microvascularization can be documented by imaging methods, particularly ultrasonography,[4-6] which stands out as an accessible, reproducible, and low-cost tool.

Recent efforts to improve ultrasonographic characterization of lipedema have included qualitative classification systems based on structural patterns.[7]

These classification systems describe progressive structural changes in lipedema, proposing pattern-based frameworks that correlate imaging findings with tissue remodeling processes. However, they are based on relatively small cohorts and require further validation to establish reproducibility and broader clinical applicability.[7, 8]

In addition, recent efforts to improve diagnostic accuracy have included quantitative and algorithm-based approaches, such as classification models derived from statistical methods; however, these strategies still do not fully integrate anatomical, fascial, and microvascular parameters, which are increasingly recognized as central components of lipedema pathophysiology.[8]

In this context, the development of a standardized ultrasonographic protocol becomes essential to objectively characterize lipedema, differentiate it from other conditions (obesity, lipohypertrophy, lymphedema), and allow comparability between centers.

To address these limitations, structured protocols that combine quantitative measurements, qualitative assessment, and functional imaging — supported by both literature and expert clinical experience — may improve diagnostic consistency and facilitate multicenter research.

The aim of this article is to propose an international, multidisciplinary, expert-based ultrasound protocol for the diagnostic evaluation of lipedema, integrating standardized anatomical measurements, fascial assessment, qualitative tissue characterization, and microvascular analysis. The protocol is supported by current literature, expert clinical experience, and previously published histopathological correlations from the authors' group, with the goal of improving reproducibility and supporting future multicenter validation.

Materials and methods

This study describes the development of an international diagnostic ultrasound protocol for lipedema, based on a structured anatomical, morphological, and functional framework.

This protocol should be interpreted as a multidisciplinary, expert-based framework developed to standardize ultrasonographic evaluation of lipedema, rather than as a prospective clinical study.

The methodological approach focuses on the systematic description of subcutaneous tissue anatomy, fascial structures, and microvascular components relevant to lipedema. The protocol was designed to allow reproducibility across different centers and to support standardized image acquisition, measurement, and interpretation.

The development process was based on the integration of current literature and expert clinical experience from a multidisciplinary international group of specialists. Technical aspects of the ultrasound examination and the step-by-step execution of the protocol are presented in the Results section.

Ethical statement

As this study describes the development of a diagnostic protocol and does not involve prospective patient inclusion or intervention, formal ethical approval and informed consent were not required for the present work.

Development of the protocol

The protocol was developed through a structured integration of: 1) relevant literature on lipedema imaging and pathophysiology; and 2) expert clinical experience.

The expert group included vascular surgeons, angiologists, imaging specialists with expertise in vascular ultrasonography, a physiotherapist, and a plastic surgeon, representing different regions of Brazil and Latin America (Chile, Argentina, and Paraguay).

The development process focused on defining reproducible anatomical landmarks, establishing measurable ultrasonographic parameters, and incorporating qualitative and functional imaging criteria, including microvascular assessment.

Integration of histopathological evidence

Histopathological correlations incorporated into this protocol are based on previously published data from the authors' group, demonstrating microvascular and inflammatory alterations in lipedema tissue, including increased capillary density, mast cell infiltration, and features consistent with inflammatory microangiopathy.[9]

These findings were used to support the interpretation of ultrasonographic patterns, particularly microvascular flow characteristics identified through high-sensitivity Doppler techniques.

Anatomy of subcutaneous tissue

Subcutaneous cellular tissue (SCT), or hypodermis, together with the dermis and deep fasciae, forms a continuous three-dimensional complex with mechanical, metabolic, endocrine, and immunological functions. From an anatomical and functional standpoint, SCT is not a homogeneous layer of fat beneath the skin, but rather an organized organ composed of adipose compartments, fibrous septa, vasculolymphatic networks, and specific innervation—features that are central to the proper interpretation of ultrasonographic findings in lipedema (Figure 1).[10, 11]

Layer organization: superficial and deep adipose tissue

Anatomical, histological, and imaging studies (such as 3T magnetic resonance imaging [MRI], dissections, and 3D reconstructions) demonstrate that SCT is organized into at least two main layers: superficial adipose tissue (SAT) and deep adipose tissue (DAT), separated by a superficial or membranous fascia. This structure is also described as the superficial fascia, panniculus carnosus, or, in specific regions, superficial aponeurosis (for example, Camper's and Scarpa's fasciae in the abdominal wall).[10, 12, 13]

SAT is located immediately beneath the reticular dermis and consists of relatively large adipocyte lobules arranged in a "honeycomb" pattern, delimited by vertical and oblique fibrous septa (retinacula cutis superficialis) that anchor the dermis to the superficial fascia. DAT,

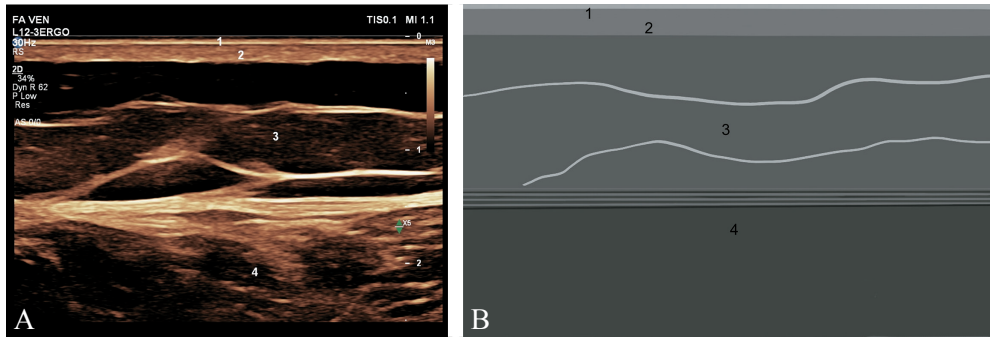


Figure 1.—Normal skin layers. A) Longitudinal B-mode ultrasonographic image of the anterior thigh demonstrating the normal skin layers: 1) epidermis; 2) dermis; 3) hypodermis (subcutaneous tissue); and 4) muscle. B) Schematic drawing illustrating the corresponding anatomical layers.

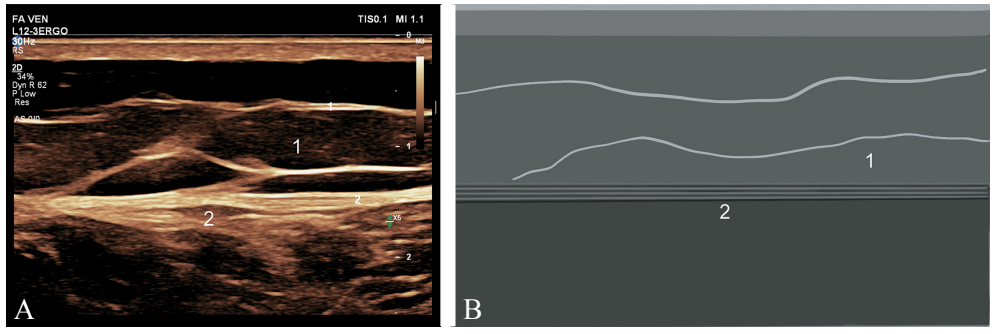


Figure 2.—Hypodermis (subcutaneous tissue). A) Longitudinal B-mode ultrasonographic image of the anterior thigh showing the superficial fascia (1) and the deep fascia (2). Note that the superficial fascia appears as a thin connective tissue layer, whereas the deep fascia is thicker and more conspicuous. B) Schematic drawing illustrating the corresponding fascial layers.

located below the superficial fascia, generally presents smaller adipose lobules, looser septa, and an intimate relationship with the deep fascia and underlying musculature (Figure 2).

