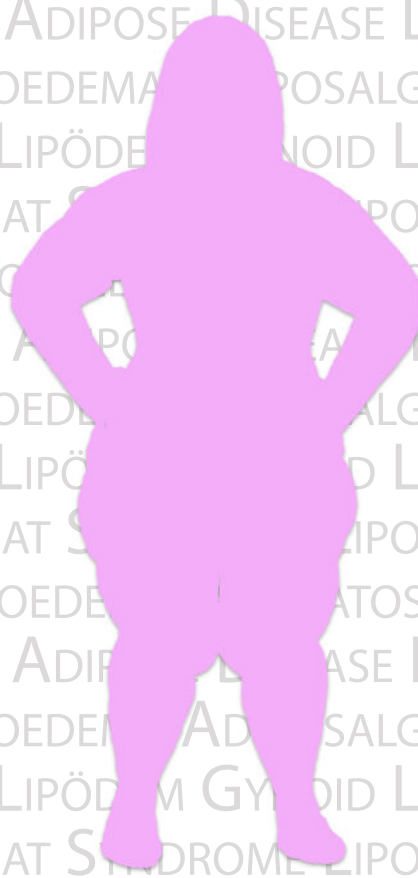
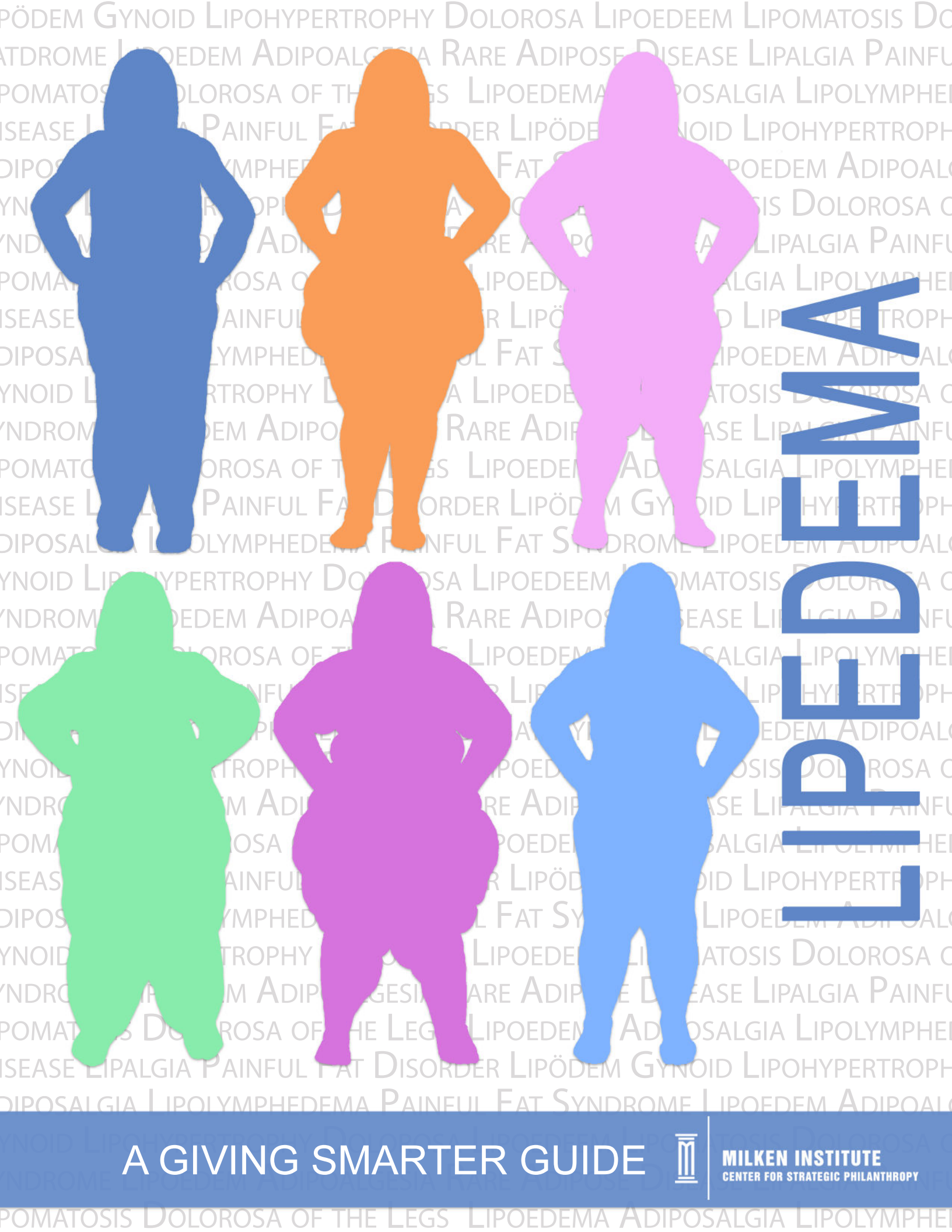




