LIPEDEMA FOUNDATION

Lipedema Research Roadmap

Executive Summary

2023

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Contributors (alphabetical)

Felicitie Daftuar[1], Guy S. Eakin[1], Stephanie Galia[1], Laura Harmacek[1], Jonathan Kartt[1], Stephanie Peterson[1]

Affiliations

[1] Lipedema Foundation, Greenwich, CT, USA

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[1] Nothing to Disclose

Corresponding contributor contact information

Jonathan Kartt - roadmap@Lipedema.org

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Their contributions have been invaluable and made this document more representative of the interests of people with Lipedema and the broader field.

Introduction

In the past decade, awareness of Lipedema, predominantly affecting women and distinct from other adipose conditions, has skyrocketed. Support groups have become sustainable, producing libraries of content and holding high-quality conferences around the world. However, clinical awareness lags; many patients still self-diagnose due to lack of knowledge.

With data suggesting the condition affects 5 to 12% of post-adolescent women and some percentage of adolescent girls, this medical response puts enormous stress on many patients. Challenges include body shame, pain, poor quality of life, and loss of mobility—which lead to psychological distress and mental health impacts. Some patients reach a state of helplessness; anecdotal reports link suicide to Lipedema.

Research also lags patient awareness but appears to be at an inflection point, with 50% of papers published in the past 5 years. However, critical factors are still missing, including adequate numbers of knowledgeable physicians, consensus on diagnostic criteria, sufficient treatment options, and large-scale, well-funded research.

The Lipedema Research Roadmap aims to enhance knowledge, reduce barriers, facilitate exchange of ideas, and advance best practices. It presents recommendations developed in collaboration with more than 60 diverse stakeholders, and incorporates more than 1,300 suggestions and comments from reviewers.

While the primary audiences are researchers, international funders, and research-oriented clinicians, execution will require an array of stakeholders. Though written for technical audiences, we hope patients find the Roadmap to be representative of their interests and suggestive of ways to help advance research.

As with other underrecognized conditions, patients and forward-thinking clinicians have led in advancing awareness of Lipedema as a legitimate condition. It is our hope that this Research Roadmap can set the stage for increasing recognition and significant research advances in the decade to come.

This Executive Summary provides an overview of the full Roadmap, highlighting top recommendations. Readers should see the full Roadmap for extensive recommendations, figures, references, and supporting documents, available here: lipedema.org/roadmap.

The maturity of any research field depends on its human and financial resources. Lipedema clinical and basic science research is driven by a nascent but growing workforce with inconsistent access to funding and critical resources such as tissue samples. Nonetheless, because Lipedema is a complex and poorly understood condition, many "niches" are available for researchers to explore the field, advance their careers, and achieve international recognition and leadership.

The recommendations below support growth of the workforce through training and incentives, with an eye toward engagement of multidisciplinary teams and stronger integration with clinical and patient stakeholders. Establishment of research networks with access to pooled data, tissues, and expertise is oriented toward elevating the capacity of the field to execute high-quality research.

Key Challenges to Progress

- Small Workforce
- Limited Collaboration, Networks, Knowledge Translation, and Exchange
- Lack of Patient Empowerment and Engagement
- Insufficient Research Infrastructure and Participant Recruitment
- Insufficient Capacity to Leverage Technology

Objective 1. Top Recommendations

- Recruit researchers and clinicians from fields not well represented in the current workforce.
- Work with professional societies to raise awareness about diagnosis, treatment, and career opportunities. Advocate for inclusion in medical curricula and licensure requirements.
- Build researcher capacity to secure available funding.
- Increase government funding support for Lipedema, especially for longer-term projects.
- Establish Lipedema biobanks and encourage better sharing of resources across labs, especially tissue.
- Engage patients to help set the course of Lipedema research.
- Work to implement Lipedema-specific International Classification of Diseases (ICD) coding, which was adopted by the World Health Organization in 2019 as part of its 11th revision (ICD-11).