From a mechanical standpoint, this layered and compartmental organization allows the absorption of tension, distribution of loads, and maintenance of skin position in response to volumetric changes (such as weight gain, edema, and pregnancy). In lipedema, alterations in this arrangement — adipocyte hypertrophy and hyperplasia, septal thickening, and matrix remodeling — directly affect the ultrasonographic pattern.[13]

Histological composition

Microscopically, SCT is composed of:

- mature adipocytes (predominantly unilocular white adipocytes), which account for most of the volume;
- stromal–vascular fractions containing preadipocytes, fibroblasts, endothelial cells, pericytes, mesenchymal stem cells, mast cells, lymphocytes, and resident macrophages;
- extracellular matrix (ECM) rich in collagen (types I and III), elastin, proteoglycans, and glycosaminoglycans, concentrated in the septa and at the periphery of the lobules.

Adipose lobules surrounded by fibrous septa form the structural and functional unit of SCT. The septa conduct blood and lymphatic vessels as well as nerve fibers and represent the primary support framework. The close relationship between the adipose component, fibroconnective stroma, and microvasculature is central to understanding the response of SCT to chronic inflammation, mechanical overload, and hormonal stimuli observed in lipedema.[12, 14, 15]

Microvasculature, lymphatic drainage, and innervation

SCT is richly vascularized by arterioles and venules originating from dermal and deep plexuses, which penetrate the adipose lobules through the septa. The capillary network is dense and dynamically adapts to the metabolic demands of adipose tissue (volumetric expansion or reduction).

Lymphatic drainage begins in lymphatic capillaries within the papillary and reticular dermis, progressing to collecting vessels located in the septa and at the SAT–DAT interface, which subsequently drain into regional lymph node chains. This anatomical arrangement explains why dysfunction of the superficial lymphatic system manifests as increased SCT thickness and altered echotexture in both lymphedema and advanced-stage lipedema.[16, 17]

Regarding innervation, SCT receives somatic sensory

fibers (pain, touch, temperature) and autonomic fibers, mainly sympathetic, which regulate vascular tone and adipose metabolism. The presence of nerve endings in the septa and at the periphery of the lobules may contribute to allodynia and pain on palpation characteristic of lipedema, especially in the context of low-grade inflammation and increased interstitial pressure.

The fascial system in lipedema

In recent years, the study of lipedema has evolved from an exclusive focus on adipose tissue to a model that includes the fascial system — superficial and deep fascia — as central elements of pathophysiology.

Superficial fascia: boundaries, thickness, and mobility

The superficial fascia is a connective tissue sheet located between the dermis–hypodermis and the deep adipose compartment, acting as an envelope, a compartment divider, and a gliding plane between superficial adipose tissue and deeper structures. On ultrasonography, it is identified as a thin hyperechoic band separating SAT from DAT.[10, 18]

Anatomically, it is located immediately below the dermis and above the deep (muscular) fascia, to which it is anchored by fibrous retinacula. Under normal conditions, its thickness ranges from approximately 0.6 to 1.0 mm in the limbs, varying according to anatomical segment, Body Mass Index, and age (Figure 3). Recent studies have demonstrated, in individuals with adipose disorders (including lipedema and associations with hypermobile Ehlers-Danlos Syndrome), a significant and measurable increase in superficial fascial thickness in the lower limbs compared with controls.[19]

From a functional standpoint, the superficial fascia acts as a gliding plane between the skin and deeper tissues. Under healthy conditions, this gliding is smooth during active or passive movements. In situations of fascial remodeling (chronic inflammation, fibrosis), gliding becomes restricted, and patients report sensations of "tightness" and "heaviness." In lipedema, although direct data on fascial mobility are still limited, the symptomatology of heaviness and resistance to movement supports the hypothesis of altered behavior at this interface.

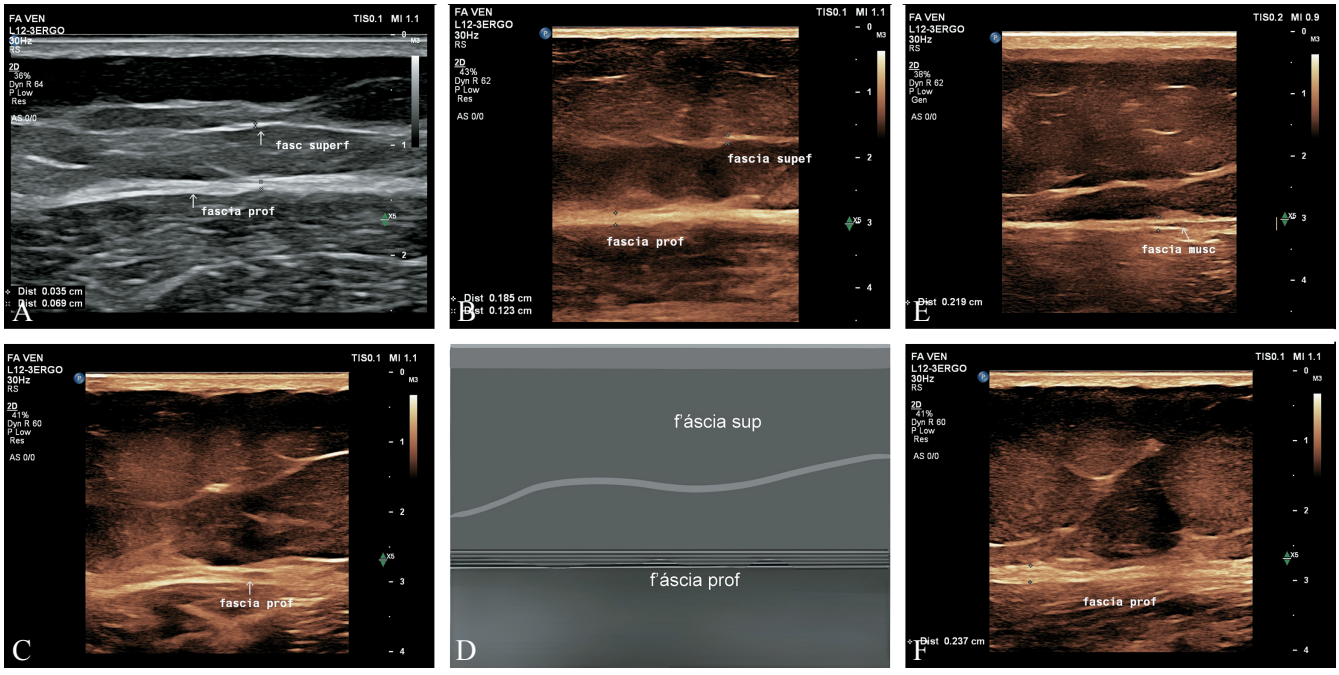


Figure 3.—Subcutaneous fascial layers in normal tissue and lipedema. A) Longitudinal B-mode ultrasonographic image of the anterior thigh in a healthy individual, showing the superficial fascia with normal thickness, ranging from 0.6 to 1.0 mm. B) Longitudinal B-mode ultrasonographic image of the anterior thigh in a patient with lipedema, demonstrating marked thickening of both the superficial fascia (1.23 mm) and the deep fascia (1.85 mm). C) Longitudinal B-mode ultrasonographic image showing thickening of the deep fascia with a hypoechoic area within the fascial layer (arrow), suggestive of interstitial fluid accumulation. D) Schematic drawing illustrating normal and thickened superficial and deep fasciae, highlighting the differences in thickness and echogenic pattern. E, F) Additional longitudinal B-mode ultrasonographic examples illustrating thickened deep fascia in patients with lipedema.