LIPOEDEMA

A GIVING SMARTER GUIDE



MILKEN INSTITUTE
CENTER FOR STRATEGIC PHILANTHROPY

AUTHORS

LEAD AUTHOR

Erik Lontok, PhD

CONTRIBUTING AUTHORS

LaTese Briggs, PhD

Maura Donlan

YooRi Kim, MS

Ebony Mosley

Ekemini A.U. Riley, PhD

Melissa Stevens, MBA

LIPEDEMA SCIENTIFIC ADVISORY GROUP

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Sara Al-Ghadban, PhD

*Postdoctoral Research Fellow,
Department of Medicine
TREAT Program
University of Arizona*

Tobias Bertsch, MD, PhD

*Senior Lecturer, Department of Health
Education, University of Freiburg
Senior Consultant,
Foeldi Clinic, Germany*

Echoe Bouta, PhD

*Research Fellow, Radiation Oncology
Massachusetts General Hospital*

Glen Brice

*Genetic Counselor, Clinical Genetics
St. George's, University of London*

Bruce A. Bunnell, PhD

*Professor, Department of Pharmacology
Director, Tulane Center for Stem Cell Research
Chairman, Division of Gene Therapy, Tulane
National Primate Research Center
Tulane University School of Medicine*

Deborah Clegg, PhD

*Professor, Department of Biomedical Research
Cedars-Sinai Diabetes and Obesity Research
Institute*

Rachelle Crescenzi, PhD

*Research Fellow, Institute of Imaging Science
Vanderbilt University*

Walter Cromer, PhD

*Assistant Research Scientist, Immunology,
Vascular Physiology, and Lymphatic Biology
Texas A&M Health Science Center*

Kristiana Gordon, MBBS, MRCP, CLT, MD(Res)

*Consultant in Dermatology and
Lymphovascular Medicine,
St. George's, University of London*

Carol Haft, PhD

*Program Director, Division of Diabetes,
Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and
Kidney Diseases, National Institutes of Health*

Natasha Harvey, PhD

*Head, Lymphatic Development Laboratory
Centre for Cancer Biology
University of South Australia*

Ad Hendrickx, BHS, Physical Therapist

*Doctoral Candidate, Hanze University of Applied
Sciences, Groningen
Head, Department of Physical Therapy, Expert
Centre for Lymphovascular Medicine
Nij Smellinghe Hospital*

Karen Herbst, PhD, MD

*Associate Professor of Medicine,
Division of Endocrinology
Director of the TREAT Program
University of Arizona*

Yann Klimentidis, PhD

*Assistant Professor, Department of
Epidemiology and Biostatistics
University of Arizona*

Amira Klip, PhD

*Senior Scientist, Cell Biology Program,
The Hospital for Sick Children,
Professor of Biochemistry, Physiology and
Paediatrics, The University of Toronto*

Babak Mehrara, MD

*Physician-scientist,
Plastic and Reconstructive Surgery
Memorial Sloan Kettering Cancer Center*

Chia-Ling Nhan-Chang, MD, MS, FACOG

*Assistant Clinical Professor of Obstetrics and
Gynecology, Division of Maternal Fetal Medicine
Department of Obstetrics & Gynecology
Columbia University Medical Center*

Pia Ostergaard, PhD

*Senior Lecturer in Human Genetics,
Institute of Cardiovascular and Cell Sciences
St. George's, University of London*

Tim Padera, PhD

*Associate Professor, Radiation Oncology,
Massachusetts General Hospital and Harvard
Medical School*

Neil Piller, PhD, FACP

*Director, Lymphoedema Clinical Research Unit
Professor, Department of Surgery
Flinders Medical Centre*

Joseph Rutkowski, PhD

*Assistant Professor, Medical Physiology
Texas A&M College of Medicine*

Philipp Scherer, PhD

*Professor, Department of Internal Medicine
Director, Touchstone Diabetes Center
The University of Texas Southwestern Medical
Center*

Hamish Scott, PhD

*Head, Department of Molecular Pathology
Centre for Cancer Biology
University of South Australia*

Eva Sevick-Muraca, PhD

*Professor, Cullen Chair in Molecular Medicine
Director, Center for Molecular Imaging
University of Texas Health Science Center,
Houston*

Carrie Shawber, PhD

*Assistant Professor, Reproductive Sciences in
OB/GYN & Surgery Department of Obstetrics &
Gynecology
Columbia University Medical Center*

