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A Review of Microvascular Dysfunction in Lipedema: Dissociation between Histopathology and Doppler Ultrasound

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ABSTRACT

Lipedema is a chronic subcutaneous adipose tissue disorder characterized by symmetric and disproportionate fat deposition in the lower or upper limbs; associated with pain, tenderness, edema and spontaneous bruising. Histopathological evidence points to chronic low-grade inflammation and microvascular alterations; however, conventional Doppler methods rarely demonstrate hyperemia or inflammatory patterns. Integrate histological and molecular evidences explaining this dissociation and introduce the potential of high-sensitivity Doppler technologies in microcirculation assessment. It is a narrative review of PubMed/MEDLINE-indexed literature, focusing on original studies involving human biopsies and microvascular-interstitial axis analyses in lipedema. The studies selected converge toward a microvascular dysfunction model, characterized by high capillary permeability, endothelial dysfunction, extracellular matrix remodeling, macrophage infiltration and activation of angiogenic pathways; without evidence of arteritis. Only one study evaluated ultra-microangiography in lipedema, with findings not yet reproduced. The lipedema constitutes a chronic functional microangiopathy; this fundamental alteration is not detectable by conventional Doppler. High-sensitivity technologies partially reduce this gap, but remain exploratory tools requiring multicenter validation.

1. INTRODUCTION

Lipedema is a chronic disease characterized by symmetric and disproportionate deposition of subcutaneous fat in the lower and upper limbs; sparing the trunk, feet, and hands; affecting approximately 12.3% of women in Brazil [1].

Clinical manifestations are heavy, painful sensations at the end of the day, hypersensitivity to touch, edema with a negative Godet sign and spontaneous bruising [1, 2]. Although the pathophysiology remains poorly understood, being complex and multifactorial; may be a relationship to dietary, genetic, and hormonal factors [3].

Advances in the pathophysiology of lipedema have been made in last decades based on histopathological analyses, showing that the microenvironment is altered due to adipocyte hypertrophy, low-grade chronic inflammation, stromal remodeling, and microvascular-lymphatic changes [4, 5].

Ultrasonography (US) already has well-defined diagnostic criteria for lipedema and has also proven effective in identifying some of these tissue alterations, especially morphological patterns of the dermis and hypodermis [6, 7]. Doppler US may be a complementary tool for evaluating microcirculation; however, its applicability looks be limited.

2. METHODOLOGY

A narrative literature review was conducted with the aim of relating the microvascular aspects, both histological and ultrasonographic, involved in lipedema; no primary data were collected.

The bibliographic search was performed by 2 independent researchers, between January and April 2026, in the PubMed/MEDLINE database using controlled descriptors (MeSH) and free-text terms combined with Boolean operators: lipedema, lipoedema, subcutaneous adipose tissue, biopsy, histopathology, microvascular, microangiopathy, lymphatic, lymphangiogenesis, perivascular inflammation, low-grade inflammation, hypoperfusion, hypoxia, VEGF-C, macrophages, capillary remodeling, and interstitial fibrosis. The search was complemented by manual screening of selected articles references.

Included all original human studies with lipedema diagnosis that performed skin and/or subcutaneous adipose tissue biopsy; and described histopathological and/or molecular findings of microvascular, lymphatic or inflammatory alterations directly related to the pathophysiology of disease. Editorials, opinion

pieces, and reports without histological analysis or microvascular correlation were excluded. Reviews were consulted only for conceptual contextualization.

Included studies have information extracted on population characteristics, biopsy technique, histopathological and immunohistochemical methods, microvascular findings, evidence of inflammation and indicators of tissue hypoperfusion or hypoxia. Vascular findings were integrated qualitatively with the physical principles and technical limitations of Doppler US, adding high-sensitivity technologies including Mindray ultra-microangiography (UMA®). Due to methodological heterogeneity, the synthesis was conducted qualitatively, acknowledging the exploratory nature of the proposed correlations.

3. RESULTS

The search in PubMed/MEDLINE database identified 7 eligible studies. Of these, 5 were predominantly based on histopathological analyses, 1 was only US comparison, and only 1 used advanced functional ultrasonography for direct assessment of microvascularization.