Deep fascia: organization and function

The deep fascia is a denser connective tissue sheet that envelops muscles, extends into aponeuroses and intermuscular septa, and connects with the epimysium and perimysium. Its functions include force transmission, stabilization of the musculoskeletal system, and participation in proprioception and nociception. Recent studies describe a high density of nerve endings and mechanoreceptors in the deep fascia, conferring it a relevant role in chronic pain.[11, 18]

In addition, the deep fascia contains vessels and nerves and participates in venous and lymphatic return, directly interacting with adjacent adipose tissue. Changes in its viscoelastic properties, thickening, or fibrosis may impair interstitial and lymphatic flow — an aspect particularly relevant in lipedema. Studies in patients with adipose disorders have also demonstrated thickening of the deep fascia compared with controls (Figure 3), reinforcing the view of lipedema as a connective-fascial tissue disease rather than merely fat accumulation.[19, 20]

Relationship with pain and functional limitation

Pain and functional limitation in lipedema may be closely related to fascial dysfunction. Proposed mechanisms include chronic low-grade inflammation, extracellular matrix deposition (collagen, proteoglycans), septal fibrosis, and increased fascial tissue viscosity. This remodeling reduces the capacity for gliding between tissue planes, increases mechanical tension on nociceptive endings present in superficial and deep fasciae, and promotes persistent pain.[21]

Ultrasonographic studies show a reduced pressure pain threshold in patients with lipedema and increased SCT stiffness in specific areas (for example, the pretibial region in intermediate stages), although stiffness alone is not a sufficient discriminative criterion. The correlation between stiffness, fascial thickening, and pain reports reinforces the role of fascial remodeling in the clinical presentation.[18]

When the deep fascia loses elasticity, force transmission between muscles and adjacent tissues is impaired, potentially resulting in fatigue, restricted joint mobility, and the characteristic sensation of heaviness in lipedema.

Ultrasonographic visualization of superficial and deep fascia

High-frequency ultrasonography is a noninvasive tool useful for visualizing superficial and deep fascia. The use of a high-frequency linear transducer (~12-18 MHz), adjusted depth (~30 mm for superficial structures), and minimal probe compression is recommended to avoid tissue distortion.[18, 22]

In B-mode imaging, the superficial fascia appears as a thin hyperechoic band beneath the dermis, while the deep fascia is identified as a thicker hyperechoic band overlying muscles or intermuscular septa. Fascial gliding can be assessed dynamically: in normal tissue, smooth movement between planes is observed; in pathological tissue, partial or complete restriction is present.

In the context of lipedema, diagnostic ultrasound studies have used defined anatomical points (anterior thigh, pretibial region, lateral leg, medial supramalleolar region) to quantify dermis + subcutaneous thickness and establish reproducible cutoff values for the ultrasonographic diagnosis of lipedema. [6, 23]

Three-dimensional ultrasound studies in lipedema have identified thickening of the superficial and deep fascia, as well as anechoic areas along the superficial fascia suggestive of interstitial fluid accumulation.[5]

Proposal of criteria for fascial abnormality

Based on recent literature, criteria for abnormality that may be incorporated into an international ultrasonographic protocol for lipedema can be proposed:

Quantitative criteria

Thickness of the dermis + subcutaneous compartment at reference points: for example, anterior thigh ≥17.9 mm; pretibial region ≥11.7 mm; lateral leg ≥8.4 mm; medial supramalleolar region ≥7.0-7.1 mm, according to Amato *et al.*[6]

Thickness of the superficial and deep fascia: although definitive cutoffs do not yet exist, studies in adipose disorders demonstrate significant thickening compared with controls. Thickening greater than two standard deviations above reference values or asymmetry >20% between contralateral limbs in the absence of other pathology is considered abnormal.[18, 19]

Qualitative criteria

Loss of lobular uniformity of the subcutaneous tissue, thickened or tortuous fibrous septa, hyperechoic nodules with or without a central anechoic area (steatonecrosis), posterior acoustic shadowing, or heterogeneous echotexture.

Thickening and heterogeneity of the superficial or deep fascia, with an irregular hyperechoic band, discontinuities, focal thickening, or a "frayed" appearance.

Visible reduction of fascial gliding on dynamic assessment between the cutaneous–subcutaneous plane and the deep fascia.

On Doppler/Power Doppler, presence of persistent or diffuse vascular signal along the fascia, suggesting inflammatory involvement.

Functional criteria and clinical correlation

Spatial association between sites of greatest pain on palpation (algometry) and ultrasonographic findings of fascial thickening or subcutaneous nodules.

Increased stiffness of subcutaneous and fascial tissue assessed by elastography (strain or shear-wave), particularly in symptomatic regions. Isolated stiffness is not sufficient for diagnosis but adds value when combined with thickness, morphology, and clinical findings.

The integration of these parameters provides a basis for a more objective, quantifiable, and reproducible international protocol, allowing differentiation of lipedema from other entities and monitoring of therapeutic response.[5, 18, 19, 21]

Results

Ultrasound mapping of lipedema

Examination technique

Abnormal fat deposition in the subcutaneous tissue alters tissue architecture, which can be detected by ultrasonography. The main changes include increased subcutaneous thickness, disorganization of the connective tissue network, thickening or disruption of septa, and changes in echotexture.[5, 6, 24]

For accurate assessment, the use of high-resolution equipment and a high-frequency linear transducer (7-18 MHz) is recommended. The preset should be adjusted for superficial structures, with an appropriate grayscale setting (dynamic range between 60-70), medium persistence, and depth adapted to the patient's body habitus. Flow assessment should use parameters with a pulse repetition frequency (PRF) that allows detection of low-amplitude flows, ideally using high-sensitivity Doppler as described in studies by Barros *et al*. and by Kempa *et al*.[9, 25, 26]

For the lower limbs, the examination is recommended with the patient in the standing position; for the upper limbs, the seated position facilitates access and reproducibility. The assessment points must be standardized and documented with schematic figures and corresponding ultrasound images, carefully selected to ensure examination accuracy.

Step-by-step protocol

Quantitative assessment: thickness of the subcutaneous tissue and fasciae

This protocol proposes a standardized approach for quantitative ultrasonographic assessment of subcutaneous tissue and fascial structures in patients with suspected lipedema.

Lower limbs

Subcutaneous thickness should be measured perpendicular to the skin surface, from the dermis to the interface between the subcutaneous tissue and the underlying muscle (deep fascia). A longitudinal scan is preferred because it allows better definition of anatomic interfaces; however, the transverse plane is acceptable whenever it provides clearer visualization of the fascial plane. Minimal transducer pressure should be applied to avoid artificial tissue compression (Figure 4).

Based on the protocol described by Amato *et al*.[6] and adapted to the present protocol, four central standardized measurement points (points A-D) are recommended in the lower limbs, as illustrated in Figure 5:

- point A – anterior thigh: measured at the midpoint between the iliac crest and the inferior border of the patella, representing the typical proximal involvement in lipedema. Subcutaneous thickness values ≥17.9-19.5 mm are suggestive of lipedema, considering laterality;
- point B – pretibial region: measured at the midpoint between the anterior tibial tuberosity and the medial malleolus, corresponding to the anterior compartment of the leg. This site showed the highest diagnostic accuracy, and a cutoff ≥11.7 mm is recommended, regardless of Body Mass Index;
- point C – lateral aspect of the leg: measured at the midpoint between the fibular head and the lateral malleolus, assessing lateral fat deposition in the leg. Thickness values ≥8.4-8.9 mm are indicative of lipedema;
- point D – medial supramalleolar region: measured immediately above the medial malleolus, allowing assessment of distal fat accumulation with sparing of the foot. A cutoff ≥7.0-7.1 mm supports the diagnosis, although this point shows moderate diagnostic performance compared with the others.

Additional points may be included according to the typical distribution of lipedema, such as the trochanteric region ("saddlebags"), calf, and paramedial knee region, especially in patients with atypical or mixed phenotypes. These complementary points aim to improve phenotypic characterization without replacing the central diagnostic points.

Bilateral assessment is recommended to confirm the characteristic symmetry of lipedema. The use of these standardized points and their respective cutoff values enable a simple, reproducible, and clinically applicable ultrasound approach for diagnosing lower-limb lipedema.