Lipedema researchers and clinicians have not reached consensus on the definition and reporting of the condition. Inconsistency is apparent in communications, published literature, and the diagnostic criteria adopted by different countries, which complicates professional communication. As a major consequence, researchers cannot easily compare results across studies, and attempts to do so can sow confusion. Additional challenges arise when incorrectly or self-diagnosed patients are enrolled in studies, or when different studies include or exclude different subpopulations (e.g., some exclude patients without pain or with central obesity), introducing analysis errors and impeding generalizability of findings.

Common terminolgy, diagnostic criteria, and reporting standards must be developed and implemented. Progress on this Roadmap objective will start the field on the path toward speaking the same language, training healthcare professionals, and enabling comprehension and comparison of data and conclusions across studies.

Key Challenges to Progress

- Use of varying criteria for diagnosis and staging across standards of care, geographies, clinics, and studies
- Inconsistent transparency and precision in reporting definitions of controls, inclusion and exclusion criteria, and other clinical measures
- Inconsistent terminology used to describe signs, symptoms, and other characteristics, especially edema, inflammation, texture, and nodules
- Reliance on a clinical diagnosis

Objective 2. Top Recommendations

- Convene the research and clinical community to develop universal diagnostic criteria for the purposes of research.
- Carefully consider and disclose definition of controls and control-matching mechanisms, especially age, body mass index (BMI), and race. Consider other parameters such as comorbid conditions, hormones, and body composition measurements.
- Develop and incentivize a common case report form (CRF) for research.
- Develop and incentivize publication reporting standards and conventions, especially around diagnosis, common terminology, demographics, and sample anatomical location.

Timely and accurate diagnosis is needed to characterize Lipedema biology, ensure comparability across studies, enable effective recruitment and stratification of study participants, and facilitate clinical trials. As research advances, accumulating evidence should enable greater standardization of clinical diagnosis and yield technologies to aid in diagnosis and treatment.

This chapter proposes a biomarker discovery framework based on categories used by the FDA-NIH Biomarker Consortium. As the bar for FDA biomarker qualification is very high, the authors do not necessarily advocate for pursuing regulatory qualification of biomarkers. This framework is used solely for organizing the pipeline of approaches.

Key Challenges to Progress

- Shared Signs and Symptoms with Common Comorbidities
- Difficulty in Diagnosing Early Stage 1 or Prodromal Stage
- Lack of Understanding of Risk and Susceptibility Factors
- Failure to Diagnose a Prodromal Stage, and to Understand Risk and Susceptibility
- Lack of Tools for Monitoring and Evaluating Progression and Prognosis

Objective 3. Top Recommendations

- Survey clinicians to refine key components of diagnosis, to support creation of a standardized clinical diagnosis method.
- Improve the current staging system to account for potential disease progression. Consider severity and impact on quality of life.
- In developing diagnostic tools, design studies to understand sensitivity, specificity, and other related measures.
- Adopt a biomarker framework. Prioritize the development of histologic, and secondarily, molecular biomarkers.

Studies of biological questions about Lipedema, such as the underlying conditions that lead to the disease or the effect on the adipose and its environment, can set the stage for advances in screening, prevention, and treatment. Scientific progress is not linear, and it is difficult to know in advance which investments will most likely generate breakthroughs. To increase the chance of discoveries that can lead to new diagnostic tools and therapies, the field must allocate resources strategically. This chapter prioritizes specific basic science fields because of their immediate potential, traditionally strong funding, existing therapeutic possibilities, and access to essential resources, skilled investigators, and adaptable tools and techniques.