Among the histopathological studies, the most frequent finding was capillary endothelial dysfunction, described in 3 studies, characterized by disruption of intercellular junctions and increased vascular permeability. Microvascular dilation, hemorrhagic areas, angiogenesis and tissue remodeling were reported in only 1 study. Only 1 study reported increased vascular resistance to flow in a specific lipedema environment, suggesting a hypoxic-ischemic pattern.

Only 1 study was able to evaluate the microcirculation with Doppler, using UMA®. No additional imaging studies capable of assessing microcirculation in lipedema were found.

4. DISCUSSION

For a long time, lipedema has been associated with a low-grade chronic tissue inflammatory process documented by biopsies. However, the absence of detectable hyperemia on conventional Doppler US may not represent a contradiction, but a method limitation, due to its low sensitivity for detecting slow flow in small vessels. New histopathological evidence shows that lipedema does not represent a classic inflammatory disease, but a set of alterations in the microenvironment of subcutaneous adipose tissue, including microvascular changes [4, 5, 8].

Michelini *et al.* (2025) demonstrated histologic differences between lipedema and non-lipedema tissue from the same patient (total patients: 10), showing widened spaces between endothelial cells, compromising vascular barrier integrity and increasing permeability. This finding supports the theory of chronic capillary hyperpermeability, in which the main event is the constant extravasation of fluid and macromolecules to interstice, rather than increased flow. This may explain why Doppler US cannot detect the flow change, because it is not designed to detect permeability or endothelial integrity, so conventional Doppler US flow remains unchanged [4].

Microscopic study on fat from liposuction of 5 lipedema and 4 non-lipedema, by Strohmeier *et al.* (2022), confirmed migration of cells to perivascular spaces due to increased endothelial permeability in early lipedema stages, possibly in subclinical patients and preceding tissue remodeling. Because the alterations involve capillary permeability, Doppler US shows no change due to its methodological limitation [8] again.

Complementarily, Felmerer *et al.* (2020), in microscopic and histochemical analysis of patients undergoing plastic surgery in 10 lipedema versus 10 non-lipedema patients, found increased VEGF-C and macrophage infiltration with preserved morphological features of lymphatic and blood vessels. This suggests that, at least in early stages, lipedema does not present structural vascular changes; there may be associated lymphatic dysfunction, with low-grade chronic inflammation, triggering a compensatory lymphangiogenic response. Functional lymphatic alteration and increased capillary permeability may occur without Doppler US correlation, because flow in these structures is so slow [9].

Al-Ghadban *et al.* (2019) studied skin biopsies of 30 lipedema and 19 non-lipedema patients; they observed in advanced stages of lipedema: microvascular and lymphatic dilation, angiogenesis, increased macrophages

present in the skin, and adipose hypertrophy. These findings suggest active microvascular remodeling, possibly driven by chronic inflammation, compression from disordered tissue expansion and hypoxia. These microscopic vessel changes would not present sufficient flow to be detected by Doppler US. Microvascular physiology does not imply that more or dilated vessels increase tissue perfusion; they may be immature and inefficient, with angiogenesis coexisting with hypoperfusion, also undetectable by Doppler US [10].

In a histopathological study of 2 painful subcutaneous nodules, identified by US in a case report of lipedema patient, Vargas *et al.* (2025) reported hemorrhage with hemosiderin deposition, steatonecrosis, eosinophilic granular content and histiocytic reaction, associated with immature and fragile neoangiogenesis. Doppler US examination showed increased arterial resistance indices in adjacent regions to the hemorrhagic area. This suggests impaired tissue perfusion, possibly related to extrinsic compression by hypertrophy of adipose tissue. It may occur due to an imbalance between local supply and metabolic demand, stimulating neoangiogenesis, which, combined with increased subcutaneous compartment pressure, would be immature and inefficient, consistent with microscopic findings reported in other studies [11].

In ultrasonographic analysis of the same painful nodules in 20 patients, Foureaux *et al.* (2025) identified 4 distinct US patterns likely corresponding to different evolutionary phases of hemorrhage. Doppler US was not assessed in that study, but it is suspected that the findings would mirror those of Vargas *et al.* [12].