Thickness should be measured from the dermis to the interface between subcutaneous tissue and muscle (deep fascia), preferably in a longitudinal scan, although the

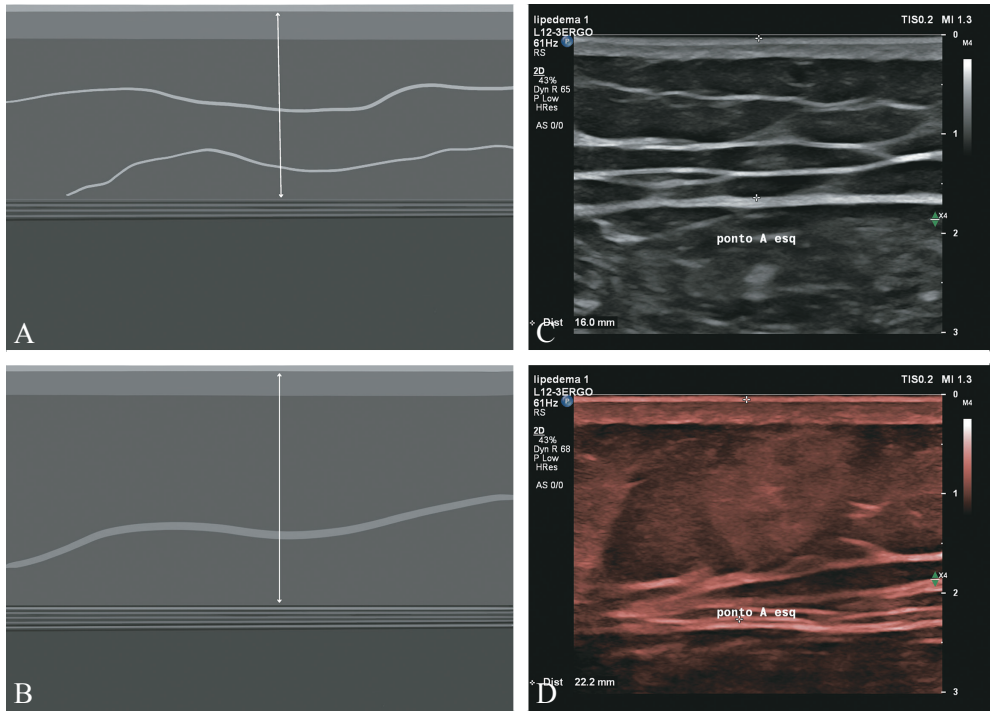


Figure 4.—Technique for measuring subcutaneous tissue thickness. A, B) Schematic drawings illustrating the standardized method for subcutaneous thickness measurement. C) Longitudinal B-mode ultrasonographic image showing measurement from the epidermis to the deep fascia in a healthy individual at point A, located at the midpoint between the iliac crest and the inferior border of the patella. D) Longitudinal B-mode ultrasonographic image demonstrating increased subcutaneous thickness measured using the same technique in a patient with lipedema.

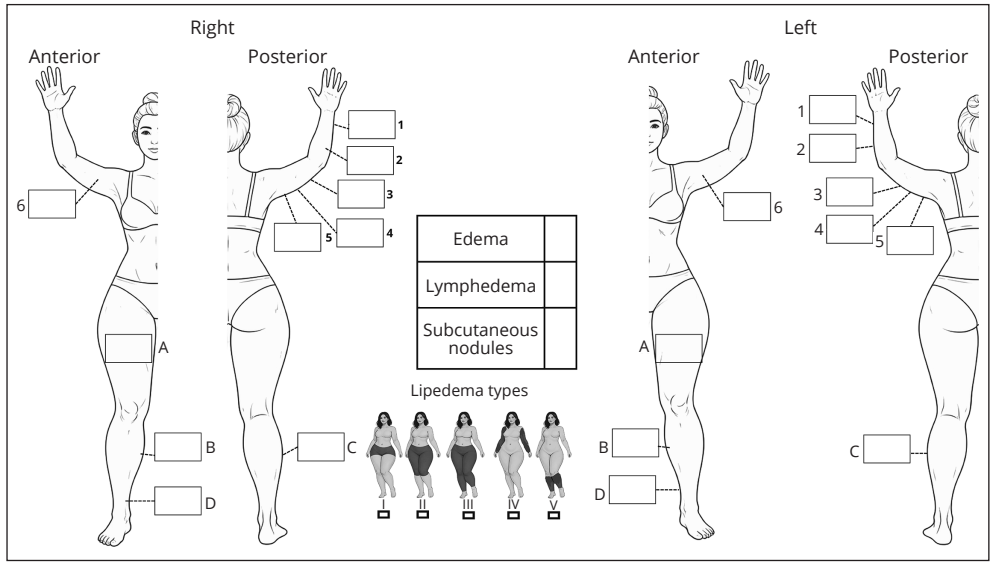


Figure 5.—Standardized anatomical mapping (cartography) of lipedema.

transverse plane is acceptable whenever it provides better definition. Recommended points, based on Amato *et al.*[6] and adapted to this protocol, include: anterior thigh, pretibial region, lateral aspect of the leg, medial supramalleolar region, as well as additional points in the trochanteric "saddlebags," calf, and paramedial knee region, according to the typical distribution of lipedema.

Upper limbs

In the upper limbs, subcutaneous thickness should be measured from the dermis–hypodermis transition to the deep fascia, perpendicular to the skin surface, preferably in a longitudinal scan, with minimal transducer compression and preservation of the best possible definition of the fas-

cial plane.[27] The transverse plane may be used when it provides better anatomic delimitation.

Six standardized measurement points (1-6) were established[27] for each upper limb, as illustrated in Figure 6:

- dorsal forearm, dorsal aspect of the forearm, 6 cm proximal to the ulnar styloid process. Cutoff: values >2.5 mm are suggestive of lipedema;
- dorsal forearm, 6 cm distal to the elbow, assessing the proximal portion of the forearm compartment. This point is considered complementary, with no isolated cutoff defined, and is used for comparative analysis and assessment of bilateral symmetry;
- posterior arm, 10 cm proximal to the olecranon, corresponding to the inferior border of the proximal arm. Cutoff: values >8.7 mm are suggestive of lipedema;
- mid posterior arm, 10 cm distal to the axillary line, corresponding to the inferior border of the mid third of the arm. This point showed the best discriminatory capacity in the upper-limb study. Recommended cutoff: values >11.4 mm;
- posterior arm, 6 cm distal to the axillary line, assessing the distal posterior portion of the arm. Cutoff: values >8.5 mm, with moderate diagnostic performance;
- anterior arm, 6 cm distal to the axillary line, assessing the anterior compartment of the arm. Cutoff: values >4.9 mm, with higher sensitivity and lower specificity.

The selection of these points was based on ease of anatomic identification, bilateral symmetry, and clinical relevance, covering regions frequently affected by lipedema in the upper limbs. These sites were defined based on expert clinical experience and anatomical reproducibility, reflecting commonly affected regions in lipedema. They are grounded in the accumulated clinical experience of Fanilda Barros and collaborators in ultrasound mapping of the arms in patients with lipedema,[27] and they complement the lower-limb assessment points previously described by Amato *et al.*[6]

Systematic bilateral assessment is recommended to confirm the characteristic symmetry of lipedema. The combined use of these points and their respective cutoff values enables a standardized, reproducible, and clinically applicable ultrasound approach for diagnosing upper-limb lipedema.

Superficial and deep fascia

Whenever possible, the thickness of the superficial fascia and deep fascia should be measured at the same points, using appropriate magnification and reduced gain to highlight the hyperechoic band. Fascial thickening above reference values (when available) or significant asymmetry between limbs is considered suspicious.[18, 20]

Qualitative assessment of the subcutaneous tissue

Qualitative assessment within this protocol is intended to complement quantitative measurements by characterizing tissue architecture and structural alterations associated with lipedema.