Melody Swartz, PhD

*William B. Ogden Professor,
Institute for Molecular Engineering
University of Chicago*

Jens Marc Titze, MD

*Associate Professor, Department of Medicine,
Molecular Physiology and Biophysics
Vanderbilt University*

Peter Wang

*Doctoral Candidate,
Department of Pathology and Immunology
Washington University, School of Medicine*

H. Eser Tolunay, PhD

*Deputy Chief, Vascular Biology and
Hypertension Branch
Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute
National Institutes of Health*

Annalisa Zecchin, PhD

*Postdoctoral Fellow,
Laboratory of Angiogenesis and Vascular
Metabolism
Vesalius Research Center (VRC)
VIB-KULeuven*

Henricus Gerardus Jacobus Voesten, MD

*General and Endovascular Surgery
Chief Surgeon, Expert Centre for
Lymphovascular Medicine
Nij Smellinghe Hospital*

LIPEDEMA FOUNDATION REPRESENTATIVES**Felicite Daftuar, MBA**

*Founder and Executive Director
Board Member and Former President, Fat Disorders Research Society*

Danielle Wildstein

Vice President, Operations

Shannon Seeberg

Vice President, Communications

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PHILANTHROPIST'S FOREWORD

I was told to stop having children by the first therapist who confirmed my suspicion of lipedema. I was told to go to Germany, get liposuction and wait 18 months before continuing to have children by an expert. I was told by my amazing GP that the lump of fat and fluid under my knee was postpartum depression, even though I wasn't depressed.

I hired a concierge medicine company to investigate 1) Is lipedema a real thing? 2) Do I have it? 3) What should I do about it? Months later: Yes, Yes, We don't know.

So I did what others before me did. I searched Pubmed and Google Scholar for research papers. I read some of them. I put them in a spreadsheet.

I joined Facebook groups and LinkedIn-ed people I thought would help. I went to patient, researcher, and therapist conferences. I helped resurrect a defunct non-profit, the Fat Disorders Research Society, and the team set up a website and hosted 2 patient conferences (one with 270 attendees!).

In 2015, I narrowed my focus to research, started the Lipedema Foundation (LF), and started funding research projects.

But I kept coming up short. How could a disease that's seemingly everywhere have so little published? Sure there are some descriptive papers, case reports, and studies with a few patients. There are even literature reviews. But no pathogenesis. No genes. No blood test. No biomarkers. No replicable imaging test. Nada zip zero. I couldn't find answers to my questions about lipedema.

Why are pain and swelling (which are subjective) recognized criteria of lipedema, but the physical change in the texture of the fat is not?

Why are there only 5 US physicians willing to diagnose lipedema, but there are 12 surgeons willing to operate, 100s of therapists willing to treat, and 2,000 patients participating in Facebook groups?

Do my relatives have it? Are my 3 daughters going to get it? How could it be that I carried 3 children, and my abdomen looks better, but my legs look worse? Is it a disease? A condition? A syndrome? I don't feel sick, but my body is different.

Why can I **feel** nodules of fat in my legs, but no one can image them with ultrasound, MRI or a highly technical piece of equipment?

Why is it that if I cook healthy meals and exercise the right way, I don't have pain, but if I go on vacation my legs burn when I lay down at night? Do I really need liposuction if my BMI is in the 20s?

Will it get worse? Will it get better? Will it ever go away? How is lipedema different from lymphedema, obesity, lipodystrophy and Dercum's disease?

Is the prevalence really 11% of post-adolescent women? Or 5%? Or 1%?

How was I now one of the world's experts in a medical condition?

Along came a small band of heroes. People who had seen this before. People who thought I wasn't crazy for hunting for answers. People who raised the level of discourse around something that had been predominantly patient-led discussions. People who know the ins and outs of the typical disease path from diagnosis to treatment to cure.

The Milken Institute's Center for Strategic Philanthropy (CSP) opened doors I couldn't. They persevered through setbacks that were tough for me to deal with. They remained objective and focused, diving down deep into many facets of the biology and then resurfacing to put the big picture together.

CSP could talk to researchers and doctors on their level. They could assess which expertise of researchers were needed in order to move forward, and brought 20 different specialties into the conversation. The heroes are so well networked around DC that they could get both the NIDDK and NHLBI represented at our first ever Lipedema Scientific Retreat. They invited me to sit at tables with other people like me.

They kept my expectations grounded and at one point told me: we are at the very beginning of the course of this disease; we know nothing. But they provided a roadmap and tools to move forward, via both this Giving Smarter Guide and an invaluable private report identifying names, tools, and projects.

I became we. We went to conferences and called people around the world. We worked together. We wondered together. We opined together. We hosted a meeting convening a global cohort of the best-of-the-best and, and together at the Scientific Retreat, we mapped out the gaps in the field of lipedema research so that we could collaborate and coordinate the research needed to define the space.