Key Challenges to Progress

- Many signs and symptoms poorly characterized
- Initiation and progression triggers not well understood
- Lack of suitable animal and other model systems
- Difficulty recruiting patients and controls

Objective 4. Top Recommendations

- Understand initiation and exacerbation events (e.g., hormonal, genetic, cellular) to characterize the risk of developing Lipedema, and suggest potential prevention strategies.
- Understand progression to develop disease-modifying therapies that reduce the likelihood that a patient will develop severe Lipedema.
- Support rigorous deep phenotyping efforts to carefully describe the diverse phenotypic characteristics present in people with Lipedema.
- Explore the menstrual cycle's relationship to signs and symptoms. Analyze, in particular, circulating sex hormones.
- Utilize simple medical tests, such as urinalysis, to understand variations in the condition.
- Understand the adipose system and adipose environment as a driver of primary disease as well as disease progression.
- Profile immune cells and cytokines in peripheral blood and adipose tissue.
- Conduct studies that confirm the prevalence of different cognitive symptoms and investigate potential biological causes (e.g., brain fog).
- Characterize the adipose microenvironment in affected areas, with attention to lobule organization and fibrosis.

Although research into the basic biological questions about Lipedema prioritized in this Roadmap can help lead to effective therapies for the disease, several other principles of therapeutic development are also critical. First, effectively managing the condition's impact on patients will require developing high-quality outcome measures that reflect patient and clinical needs—which requires the identification of appropriate controls. Second, treatment development should respect the need for a broad array of options for patients, acknowledging differences in signs and symptoms and individual therapeutic goals. Finally, interventions should be evaluated for cost-effectiveness.

Recommendations to efficiently create opportunities to improve existing therapies or discover new interventions are summarized below.

Key Challenges to Progress

- Evidence on efficacy and safety of existing treatments is minimal
- Lack of mechanistic understanding limits ability to target and investigate repurposed and new therapies
- Limited understanding of which outcomes are most meaningful to patients
- Few studies focus on endpoints that assess functonal domains such as impact on daily life and physical activity

Objective 5. Top Recommendations

- Investigate the canonical belief that Lipedema tissue is resistant to caloric restriction.
- Conduct rigorous, sufficiently powered research on the contribution of diet, exercise, and other modifiable behavioral approaches to stopping or slowing disease progression, reversing disease, and improving quality of life.
- Leverage and validate patient-reported outcome measures (PROMs), clinician-reported outcomes measures (CROMs), integrative measurements of HRQOL in Lipedema populations, and measures of physical function and daily life.
- Conduct studies that disaggregate the effects of individual elements of therapy, and build upon existing small studies on conservative therapy.
- Understand patient prioritization of outcomes.
- Investigate the potential of GLP-1 receptor agonists (e.g., semaglutide) and future related drugs and drug classes in Lipedema patients.
- Further develop the research base around safety and efficacy of liposuction.

Epidemiological evidence is lacking for Lipedema—often limited to estimates of population prevalence and widely inclusive of self-assessment data and patients who are self-diagnosed. These data, however, are fundamentally important to estimating both the burden of disease to patients and costs to healthcare systems. Better epidemiological data and understanding would increase research interest, strengthen applications for public and private funding, better articulate the aggregate burden of the disease on the patient population and society at large, and inform further development of healthcare coverage. In the absence of strong diagnostic strategies or consistent medical coding, novel approaches to epidemiology will be required to estimate impacts.

Key Challenges to Progress

- Limited epidemiology data to date around prevalence, disease burden, cost, and all-cause mortality
- Insufficient diversity in currently published studies, including race, geography, culture, ethnicity
- Prevalence research is clinically intensive, expensive, and often requires larger-scale recruitment tactics
- Inconsistent definitions, application of diagnostic criteria, and coding make it difficult to rely on existing public health databases and dataset
- Prevalence estimates may need more rigor to create broader awareness, demonstrate the cost burden of disease, and motivate further research

Objective 6. Top Recommendations

- Convene stakeholders, including subject matter experts, to develop a rational approach to advancing understanding of epidemiology.
- Consider opportunities to leverage existing studies and resources to make estimates for Lipedema.
- Gain a better understanding of prevalence across demographic subpopulations, the cost burden of disease, impact on quality of life, and mental health burden.