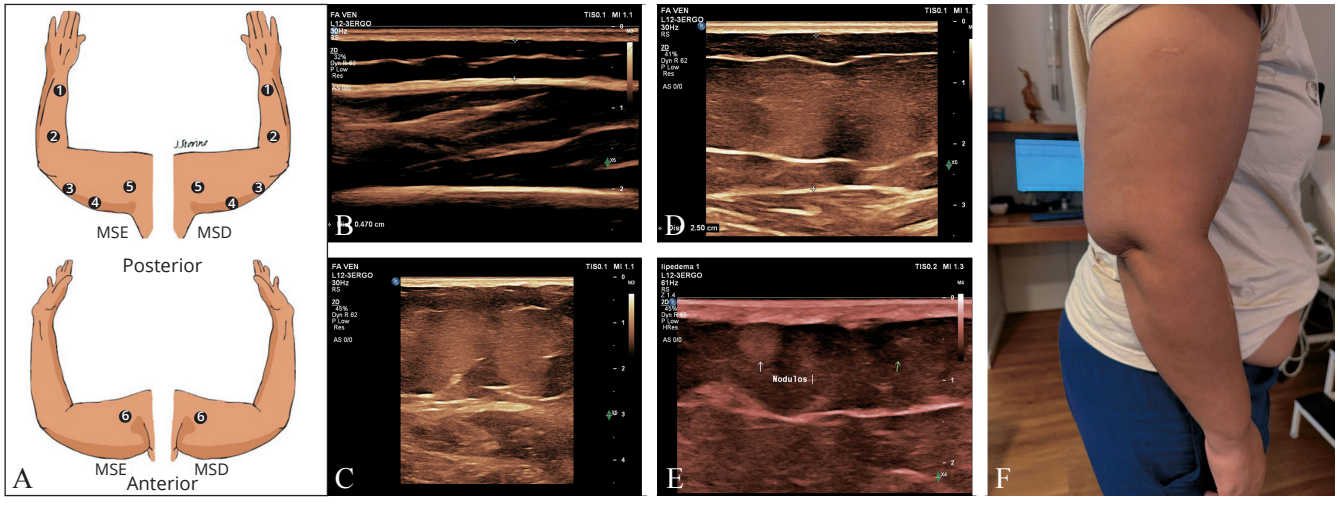


Figure 6.—Schematic model of upper-limb lipedema assessment points: posterior arm at point 3. A) Schematic drawing illustrating the method for measuring subcutaneous tissue thickness. B) Longitudinal B-mode ultrasonographic image showing subcutaneous thickness measurement from the inferior border of the dermis to the deep fascia (transition structure with the underlying musculature) in a control subject. C) Longitudinal B-mode ultrasonographic image demonstrating increased subcutaneous thickness measured using the same technique in a patient with lipedema. D) Ultrasonographic image showing discontinuity of connective tissue fibers and fascial layers. E) Ultrasonographic image demonstrating subcutaneous nodules, which may correspond to lipedematous fat accumulation or areas of steatonecrosis. F) Clinical image of a patient with upper-limb lipedema.

In normal subcutaneous tissue, ultrasonography shows thin, hyperechoic connective tissue septa and fibers distributed in a linear and continuous pattern, without significant distortion by fat, and superficial and deep fasciae as thin hyperechoic bands. Subcutaneous echogenicity tends to be lower than that of the dermis and similar to or slightly lower than that of the adjacent muscle.[7, 22, 24]

In lipedema, the organized architecture of the subcutaneous tissue is altered by adipocyte hyperplasia and immune infiltrate. Fasciae may show an interrupted course, thickening, displacement, or an ill-defined nodular appearance, with echogenicity similar to or greater than that of muscle and dermis (Figure 7). Hyperechoic nodules may be observed (Figure 8), corresponding to fat aggregates, or lesions with an anechoic center compatible with cystic areas or steatonecrosis, in agreement with previously published histologic findings.[3, 5]

Recommended sites for qualitative evaluation include, in the lower limbs:

- upper third of the leg (Hoffa fat);
- lower third of the thigh (paramedial knee region);
- upper third of the thigh;
- trochanteric region ("saddlebags");
- calf.

In the upper limbs:

- arm (posterior aspect, 6 and 10 cm above the olecranon);
- forearm (anterior aspect, 6 cm above the ulnar head).

These regions reflect areas of greater fat deposition and higher symptom burden described in clinical and observational studies in patients with lipedema.[6, 28]

Circulation and microcirculation

Microvascular assessment represents a functional component of this protocol, aimed at identifying inflammatory activity and microangiopathic patterns associated with lipedema.

Ultrasonography, especially at high resolution, is a continuously expanding tool in the assessment of cutaneous and subcutaneous lesions and is useful both for diagnosis and follow-up of benign and malignant lesions.[22, 29]

The use of color Doppler, pulsed Doppler, and microvascular imaging techniques increases diagnostic accuracy in the differential diagnosis of conditions involving the epidermis, dermis, and hypodermis. In inflammatory and rheumatologic diseases, increased vascularization and/or neovascularization is a recognized marker of inflammatory activity.[26]

Inflammation in lipedema is considered an established finding, with reports of increased capillarity, angiogenesis, and signs of microangiopathy.[21, 30] Therefore, vascular assessment is promising, and high-sensitivity Doppler emerges as a relevant tool to evaluate microcirculation in regions affected by the disease. Histological analysis

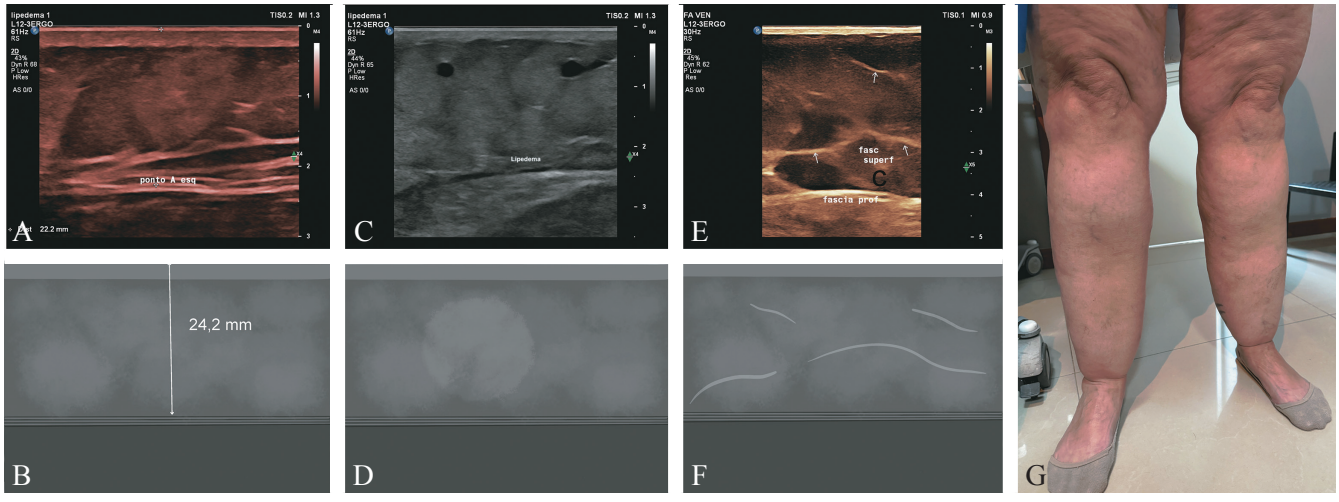


Figure 7.—Abnormal subcutaneous findings in a patient with lipedema. A) Increased thickness of the subcutaneous tissue. Note the abnormal fat deposition leading to thickening of the subcutaneous layer. B) Schematic drawing illustrating increased subcutaneous thickness. C) Disorganization of the connective tissue framework with disruption and loss of connective tissue fibers secondary to adipose deposition. The hypodermis (subcutaneous tissue) shows a relatively homogeneous texture, with lower echogenicity than the dermis and similar to or greater than the echogenicity of the underlying muscle, with a poorly defined nodular appearance. D) Schematic drawing illustrating diffuse nodular pattern. E) Discontinuity of the fasciae and connective tissue fibers. F) Schematic drawing illustrating discontinuity of connective tissue fibers. G) Clinical photograph of a patient with lipedema.