We have chosen to strategically address key research challenges of lipedema. For the short term, LF's first priority is the science behind the cause(s) of lipedema. We cannot do meaningful research into lipedema treatments until we understand the scientific cause(s) of the condition. There is a lack of scientific consensus on the most basic elements of this disease, and LF has set about to fix that. We can't get anywhere until we tackle the fundamentals.

Please, read on and become part of our journey. Take notes and jot down ideas, then call LF. We'll be happy to talk to you about your ideas to move this forward. We have a long road ahead of us and we'd like your company, because it takes a village to move diseases forward.

Felicite Daftuar
Founder and Executive Director
Lipedema Foundation

EXECUTIVE SUMMARY

Lipedema is a chronic condition that occurs almost exclusively in women and manifests as symmetrical buildup of painful fat and swelling in the limbs, sparing the hands and feet. A critical issue is the poorly understood disease biology, which for diagnosed patients results in limited treatment options that, at best, ameliorate the symptoms of lipedema. Individuals who suffer from the disease are further impacted by the absence of diagnostic tools, the lack of public and medical awareness of lipedema, and the stigma associated with weight gain. As a result, the true number of women with lipedema, or its epidemiology, is unknown.

Braving these challenges is an active, numerous, and engaged patient community eager to participate in lipedema research. Supported by equally devoted caregivers and researchers, the lipedema field presents an immense opportunity for scientific and medical advancements. To capitalize on this potential, the Lipedema Foundation and the Milken Institute's Center for Strategic Philanthropy convened leading stakeholders to discuss the current state of lipedema science and identify the key philanthropic research opportunities to advance the field.

Little is known about how and why lipedema develops in a patient. Although the disease is reported to occur during puberty and other periods of hormonal changes, why this happens is not understood. The painful fat and swelling in some patients can be so debilitating that their mobility is impaired; yet what drives these symptoms is unknown. Psychosocial issues are also prevalent in women with lipedema, contributing to health burden and complexity of disease management. Furthermore, many patients develop the disease alongside obesity; however, diet, exercise, and weight loss surgery have limited effect on lipedema fat. Although the lack of disease biology is staggering, philanthropic investments in research can leverage the desire of patients to participate in studies to improve their and the entire field's understanding of lipedema. The convergence of multiple scientific topics around lipedema indicates that addressing these gaps in research will also improve the understanding of hormone, pain and edema, mental health, and metabolic biology.

There are no diagnostic tools or tests for lipedema. Diagnosis of lipedema involves a clinical assessment and discussion of the individual's medical history, a process that is difficult to scale within the current healthcare system. The absence of diagnostic tools to streamline or confirm a clinical diagnosis is a key unmet need, which if addressed by philanthropy, has the potential to dramatically change the trajectory of the disease. Investing in research efforts to advance novel imaging technologies to diagnose lipedema is a promising research avenue that would simultaneously benefit individuals who suffer from the disease and healthcare providers unfamiliar with the condition.

The public and medical community are not aware of lipedema. Lipedema was initially described in 1940, yet little knowledge about the disease has permeated the general public, with a concomitant lack of mention in the educational curriculum of medical trainees. Addressing this challenge will require philanthropic efforts to define the disease from a basic, clinical, and diagnostic perspective. A key philanthropic opportunity is support for a lipedema patient registry linked to a tissue biorepository. This effort has the potential to generate and support the needed disease research, while engaging patients as partners in understanding the science of lipedema.

OVERVIEW

First described in the 1940s, lipedema is a chronic condition that presents as symmetrical accumulation of fat in the subcutaneous tissue with almost exclusive occurrence in women.^{1,2} Fat tissue expands primarily in the lower limbs, from buttocks to ankles, as well as in the arms, with weight loss strategies exhibiting limited effects on limb fat.^{1,3,4}

Lipedema is further characterized by pain, tenderness upon contact, easy bruising, swelling (edema), and psychosocial issues that all impact a patient's overall quality of life. Onset of lipedema is reported to occur during puberty.⁵ However, it can occur or be exacerbated by periods of hormonal shifts, such as pregnancy or menopause, although data as to why are limited.⁶ Weight gain and obesity are also considered to play a role in lipedema onset and exacerbation of symptoms.⁷

Unmet Clinical and Research Needs

The lack of a consistent and scalable diagnostic procedure, multiple names (see box), and limited awareness of the disease in the medical field stymie lipedema diagnosis, culminating in sparse epidemiological information.