Facing the dilemma of vasodilation and inflammation versus hypoxia and hemorrhage, Kempa *et al.* (2024) evaluated microvascularization by US using an ultrasensitive flow detection technology, called ultra-microangiography (UMA®), in 25 lipedema and 10 non-lipedema patients. They demonstrated increased detection of low-velocity flow compared with conventional Doppler US, representing a technological advance for detecting small and slow-flow vessels. UMA® showed an increased number of detectable vessels in the subcutaneous tissue of lipedema patients versus controls, suggesting promise for microvascular flow detection and inflammatory hyperemia. However, it is the single study evidence in the literature, dependent on the technology available in only one device, without validation or reproducibility. Results are imaging-only based, without histopathologic correlation, so it cannot be concluded that this quantification directly reflects dilated microvessels or tissue perfusion; it might correspond to intermittent flow, amplification of marginal signals, or even clutter [13].

The 7 studies, despite some contradictory findings, agree that lipedema involves microscopic or functional changes in the capillaries or lymphatic system, named microvascular dysfunction or functional microangiopathy, although it has not yet been correlated with lipedema stages. At certain stages, there may be hyperemia with increased flow; in others, there may be hypoperfusion associated with increased capillary permeability, interstitial invasion by fluid and inflammatory cells, leading to extracellular matrix remodeling, disorganized immature angiogenesis, and probable impairment of tissue perfusion [11, 12, 14]. Adipocyte hypertrophy and hyperplasia increase the tissue volume to be perfused, making the distance greater between vessels and target tissue, challenging homogeneous diffusion throughout the tissue [15]. Interstitial extravasation and microvascular compression may maintain a state of chronic hypoxia; despite neoangiogenesis and capillary dilation, perfusion would remain insufficient [16, 17].

Among the physical principles of Doppler US, flow detection is via frequency shift generated by moving erythrocytes; its sensitivity depends on flow velocity, vessel caliber, insonation angle, transducer frequency and type, and above all, the signal-to-noise ratio [18, 19]. The capillary bed is so thin, with low velocities and reduced intraluminal volume, which can produce weak reflected signals and reduce Doppler US sensitivity. Additionally, lipedema adipose tissue with fibrosis, thickened septa, acoustic heterogeneity, and interstitial inflammatory changes that increase artifacts; complicating to differentiate true flow signals from clutter [20]. Doppler US detects blood movement, not tissue extraction of oxygen and nutrients; capillary permeability and impaired tissue diffusion may prevent transport to the more distant cells.

The ultrasensitive flow-detection technologies, such as UMA® (Mindray), MV-Flow® (Samsung), LumiFlow® (Samsung), rely on complex noise-suppression and low-intensity signal enhancement algorithms; as sensitivity increases, susceptibility to acoustic noise also rises. Thus, these methods can approach the physical limit between true microflow and low-frequency artifacts, tissue vibration, or residual electronic

noise [21]. In lipedema, this issue is more pronounced due to subcutaneous structural disorganization, creating an acoustically unfavorable environment in which detection of minimal flow signals must be interpreted cautiously.

Evaluation of microvascular flow in lipedema by ultrasensitive methods remains problematic, mainly due to lack of technical parameters (depth, frequency, wall filter, gain, and interpretation criteria), making reproducibility difficult and underscoring the immature stage of flow-assessment methodology in lipedema [22].

The most important points from the 7 available studies and their implications for circulation and Doppler US are summarized in **Table 1**. These data suggest that lipedema comprises a true microvascular dysfunction demonstrated by histopathology, but not yet adequately correlated with Doppler US, despite promising emerging technologies. Current knowledge of microvascular Doppler US in lipedema should be interpreted as an exploratory tool to assess inflammatory activity, microperfusion, or therapeutic response.

Table 1. Summary of the main histopathological and microvascular findings in lipedema biopsies and their implications for Doppler US assessment.

Study	Main Findings in Lipedema	Implication for Doppler US
Michelini *et al.*, 2025 [4]	Endothelial and capillary alterations in adipose tissue; increased intercellular spaces	No implications
Strohmeier *et al.*, 2022 [8]	Cellular migration into the perivascular space; increased endothelial permeability in early stages	No implications
Felmerer *et al.*, 2020 [9]	Elevated VEGF-C levels; macrophage infiltration; preserved lymphatic morphology; functional (non-structural) lymphatic dysfunction with lymphangiogenesis	No implications
Al-Ghadban *et al.*, 2019 [10]	Dilated blood and lymphatic microvessels; angiogenesis; microvascular remodeling; macrophage infiltrates; subcutaneous hypertrophy; chronic inflammation	No implications
Vargas *et al.*, 2025 [11]	Hemorrhage; immature angiogenesis; steatonecrosis; increased Doppler US resistance in subcutaneous nodules	Suggestive of hypoxic-ischemic distress
Foureaux *et al.*, 2025 [12]	Distinct patterns of painful nodules (different evolutionary phases?)	No implications
Kempa *et al.*, 2024 [13]	UMA® (capable of detecting flow in microvessels; more sensitive than conventional Doppler); increased number of vessels in lipedema vs. controls	Potential technology for advancing microvascular assessment, though not yet reproduced