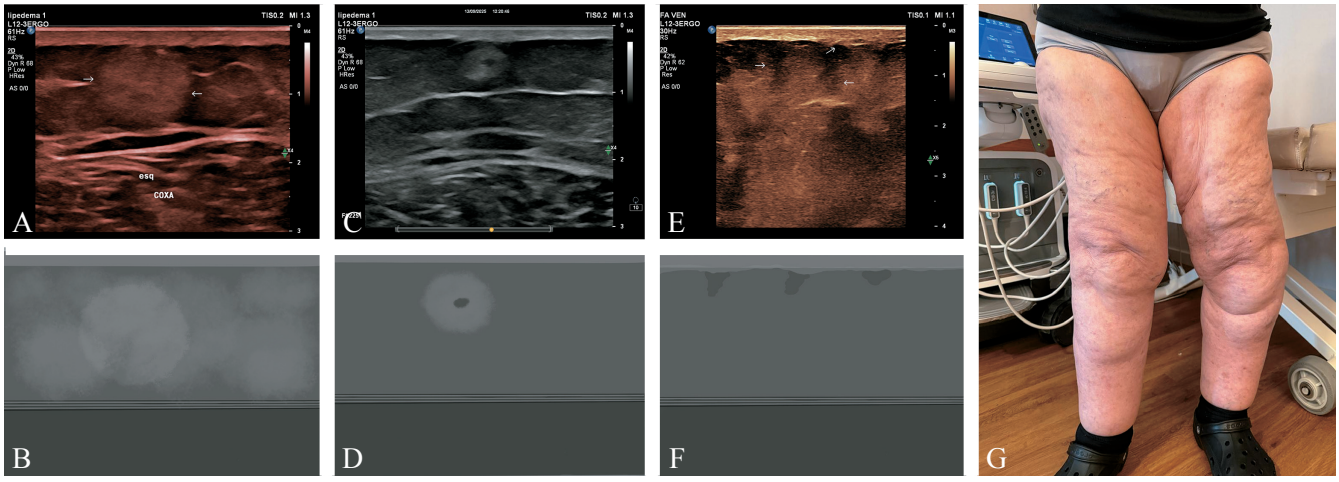


Figure 8.—Abnormal subcutaneous findings in patients with lipedema (continued). A) B-mode ultrasonographic image showing subcutaneous nodules, which may be present in lipedema but are not pathognomonic. B) Schematic drawing illustrating subcutaneous nodules. C) Ultrasonographic image demonstrating nodules with a central anechoic area, compatible with cystic change or steatonecrosis. D) Schematic drawing illustrating a nodule with steatonecrosis. E) Ultrasonographic image of the trochanteric region showing dermal irregularity associated with attenuation artifacts, likely related to fibrotic changes. F) Schematic drawing illustrating dermal irregularity and the resulting attenuation artifacts. G) Clinical image of a patient with stage IV lipedema.

previously reported in the literature[9] confirms adipocyte hyperplasia, mast cell infiltration, and foci of steatonecrosis, supporting the inflammatory and remodeling processes observed on imaging (Figure 9).

Kempa *et al.*[25] demonstrated the value of microvascular imaging in the evaluation of lipedema (sonographic microvascular imaging), identifying low-resistance flow patterns in small intrasubcutaneous vessels. In a complementary study, Barros and collaborators used Micro Flow Imaging (MFI) and demonstrated vascularization in small vessels involving the subcutaneous connective tissue in patients with lipedema (Figure 10), highlighting a low-resistance pattern typical of chronic inflammatory processes.[9, 21, 25]

The microcirculatory assessment in the proposed protocol includes:

• dermal and subcutaneous microvascularization: analysis of the presence, distribution, and flow pattern in small vessels using high-sensitivity color Doppler or MFI;

• capillary fragility and inflammation: correlation with echotexture (heterogeneity, relative hypoechogenicity,

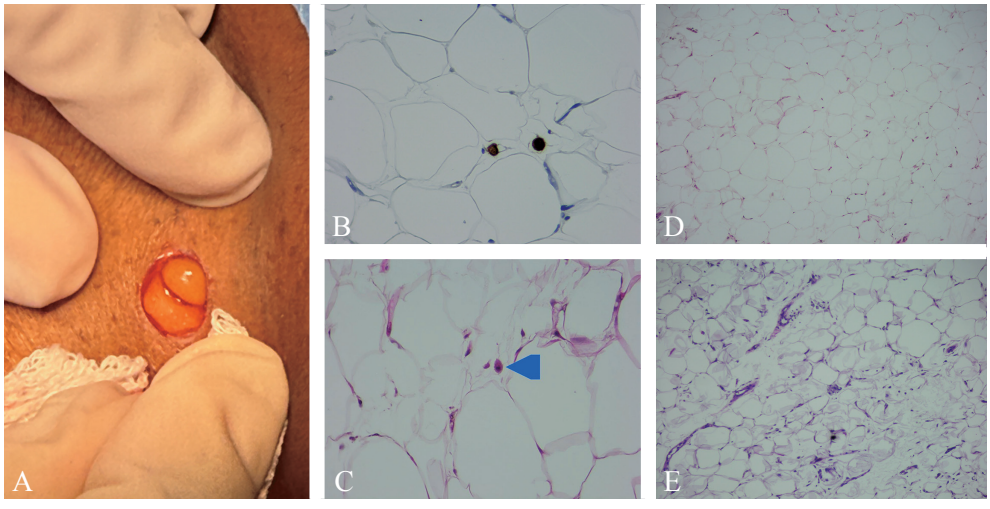


Figure 9.—Correlation with histology in lipedema. A) Histological image of a biopsy specimen obtained from the trochanteric region of a patient with grade II lipedema. B) Adipocyte hyperplasia within the subcutaneous tissue. C) Mast cell infiltration stained with hematoxylin and eosin. D) Mast cell infiltration highlighted by immunohistochemistry. E) Foci of cystic change consistent with steatonecrosis.

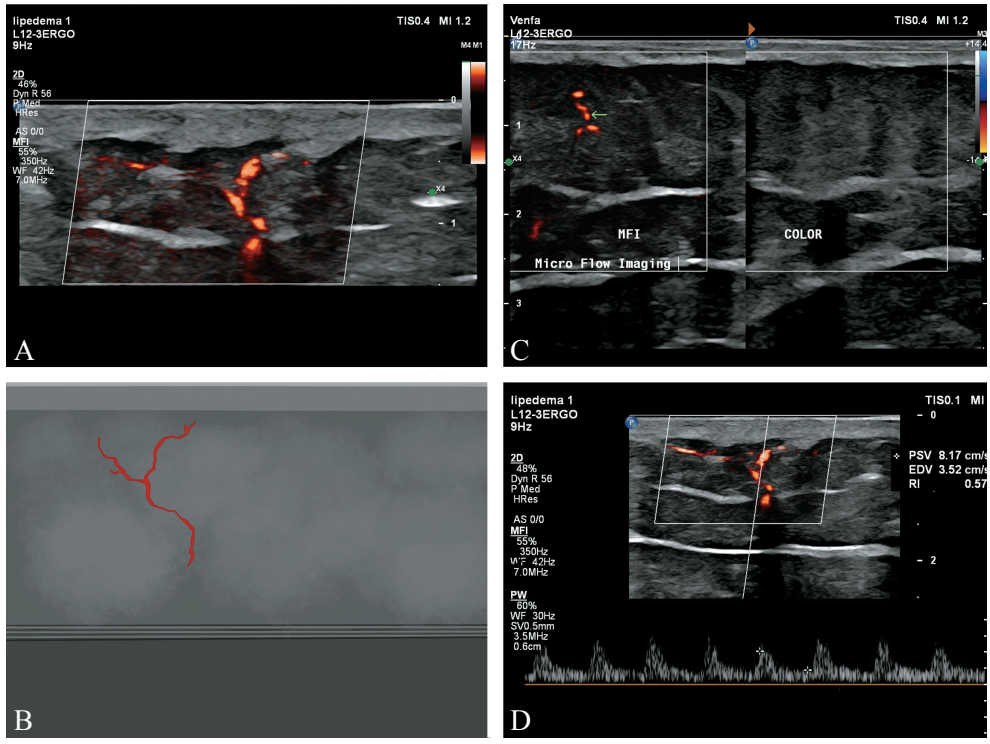


Figure 10.—Vascularization in lipedematous tissue. A) MFI of the trochanteric ("saddlebag") region demonstrating small vessels surrounding disorganized subcutaneous fibers, detected using high-sensitivity Doppler. B) Schematic drawing illustrating the microcirculation pattern within the subcutaneous tissue. C) Conventional color Doppler mapping of the same region, in which these small vessels are not identified. D) Spectral Doppler analysis showing a low-resistance flow pattern (Resistive Index <0.7).
MFI: Micro Flow Imaging.

anechoic areas) and with clinical data (easy bruising, pain, edema).