The clinical presentation and symptoms of lipedema can commonly result in a misdiagnosis of lymphedema, obesity, Dercum's disease, or chronic venous insufficiency, resulting in incorrect treatment (see Diagnosis). Thus affected individual and the field would greatly benefit from a diagnostic tool to serve as an initial test or confirmatory test of a clinical diagnosis.

In addition, the staggering lack of lipedema basic biology research has limited understanding of the disease etiology, or origin and drivers of onset.

Consequently, patients contend with a poorly understood chronic condition with therapeutic options that, at best, only ameliorate symptoms.

Synonyms and related terms for lipedema

- ❖ Lipoedema
 - ❖ Lipödem
 - ❖ Lipoedem
 - ❖ Lipoedeem
 - ❖ Lipolymphedema
 - ❖ Painful Fat Disorder
 - ❖ Lympholipedema
 - ❖ Lipohypertrophy
 - ❖ Lipohypertrophy dolorosa
 - ❖ Lipomatosis dolorosa of the legs
 - ❖ Lipalgia
 - ❖ Adiposalgia
 - ❖ Adipoalgesia
 - ❖ Rare Adipose Disease
 - ❖ Adiposis dolorosa
 - ❖ Dercum's disease
-

EPIDEMIOLOGY OF LIPEDEMA

Unfortunately, data on the incidence (occurrence, rate, or frequency) and prevalence (commonness) of lipedema are unknown. Because many people with lipedema are misdiagnosed with lymphedema, the majority of prevalence values are based on the percentage of patients seen in lymphedema clinics. The following are currently available but limited lipedema epidemiological data:

- The Földi Clinic in Germany stated a prevalence in women of 11 percent. However, this percentage was derived by extrapolating an estimate of misdiagnosed lipedema patients seeking medical attention in the clinic to the general population.⁸
- The Lymphedema Unit of University Hospital La Fe (Valencia, Spain) reported that 18.8 percent of the 843 patients seen by its clinic from 2005 to 2011 have lipedema.⁹
- A review of patients treated by a lymphedema clinic in Germany from 1995 to 1996 found that 15 percent have lipedema.¹⁰
- In 2003, four lymphedema clinics in Germany reported that 8 to 17 percent of their patients have lipedema.⁴
- Using data about people seen by the regional Dermatology Department of St. Georges Hospital (London, United Kingdom), researchers estimated that, at a minimum, 0.0014 percent of women have lipedema. However, they stress that this percentage is likely a significant underestimate because of problems with misdiagnosis or failure by community physicians to refer patients.¹¹

It is notable that most of these epidemiological data come from misdiagnoses captured by lymphedema clinics. Given the potential for disease onset during periods of hormonal shift, the close relationship with obesity, and disease-associated changes in the skin (see Differential Diagnosis section), research is needed to determine whether undiagnosed patients can be found in Obstetrics and Gynecological, Endocrine and Obesity, and Dermatology departments, respectively, to understand better the true population burden of lipedema.

HEALTH BURDEN AND QUALITY OF LIFE

The chronic nature of lipedema greatly impacts the physical well-being and mental health (psychosocial stress) of patients. In 2012, Lipoedema UK and The British Lymphology Society launched a survey to provide objective data and statistics on how women with lipedema were diagnosed and treated by the medical profession, the range of symptoms, the efficacy of interventions, and to understand better the patient experience of living with the disease. The survey's key findings from 250 women with lipedema follow.⁵

DIAGNOSIS CHALLENGES

- Lipedema is poorly understood by the medical community. Only 9 percent of respondents reported that their health professional diagnosed lipedema the first time they reported their symptoms. Only 5 percent were diagnosed by their general practitioner.
- 46 percent of respondents reported that lipedema onset coincided with puberty; however, the average age of diagnosis was 44 years old.
- The majority of respondents reported that medical professionals were dismissive of the condition and misdiagnosed their lipedema as excess weight/bad diet/lack of exercise.
- The most commonly reported response to diagnosis was relief. Respondents also felt angry and frustrated that diagnosis had taken so long, as well as scared about a future with no cure and few options to ameliorate symptoms.

IMPACT ON QUALITY OF LIFE

- Lipedema affects a patient's emotional state: 87 percent of respondents agreed that their lipedema has had a negative effect on their quality of life.
- Lipedema also affects patients' careers: 51 percent reported that lipedema has affected their ability to succeed in their chosen career, commonly citing a lack of mobility, discomfort, and inability to stand. In addition, 39 percent believed that their lipedema restricted their career choices.
- When asked "Has your body shape lead to any of the following?"
 - 95 percent reported difficulty in buying clothes and boots
 - 86 percent reported low self-esteem
 - 83 percent reported avoiding being photographed, or ensuring that their body did not appear in the image
 - 76 percent reported lack of energy
 - 60 percent reported restricted social life
 - 60 percent reported feelings of hopelessness
 - 55 percent reported restricted mobility
 - 50 percent reported restricted sex life