Resources Available Now

1. **Existing workforce** of researchers, clinicians, therapists, surgeons, nonprofits, and patient experts, including both those vetted by the Lipedema Foundation (LF) and unvetted lists of providers such as that of the Lipedema Project

2. Mechanisms to obtain and analyze **new patient input**

Lipedema Foundation Registry (LFR) with researcher access and ability to send out new surveys

Other patient groups' surveys, survey question sets, and publications, for example, Lipoedema UK's surveys

3. Significant social media and digital resources enabling **access to patients and methods of recruitment**

- Social media influencers

Facebook groups (e.g., Lipedema Sisters USA)

LF Resources: Lipedema.org, LF Newsletter, Instagram, Facebook, LinkedIn, SmugMug, LF Blog, and LF Brochure

4. **Literature reviews** and key papers

- Duhon et al., 2022
- Ernst et al., 2023
- Kruppa et al., 2020
- Poojari et al., 2022
- Lipedema Foundation, 2023

Visit LF's website to view these and other key papers.

Access to existing literature through LF LEGATO Library, PubMed, and Google Scholar

Clinical trial finders: LEGWORK Clinical Trial Finder and ClinicalTrials.gov

Research conferences: Lipedema World Congress and LF Scientific Retreats

Patient conferences: FDRS, Lipoedema UK, Lipoedema Australia, as well as the unique ability to **perform research during FDRS Conferences**

Alliances between LF, FDRS, LipoedemaUK, and Lipoedema Australia

LF Request for Proposals (For updates on future **RFPs**, sign up for LF Newsletter.)

FDRS's YouTube library and corresponding clinician **continuing medical education**

5. Existing and future **biobanks**

Lipedema Biobank of the University Hospital Zurich. Contact: Dr. Gousopoulos, epagousopoulos@gmail.com

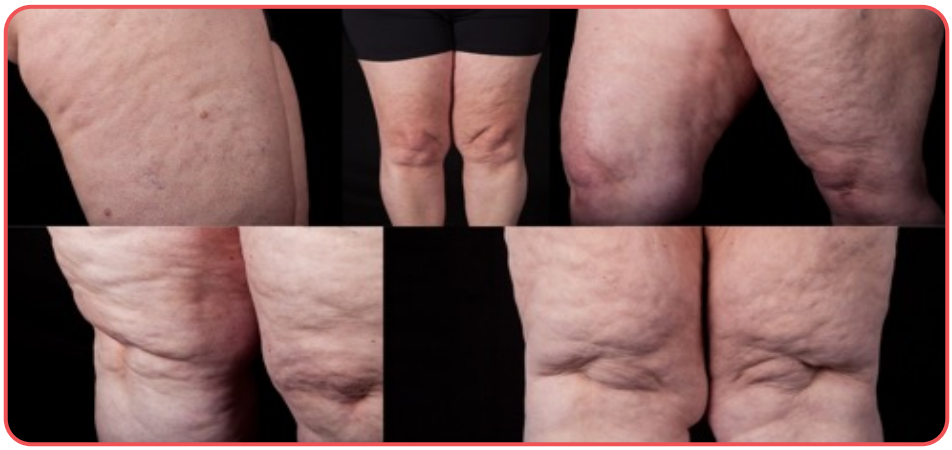
Leipzig Obesity Biobank. Contacts: Dr. Anne Hoffmann: anne.hoffmann@helmholtz-munich.de and Prof. Matthias Blüher: matthias.blueher@medizin.uni-leipzig.de Website

Lipedema Biorepository at Vanderbilt Medical Center funded by Lipedema Foundation; Contact forthcoming