5. CONCLUSIONS

Lipedema should be considered a complex pathology, far beyond simple subcutaneous adipocyte proliferation. It is associated with chronic functional microangiopathy, resulting from endothelial dysfunction, increased capillary permeability and tissue hypoxia; in the absence of vasculitis. The lack of hemodynamic changes on conventional Doppler US is expected, primarily because the alterations occur at the capillary level, representing a method limitation.

Doppler US should not be used as a marker of disease activity, nor as an indicator of therapeutic response; its primary role remains the exclusion of macrovascular conditions, particularly chronic venous insufficiency.

Emerging technologies sensitive to low-velocity microvascular flow are expected to expand the ability to assess microcirculation in lipedema. However, these tools remain limited in availability and study; they depend on standardization, reproducibility and multicenter validation.

Prospective controlled studies correlating histology, microcirculation, and clinical progression are necessary to determine whether UMA®-based assessment may. In the future, it may serve as a reliable pathophysiological marker for diagnosis, monitoring, or evaluation of therapeutic response in lipedema.

ETHICAL APPROVAL

As a literature review without primary data collection, this study did not require approval from a research ethics committee.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Amato, A.C.M., Amato, F.C.M., Amato, J.L.S. and Benitti, D.A. (2022) Lipedema Prevalence and Risk Factors in Brazil. *Jornal Vascular Brasileiro*, **21**, e20210198. https://doi.org/10.1590/1677-5449.202101982
2. Herbst, K.L. (2012) Rare Adipose Disorders (RADs) Masquerading as Obesity. *Acta Pharmacologica Sinica*, **33**, 155-172. https://doi.org/10.1038/aps.2011.153
3. Faerber, G., Cornely, M., Daubert, C., Erbacher, G., Fink, J., Hirsch, T., *et al.* (2024) S2K Guideline Lipedema. *JDDG*: *Journal der Deutschen Dermatologischen Gesellschaft*, **22**, 1303-1315. https://doi.org/10.1111/ddg.15513
4. Michelini, S., Greco, S., Vaia, N., Puleo, V., Pellegrino, P., Di Vincenzo, A., *et al.* (2025) Endothelial Cell Alterations in Capillaries of Adipose Tissue from Patients Affected by Lipedema. *Obesity*, **33**, 695-708. https://doi.org/10.1002/oby.24244
5. Kruppa, P., Gohlke, S., Łapiński, K., Garcia-Carrizo, F., Soultoukis, G.A., Infanger, M., *et al.* (2023) Lipedema Stage Affects Adipocyte Hypertrophy, Subcutaneous Adipose Tissue Inflammation and Interstitial Fibrosis. *Frontiers in Immunology*, **14**, Article ID: 1223264. https://doi.org/10.3389/fimmu.2023.1223264
6. Amato, A.C.M., Saucedo, D.Z., Santos, K.d.S. and Benitti, D.A. (2021) Ultrasound Criteria for Lipedema Diagnosis. *Phlebology*: *The Journal of Venous Disease*, **36**, 651-658. https://doi.org/10.1177/02683555211002340
7. Vargas, D., Santos, A.M.R., Bueno, A.N., Bezerra, A.S., Bianchi, M.d.A. and Amato, A.C.M. (2025) The Challenge of a Qualitative Ultrasonographic Classification in Lipedema. *Journal of Biomedical Science and Engineering*, **18**, 106-112. https://doi.org/10.4236/jbise.2025.184008
8. Strohmeier, K., Hofmann, M., Jacak, J., Narzt, M., Wahlmueller, M., Mairhofer, M., *et al.* (2022) Multi-Level Analysis of Adipose Tissue Reveals the Relevance of Perivascular Subpopulations and an Increased Endothelial Permeability in Early-Stage Lipedema. *Biomedicines*, **10**, Article No. 1163.