PAIN

Pain and tenderness of lipedema-affected areas is a consistently reported problem and poses a significant health burden. Generally reported as chronic, this pain can significantly impact mobility and overall quality of life. **77 percent of respondents to the Lipoedema UK survey experience leg pain.**⁵ The following results from lipedema publications and patient surveys that further describe the effect of pain on patient lives:

- In Allen and Hines (1940), and an expanded disease description by Wold et al. based on 119 lipedema case reports, found that pain was the distinguishing characteristic for **40 percent** of patients.^{1,3}
- A contextual behavioral approach assessment of the quality of life of 120 women with lipedema, who were recruited through online and Facebook patient discussion groups, found that **93 percent** of these women experienced lipedema-associated pain and tenderness (sensitivity to touch), with almost half of them rating the symptoms as **severe to extremely severe.**¹²
- A medical chart review and survey of 50 lipedema patients seen by an academic medical center reported that nearly **90 percent experienced daily pain.**¹³
- An application of the visual analogue scale (VAS), which is a psychometric response scale used in questionnaires to measure subjective characteristics or attitudes that cannot be directly measured, was used to quantitatively assess lipedema-associated characteristics in 25 pre-liposuction surgery patients. Most patients reported pain in lipedema-affected areas, and, six months after surgery, they reported a **significant reduction in pain from 7.2 to 2.1 VAS points** with a concomitant improvement in psychological stress from 8.7 to 3.6 VAS points.¹⁴

As described by the Lipoedema UK survey, patients' quality of life can be affected by more than the symptoms and physical issues associated with the disease.^{5,12,15,16} Patients must also contend with the mental health issues that often accompany the challenges of managing lipedema. It is currently unknown whether mental health issues precede or occur with onset of lipedema; however, such stressors affect patient quality of life in terms of:

- Psychological health (e.g., anxiety, depression)
- Level and quality of social relationships, including support and engagement of friends and other lipedema patients (see box)
- Perception of the environment (e.g., stigma)

To account for psychosocial stress, the Dutch Society of Dermatology and Venereology developed a guidelines document (Dutch Lipedema Guidelines) which included a holistic assessment and care model that assesses a patient's physical state and levels of psychosocial distress.^{7,17} This model was based on evidence- and expert-based recommendations to inform and define the criteria for a medical diagnosis of lipedema.

Importantly, the guidelines propose a minimum data set of repeated clinical measurements, or clinimetrics, to outline and assess a chronic care model for lipedema measuring the impact and success of conservative treatment programs for the disease (see Treatments section).¹⁷⁻¹⁹ The value of this clinimetrics-based care model is derived from its holistic approach to assessing a patient's physical state, daily and individual-driven treatment program, and levels of lipedema-associated psychosocial distress.

The application of clinimetrics to evaluate diagnosis and treatment is exemplified by the calculation of mean VAS values before and after liposuction surgery to assess changes in pain and psychosocial stress.¹⁴

Along with the active and connected lipedema patient community, these efforts set the stage for a holistic and quantitatively driven approach that will hopefully capture and understand the true health burden of lipedema.

Facebook Lipedema Patient Groups

High levels of social connectedness were found to correlate with high levels of quality of life and satisfaction of life. Listed below are online patient groups focused on lipedema:

- ❖ Friends of Lipedema Sisters USA (anyone can join)
- ❖ Fat Disorders Research Society (FDRS)
- ❖ Lipedema Sisters USA
- ❖ Lipedema Education
- ❖ Loving Life with Stage 1 and 2 Lipedema
- ❖ Lipedema Stage 3 and 4
- ❖ Lipedema Fitness
- ❖ Liposuction for Lipedema
- ❖ Lipedema USA Español
- ❖ Lipedema Canadian Support Group
- ❖ Lipoedema Australia Support Society
- ❖ Lipoedema UK
- ❖ Lipoedema Ladies UK
- ❖ Talk Lipoedema

Some groups are private and request that interested people agree to their rules before contacting or joining the group.

LIPDEMA DIAGNOSIS, STAGING, AND PROGNOSIS

DIAGNOSTIC CRITERIA

Diagnosing lipedema involves a taking the medical history and performing a physical examination of the patient.⁷ As the field lacks a diagnostic test, clinicians consider multiple criteria to determine whether an individual has lipedema. The following sections describe these criteria, as well as how lipedema is differentially diagnosed from lymphedema, obesity, Dercum's disease, and chronic venous insufficiency.