These findings contribute to characterizing lipedema as a chronic inflammatory condition of adipose tissue and the microvasculature, with potential implications for therapeutic management, especially regarding compression therapy and surgical intervention.

Differential diagnosis

The proposed protocol facilitates differential diagnosis by integrating structural, fascial, and microvascular ultrasonographic findings.

Differential diagnosis of lipedema requires integration of clinical and ultrasonographic findings, as several conditions may present with limb enlargement or adipose tissue alterations (Figure 11). High-resolution ultrasonography, complemented by fascial assessment and microcirculation evaluation, allows differentiation of lipedema from lymphedema, obesity, lipohypertrophy, and subcutaneous nodules of other etiologies.

Lipedema vs. *lymphedema*

Lymphedema has a pathophysiology related to lymphatic system dysfunction, often involving the dorsum of the foot and potentially presenting a positive Stemmer sign, unlike lipedema, which spares the feet and maintains a symmetric limb distribution.[35]

On ultrasound, lymphedema shows the classic "honeycomb" pattern, with multiple hypoechoic interlobular spaces, dermal thickening, and loss of fascial definition. Lipedema, in contrast, shows homogeneous subcutaneous thickening, thickened but organized septa, hypoechoic nodules or nodules with an anechoic center, and preservation of the superficial fascia. The computer-assisted dermal echogenicity analysis described by Iker[24] further supports the ability to distinguish between the two entities.

Lipedema vs. *obesity*

In obesity, adipose tissue enlargement is diffuse, without pain on palpation, allodynia, or bruising — features characteristic of lipedema.

On ultrasound, obesity shows thickened subcutaneous tissue with homogeneous echotexture, preserved septa, and absence of specific nodules.

In contrast, lipedema shows tissue heterogeneity, septal thickening and tortuosity, and variable changes in the superficial and deep fasciae.[5, 18] Histologic alterations such as chronic low-grade inflammation, fibrosis, and extracellular remodeling described by von Atzigen3 are absent in isolated obesity.

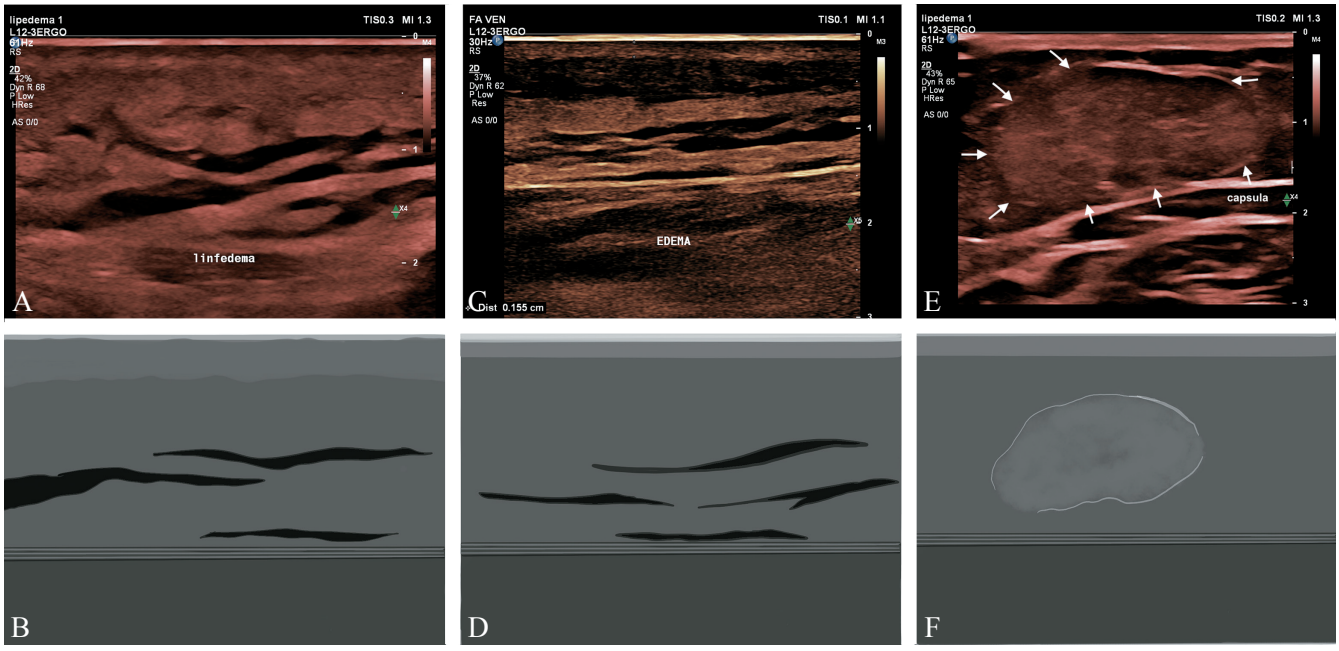


Figure 11.—Differential diagnosis of lipedema by ultrasonography. A) Lymphedema: ultrasonographic image showing dermal thickening with hypoechoic lamellae corresponding to lymphatic fluid accumulation, a feature not observed in lipedema. B) Schematic drawing illustrating the ultrasonographic appearance of lymphedema. C) Edema: ultrasonographic image demonstrating absence of dermal thickening with the presence of hypoechoic lamellae corresponding to interstitial fluid. D) Schematic drawing illustrating edema. E) Lipoma: ultrasonographic image showing a nodular lesion surrounded by a well-defined capsule, a feature not observed in lipedema-related nodules. F) Schematic drawing illustrating a lipoma.

Lipedema vs. *lipohypertrophy*

Lipohypertrophy is characterized by regional fat enlargement without pain, bruising, or functional symptoms.

On ultrasonography, there is a uniform increase in superficial adipose tissue, preserved septa, absence of nodules, and a normal superficial fascia. There is no fascial remodeling or increased vascularization.

Von Atzigen *et al.*[3] demonstrated that lipohypertrophy lacks the inflammation and fibrosis present in lipedema, reinforcing its physiopathologic and ultrasonographic distinction.

Subcutaneous nodules of other etiologies

Lipomas, angiolipomas, panniculitis, and foci of steatonecrosis may mimic palpable nodules. Lipomas show well-defined contours and homogeneous echotexture; angiolipomas exhibit internal vascularization; panniculitis presents diffuse edema and hyperemia; steatonecrosis nodules tend to be focal and asymmetric.

In lipedema, nodules are multiple, diffuse, and associated with septal disorganization and fascial changes, and may show anechoic areas corresponding to microsteatonecrosis.[3, 5]

Discussion

The present protocol consolidates an integrative approach combining clinical, histologic, and ultrasonographic findings in lipedema, emphasizing the role of tissue, fascial, and microvascular analysis in characterizing the disease. The proposal has clinical applicability, potential reproducibility, and aims toward multicenter standardization, in line with the most recent international guidelines.[1, 31, 32]

Unlike previous approaches focused on isolated structural or qualitative features, this protocol integrates quantitative, qualitative, and functional parameters into a unified diagnostic framework.