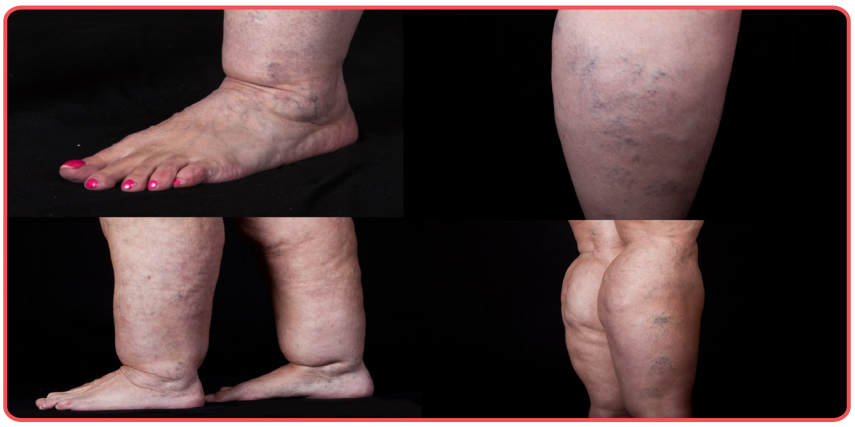
Berlin Institute of Health at Charité – Universitätsmedizin Berlin, BIH Center for Regenerative Therapies "Lymphovascular Medicine and Translational 3D-Histopathology" Laboratory Biobank. Contact: Rose Behncke, Rose.Behncke@charite.de

Paraffin embedded subcutaneous tissue samples from Dr. Manuel Cornely are being stored at the Institute of Clinical and Functional Anatomy. To discuss sample availability, reach out to Dr. Erich Brenner at erich.brenner@i-med.ac.at or Dr. Cornely at info@cornely.org.

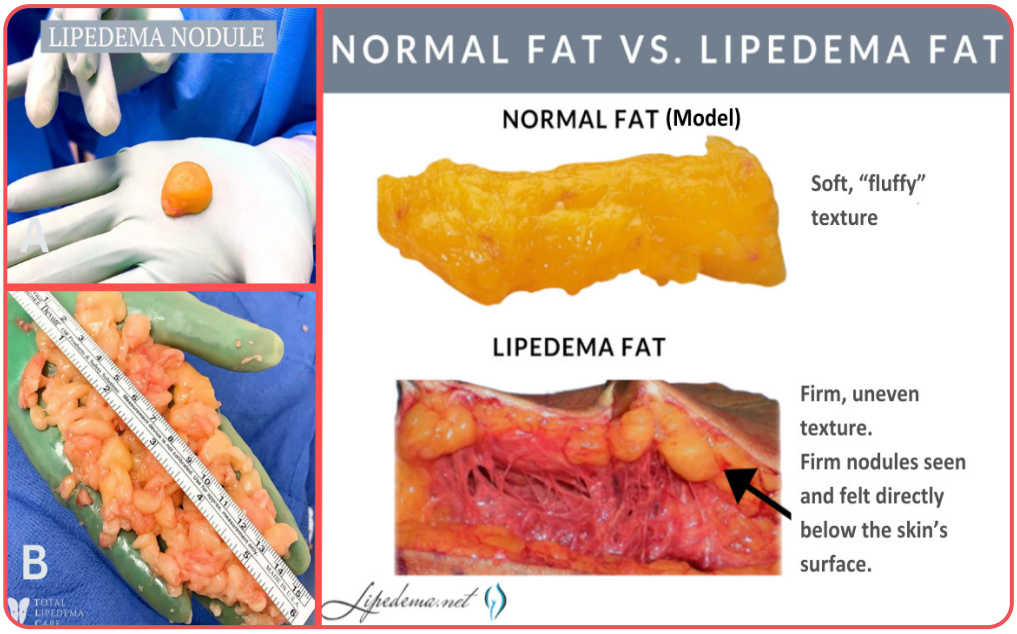
Left image: Lipedema is often characterized by a symmetric buildup of adipose tissue in the legs and arms.
Right image: Visualization of a common Lipedema clinical sign: front, side, and rear view of a Lipedema patient's ankle cuffs.