Allen & Hines diagnostic criteria

Lipedema was first described in 1940 by Allen and Hines. In 1949, Wold, Allen, and Hines published a seminal report that elaborated on the clinical presentation and proposed diagnostic criteria, based on 119 cases.^{1,3} Because lipedema is commonly misdiagnosed as lymphedema (see box), the proposed diagnostic criteria were designed to distinguish between the two diseases. Still used today the criteria include:

1. Almost exclusive occurrence in women
2. A bilateral and symmetrical accumulation of adipose tissue (body fat) on the legs with minimal involvement of the feet, resulting in a bracelet effect or cuff at the ankle (Figure 1, A)
3. Minimal pitting edema and negative Stemmer's Test (Figure 1, B)
4. Pain and tenderness of affected tissue
5. Persistence of the tissue enlargement despite caloric restriction or stimulation of lymphatic flow through elevation of the extremities
6. Increased vascular fragility, and easy bruising

Lymphedema is a buildup of the fluid surrounding tissues, or interstitial fluid, in the muscle and skin leading to increased fat deposition. The disease can be hereditary (primary lymphedema) or arise from damage to the lymphatic system from different insults such as cancer, surgery, radiation therapy, trauma, or infection (secondary lymphedema).

It can occur in *both men and women* and presents as *unilateral or bilateral swelling*—most often in the arms or legs. Common presentations include *pitting edema* and *positive Stemmer's Test*; *swelling that responds to elevation changes*; a feeling of heaviness; restricted range or motion; discomfort; recurring infections; and hardening and thickening of the skin.

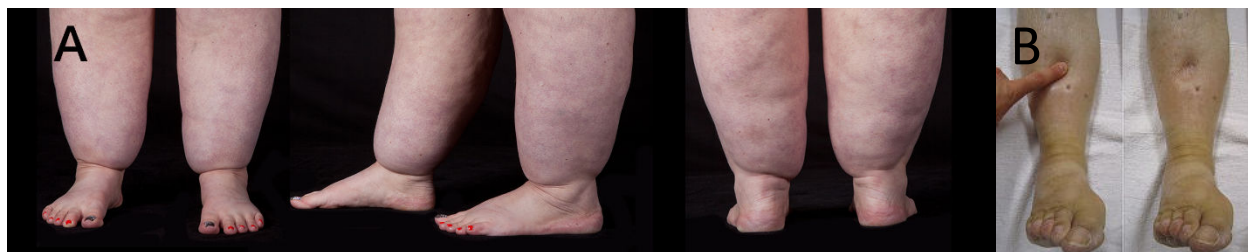


Figure 1: Visualization of Lipedema Diagnostic Criteria. (A) Front, side, and rear view of a lipedema patient's ankle cuffs. Wold *et al.* noted the presence of prominent inner ankle, or malleolar fat pads (rear). (B) Pitting edema is common in lymphedema, wherein application of pressure (left) leaves an indentation in the tissue (right). Images courtesy of the Fat Disorders Research Society (A) and Wikimedia Commons (B).

Clinical characteristics of lipedema

Treatment providers use the following criteria to facilitate a differential diagnosis of lipedema from other diseases.

Lipedema is characterized by **accumulation of fat on the limbs**, which can be **painful** and **feel nodular**. This fat build-up necessitates a differential diagnosis of lipedema from obesity and Dercum's disease. (Table 1)

- **Disproportional fat distribution** on the legs, without a similarly proportional buildup in the upper body/trunk region, is a key distinguishing characteristic of lipedema. This fat distribution is unlike that for [obesity](#) or Dercum's disease, in which fat accumulates at the trunk and throughout the body^{4,20,21}. Because many lipedema patients are also obese, considerable debate exists regarding whether obesity begets lipedema or vice versa.²²
- Unlike the smooth feel of obese fat, reports indicate that lipedema fat can present with **palpable nodules** – described as feeling like frozen peas in a bag or pearls – which can be more noticeably felt at later stages of the disease.^{4,6} This nodularity is similar to the diffuse type of Dercum's disease.^{6,24}

Dercum's disease, also known as adiposis dolorosa and Morbid Dercums, is a rare disease that often presents with general obesity and painful fat in affected areas.²¹ Unlike the smooth feel of obesity fat, Dercum's disease fat can feel nodular when palpated, and form masses of fat tissue (lipomas or angiolipomas).