Histologic studies describe increased interstitial space, expansion of the extracellular matrix with proteoglycan deposition, macrophage infiltration, and perivascular fibrosis, consistent with chronic low-grade inflammation.[1, 3, 33] Some studies show elevated levels of angiogenic mediators (such as vascular endothelial growth factor C [VEGF-C]) and infiltration of M2 macrophages, without marked structural changes in the lymphatic network, suggesting functional microangiopathy rather than classic lymphatic obstruction.[33]

These findings largely explain the ultrasonographic

characteristics described by Amato *et al.*[6] and Cestari,[5] who report subcutaneous thickening, hypoechoic or heterogeneous nodules, superficial fascia thickening, and microvascular changes, with relative preservation of fascial architecture compared with classic lymphedema. Such changes may be interpreted as markers of connective tissue remodeling with biomechanical and sensory repercussions.

Recent efforts to improve ultrasonographic characterization of lipedema have included qualitative classification systems based on structural patterns, which highlight the potential of imaging but remain limited by subjectivity and interobserver variability.[7]

In parallel, algorithm-based and quantitative diagnostic approaches, such as classification models derived from statistical analysis, have been proposed to improve diagnostic accuracy.[8] While these models provide a simplified and useful approach for differential diagnosis, they rely exclusively on clinical variables and do not incorporate imaging-based parameters such as subcutaneous thickness, tissue architecture (including nodularity), fascial assessment, and microvascular analysis, which are integrated in the present protocol.

The present protocol builds upon these approaches by integrating structural, functional, and anatomical parameters into a single, standardized framework, aiming to improve reproducibility and clinical applicability.

The use of high-resolution ultrasonography, elastography, and microvascular imaging techniques to characterize lipedema has been rapidly expanding. Amato *et al.*[6] proposed anatomic reference points for subcutaneous measurement, establishing cutoffs with sensitivity and specificity above 85% for sonographic diagnosis. Pirri *et al.*[18] demonstrated that fascial thickening and reduced mobility are associated with greater reported pain and tissue stiffness, supporting the hypothesis of myofascial dysfunction secondary to interstitial edema and fibrosis.

German guidelines (S1 and S2K) emphasize that lipedema is associated with increased lymph flow in early phases and progressive slowing in advanced stages, outlining a functional evolution parallel to anatomic changes, which aligns with sonographic findings of thickening, remodeling, and microvascular alteration.[31, 32]

In addition, several studies indicate that ultrasonography can help distinguish lipedema from lymphedema, especially through the relative preservation of fasciae and the absence of the classic "honeycomb" pattern typical of lymphedema, as well as differences in dermal and subcutaneous echogenicity.[24, 34, 35]

Reproducibility and challenges

The main advantage of the proposed protocol is the possibility of reproducibility across different centers using objective, measurable parameters in well-defined anatomic regions.

By combining quantitative thresholds, qualitative characterization, and functional microvascular assessment, the protocol aims to reduce subjectivity and improve interobserver agreement.

However, interpretation requires specific training and familiarity with ultrasound anatomy of the subcutaneous tissue and fasciae. Distinguishing stable adipose hypertrophy, interstitial edema, and fascial remodeling can be subtle.

Studies such as Iker *et al.*[24] show that computer-assisted tools to measure dermal and subcutaneous echogenicity can increase objectivity and reduce interobserver variability. Another difficulty is the influence of factors such as BMI, hormonal profile, and vascular comorbidities (venous insufficiency, mixed lymphedema), which may overlap and modify the ultrasound pattern.[17, 36]

Limitations of the study

Limitations include:

- lack, to date, of definitive international standardization of anatomic points and cutoffs for superficial and deep fascia;
- scarcity of multicenter studies comparing populations with different BMI profiles, ethnicity, age, and disease stage;
- influence of comorbidities (venous insufficiency, secondary lymphedema, severe obesity) still insufficiently stratified in ultrasound series.

In addition, this protocol represents an expert-based framework and has not yet undergone formal prospective validation, which is necessary to confirm its diagnostic accuracy and reproducibility across different populations.

As highlighted by Herbst *et al.*,[1] many symptoms reported by patients — tension, heaviness in the legs — do not always correlate with classic fluid retention, but rather with changes in the extracellular matrix, mechanotransduction, and the fascial system, requiring an integrated approach and careful interpretation of imaging findings.

Multicenter perspectives and clinical impact

Standardization of the protocol described paves the way for multicenter studies aimed at validating parameters in different contexts.

Future studies should focus on prospective validation,

interobserver agreement, and correlation with clinical severity and histopathological findings.

Integration of structural ultrasonography, elastography, microvascular assessment, and complementary methods (such as 3D bioimpedance and 3T MRL) may contribute to more refined clinical and therapeutic stratification algorithms.[5, 20]

A standardized anatomical mapping (cartography) of lipedema was developed to document bilateral involvement and distribution patterns in both lower and upper limbs (Figure 5). Early recognition of the fascial and microvascular pattern of lipedema is essential to guide conservative treatment (including supervised exercise, compression therapy, and metabolic interventions), as well as to plan liposuction and other surgical approaches more safely and rationally.

Conclusions

The protocol presented here proposes a detailed standardization of the ultrasound evaluation of lipedema, based on measurable parameters and previously described histologic correlations.

This protocol should be interpreted as a multidisciplinary, expert-based framework designed to support the standardized assessment of lipedema using ultrasonography.

Integration of clinical, morphologic (subcutaneous tissue and fasciae), and functional (microcirculation, elastography) findings advances understanding of the disease pathophysiology, reinforcing its distinct nature compared with simple obesity and lymphedema.

By combining quantitative measurements, qualitative assessment, and microvascular analysis, the proposed approach addresses current limitations of isolated imaging strategies and may improve diagnostic consistency across centers.

Dissemination of this methodology in multicenter studies may contribute to global validation of diagnostic criteria, with direct impact on clinical practice, on the indication and optimal timing of surgical interventions, and on individualized selection of conservative therapies.

However, prospective multicenter studies are required to validate the reproducibility, diagnostic accuracy, and clinical applicability of this protocol in different populations.

International standardization of fascial imaging and ultrasound mapping therefore represents an essential step toward recognition of lipedema as a specific entity within the vascular and metabolic spectrum, with its own diagnostic and therapeutic approach.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Data availability
The data associated with the paper are available from the corresponding author upon reasonable request.

Ethical approval
As this study describes the development of a diagnostic protocol and does not involve prospective patient inclusion or intervention, Ethical approval was waived in accordance with institutional policies. The authors confirm that this article does not report any studies involving embryos, gametes and human embryonic stem cells conducted by the authors. The authors confirm that this article does not report any studies involving animals conducted by the authors.

Informed consent
Informed consent was waived as this study describes the development of a diagnostic protocol and does not involve prospective patient inclusion or intervention, as described in the appropriate section of the manuscript.

Authors' contributions
Fanilda Souto Barros and Nathalia Cardoso Oliveira have given substantial contributions to the study conception; Nathalia Cardoso Oliveira contributed to the protocol design, to the manuscript draft, and to the coordination of the multicenter framework; Fanilda Souto Barros contributed to the development of the ultrasound protocol, to the microvascular imaging analysis; Joana Storino contributed to the imaging acquisition, to the illustrations, and to the protocol validation; Jubiza Pusic contributed to the protocol refinement; Chantal Agüero Wagner contributed to the imaging analysis; Fanny Rodríguez Santos contributed to the histological correlation; Chantal Agüero Wagner and Patrícia Henriques Lyra contributed to the data acquisition; Jubiza Pusic, Fanny Rodríguez Santos, and Patrícia Henriques Lyra contributed to the data interpretation; Fanilda Souto Barros, Joana Storino, Jubiza Pusic, Chantal Agüero Wagner, Fanny Rodríguez Santos, and Patrícia Henriques Lyra contributed to the manuscript critical revision for important intellectual content. All authors read and approved the final version of the manuscript.

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