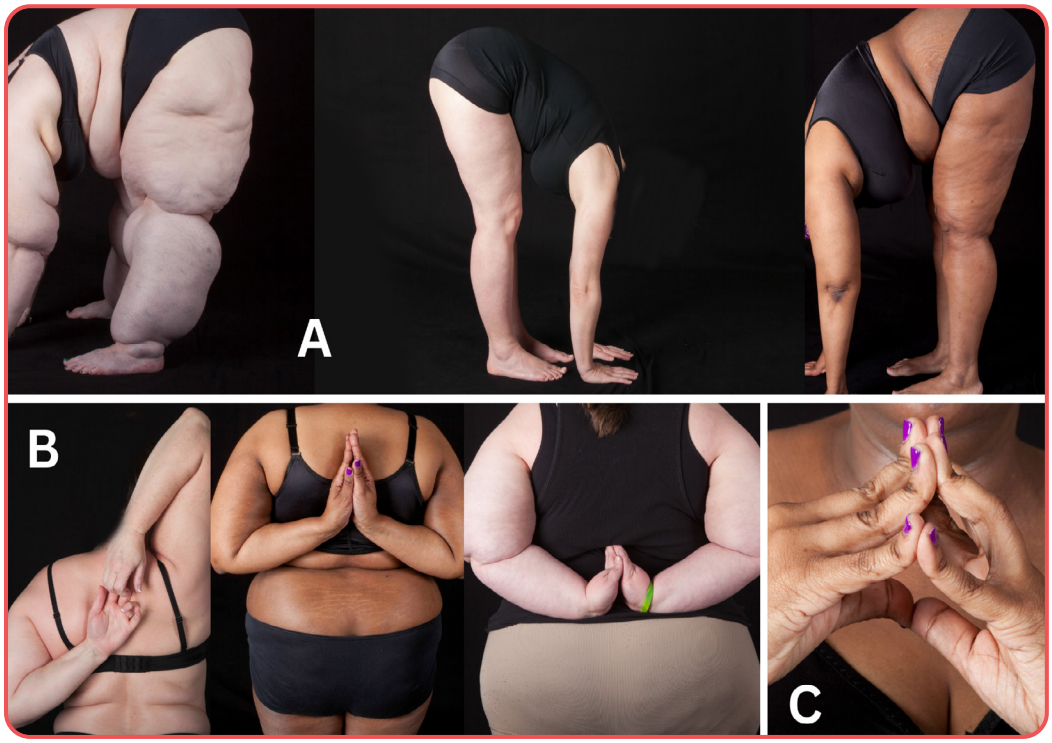
An unusual texture is often present within the fat of Lipedema patients. Lipedema fat can feel like rice, peas, or walnuts beneath the surface of the skin.



Manifestations of venous insufficiency on women with Lipedema. (Top Left) foot, (Top Right) right calf, (Bottom Left) feet, calves, and ankles, and (Bottom Right) bilateral calves.



Visual examples of Lipedema fat samples. (A, B) Lipedema fat nodules extracted by Dr. Jaime Schwartz, TotalLipedemaCare.com; (C) Normal fat compared to a Lipedema fat sample from Dr. Jaime Schwartz. Publication credit to Dr. Thomas Wright, Lipedema.net.



Hypermobility in women with Lipedema. Examples of hypermobility of (A) hip joints, (B) shoulder, elbow, and wrist joints, and (C) finger joints.

Hypotheses about Pathogenesis

Those new to the field may benefit from understanding big picture hypotheses about etiology and pathogenesis that have been proposed to date. The excellent review article "Lipedema—Pathogenesis, Diagnosis, and Treatment Options" elaborates on several of the below ideas about natural history. In particular, a figure reproduced from that article, "Hypotheses about pathogenesis," summarizes leading theories about natural history as of the time of that article's publication, including ideas around genetics, hormonal factors, inflammation and fibrosis, vascular issues, adiposity, hypoxia, mobility and pain.