https://doi.org/10.3390/biomedicines10051163

9. Felmerer, G., Stylianaki, A., Hollmén, M., Ströbel, P., Stepniewski, A., Wang, A., *et al.* (2020) Increased Levels of VEGF-C and Macrophage Infiltration in Lipedema Patients without Changes in Lymphatic Vascular Morphology. *Scientific Reports*, **10**, Article No. 10947. https://doi.org/10.1038/s41598-020-67987-3
10. AL-Ghadban, S., Cromer, W., Allen, M., Ussery, C., Badowski, M., Harris, D., *et al.* (2019) Dilated Blood and Lymphatic Microvessels, Angiogenesis, Increased Macrophages, and Adipocyte Hypertrophy in Lipedema Thigh Skin and Fat Tissue. *Journal of Obesity*, **2019**, Article ID: 8747461. https://doi.org/10.1155/2019/8747461
11. Vargas, D., Lellis, R.F., Chagas, L.C., Saiki, P.Y., Santos, A.M.R., Bianchi, M.d.A., *et al.* (2025) Case Report of Painful Nodules in Lipedema: Correlation between Qualitative Ultrasonographic Classification and Histological Findings. *Journal of Biomedical Science and Engineering*, **18**, 372-383. https://doi.org/10.4236/jbise.2025.188026
12. Foureaux, T.O., Vargas, D., Lellis, R.F., Chagas, L.C., Cunha, I.W.d., Saiki, P.Y., *et al.* (2025) The Hyperechoic Nodules in Lipedema Are Not All the Same: Description of Criteria and Their Qualitative Patterns. *Journal of Biomedical Science and Engineering*, **18**, 401-407. https://doi.org/10.4236/jbise.2025.1810029
13. Kempa, S., Tessmann, V., Prantl, L., Schmid, S., Müller, M., *et al.* (2024) The Value of Sonographic Microvascular Imaging in the Diagnosis of Lipedema. *Clinical Hemorheology and Microcirculation*, **86**, 99-108. https://doi.org/10.3233/ch-238103
14. Poojari, A., Dev, K. and Rabiee, A. (2022) Lipedema: Insights into Morphology, Pathophysiology, and Challenges. *Biomedicines*, **10**, Article No. 3081. https://doi.org/10.3390/biomedicines10123081
15. von Atzigen, J., Burger, A., Grünherz, L., Barbon, C., Felmerer, G., Giovanoli, P., *et al.* (2023) A Comparative Analysis to Dissect the Histological and Molecular Differences among Lipedema, Lipohypertrophy and Secondary Lymphedema. *International Journal of Molecular Sciences*, **24**, Article No. 7591. https://doi.org/10.3390/ijms24087591
16. Hines, E.A. (1952) Lipedema and "Physiologic" Edema. *Mayo Clinic Proceedings*, **27**, 7-9. https://doi.org/10.1016/s0025-6196(26)02414-6
17. Allen, M., Schwartz, M. and Herbst, K.L. (2020) Interstitial Fluid in Lipedema and Control Skin. *Women's Health Reports*, **1**, 480-487. https://doi.org/10.1089/whr.2020.0086
18. Waggoner, A.D. and Perez, J.E. (1990) Principles and Physics of Doppler. *Cardiology Clinics*, **8**, 173-190. https://doi.org/10.1016/s0733-8651(18)30361-8
19. Burns, P.N. (1993) Principles of Doppler and Color Flow. *Radiologia Medica*, **85**, 3-16.
20. Rubin, J.M. (1994) Spectral Doppler US. *RadioGraphics*, **14**, 139-150. https://doi.org/10.1148/radiographics.14.1.8128046
21. Blair, W.F., Brown, T.D. and Greene, E.R. (1988) Pulsed Ultrasound Doppler Velocimetry in the Assessment of Microvascular Hemodynamics. *Journal of Orthopaedic Research*, **6**, 300-309. https://doi.org/10.1002/jor.1100060219
22. Faria, A.M., Valerio, C.M., Barcellos, C.R., Oliveira, R.A., Trujilho, F.R., Baiocchi, J.M.T., *et al.* (2026) Unraveling Lipedema: Comprehensive Insights and the Path to Future Discoveries. *NPJ Metabolic Health and Disease*, **4**, Article No. 3. https://doi.org/10.1038/s44324-025-00093-y