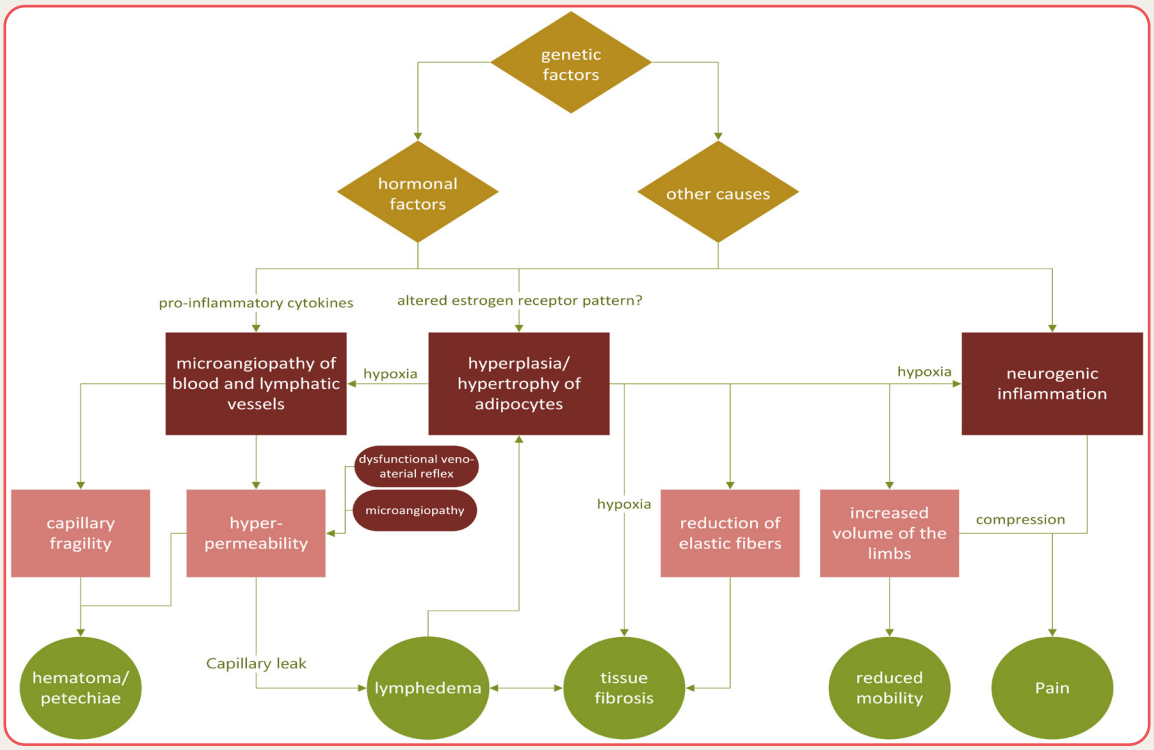


Figure reproduced with permission from the authors.

In addition, other proposed and notable hypotheses about pathogenesis, still to be investigated, include:

Lipedema as chronic compartment syndrome. It has been hypothesized that the condition may be related to a form of subclinical chronic compartment syndrome, related especially to dysfunction in the saphenous compartment.

Glycosaminoglycan (GAG) hypothesis. In this hypothesis, the glycosaminoglycans of the endothelial and adipocyte glycocalyx may be perturbed by increased presence of sodium ions, creating an environment that has the potential to cause microangiopathy and inflammation. Such conditions would also be predicted to contribute to microedema.

Lymphatic dysfunction. Though gross morphological deficiencies have not to date been demonstrated in Lipedema, one hypothesis is that there may be deficiencies in lymphatic micro-architecture that could correspond to suboptimal lymphatic function. As failure to clear lymphatic fluid has been demonstrated to lead to adipose deposition, this proposed mechanism could represent a potential pathogenic role of the lymphatic system in Lipedema. It is also possible that lymphatic dysfunction and adipose deposition could work together in a feedback loop that causes disease progression.

Adipose stem cell involvement. In the adipose tissue niche of Lipedema patients, the adipocyte stem cells (ASCs) have been shown to be altered by the disease. Research to date suggests that the ASCs are stimulated by a plethora of inflammatory factors, resulting in enhanced adipogenesis and angiogenesis . These phenomena in turn contribute to endothelium dysfunction, fibrosis, and extracellular matrix remodeling of tissue.

Kruppa P, Georgiou I, Biermann N, Prantl L, Klein-Weigel P, Ghods M. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. *Dtsch Arzteblatt Int*. 2020;117(22-23):396-403. doi:10.3238/arztebl.2020.0396