Dercum's disease is classified based on the areas of fat that experience pain: diffuse, widespread pain from in areas with fat tissue; nodular, intense pain in and around fat tissue with nodules or lipomas; and mixed.⁶ The disease is more common in women than men, with the average of onset between the ages of 35-50, but has been reported to occur earlier.²²

Table 1: Differential Diagnosis between Obesity, Dercum's Disease and Lipedema^{4,6,20,23}

	Obesity	Dercum's Disease	Lipedema
Areas of excess fat accumulation	Trunk, throughout body	Trunk, throughout body	Arms and Legs
Tendency to bruise	Mild	Mild-Moderate	Moderate-Severe
Pain associated with fat	Mild	Severe	Moderate-Severe
Presence of nodular fat	No	Yes	Yes, especially at later stages
Comorbid with diabetes	Yes	Yes	No
Comorbid with hypertension	Yes	Yes	No

- Although the fat distribution between lipedema and Dercum's disease is different, the high prevalence of obesity in both populations increases the challenge of accurately diagnosing lipedema. The nodularity and pain associated with the fat lipedema and Dercum's disease further increases the complexity of differential diagnosis.

The **age of onset** for lipedema has been reported to occur primarily during puberty.⁵ Furthermore, patients have reported development or exacerbation of lipedema during time periods surrounding pregnancy or menopause.^{3,9,11}

Swelling or edema of affected regions worsens while standing upright (orthostasis) and during hot weather.^{3,6} The presence of edema in lipedema contributes to a misdiagnosis of [lymphedema](#).⁴

Vascular changes like **spider veins** and **telangiectasia** are present in lipedema-affected areas (Figure 2).^{3,11} Because these vascular manifestations also occur in patients with [chronic venous insufficiency](#) (CVI), with advanced cases developing uni- or bilateral edema and swelling of the legs known as phlebedema, CVI is a differential diagnosis that requires consideration.^{4,25}

The **skin elasticity** is reduced in lipedema-affected areas, suggesting impaired connective tissue beneath the epidermis.^{6,26} In some cases, the **skin** also feels cold to the touch but is not firm or hardened as in lymphedema.^{6,27}

Lipedema is also considered to have a **heritability** component, because patient histories often refer to relatives with similar leg and body structure.³ Pedigree studies from a single academic medical center suggest either an X-linked dominant inheritance, or autosomal dominant inheritance with sex limitation.¹¹ However, more studies are required to accurately determine the genetic architecture of lipedema.



Figure 2: Spider Veins and Venous Manifestations on a Woman with Lipedema. (Top) Right leg, (Bottom left) right foot, and (Bottom right) left calf. Images courtesy of the Fat Disorders Research Society.

Table 2: Differential Diagnosis of Lipedema vs Lymphedema vs Obesity vs CVI ^{6,25,28–31}				
	Lipedema	Lymphedema (Primary and Secondary)	Obesity	Phlebedema, Chronic Venous Insufficiency
Disease Presentation	Symmetrical fat deposition and swelling in legs and/or arms, but not the feet or hands	Fat deposition and swelling in affected limb, including hands or feet	Widespread fat deposition, with the potential for swelling due to comorbidities	No fat, but swelling and itchy areas near ankles with a brownish discoloration of lower legs
Sex	Almost all female	Males and females	Males and females	Males and females
Disease Onset	During hormonal shifts (puberty, pregnancy, menopause) and periods of weight gain	<u>Primary</u> : Congenital, due to presence of genetic mutations <u>Secondary</u> : Due to damage to the lymphatic system	Age independent	During pregnancy or onset of comorbidities such as obesity, diabetes, or hypertension
Presence of Pain	Yes, in affected tissues	Discomfort and aching can occur over time	Yes, chronic pain associated with comorbidities	Yes, in affected areas
Impact of Caloric Restriction and Exercise on Fat	Limited	None	Weight-loss strategies can be effective	Not applicable
Risk of Cellulitis	No	Increased	Increased	Increased risk in areas affected by edema. Itchy and discolored areas with eczema can look like cellulitis
Heritability	Potential	Primary lymphedema can be inherited	Potential	Potential

For further differential diagnosis tools, see:

- [Differential Diagnosis: Approach to the Patient with Swollen Legs](#)
- [Fat Disorders Research Society Continuing Medical Education](#)

Hypermobility in lipedema patients

According to a recent study of 160 lipedema patients from a single academic medical center, 58 percent demonstrated hypermobility of the joints, as determined by Beighton Score²³ (Figure 3). Hypermobility is the ability to move joints beyond the normal range of movement, although a Beighton Score of higher than 5 is not the only criterion for hypermobility, because other signs and symptoms of the syndrome are required for an accurate diagnosis.^{32,33}



Figure 3: Hypermobility in Women with Lipedema. Examples of hypermobility of (A) hip joints, (B) shoulder, elbow, and wrist joints, and (C) finger joints. Images courtesy of the Fat Disorders Research Society.

Diagnostic devices and lipedema

To date, no imaging assay is approved as an initial diagnostic tool or test to confirm a clinical diagnosis of lipedema. Although multiple imaging techniques such as [magnetic resonance imaging](#),^{34,35} [computed tomography](#),³⁶ [lymphoscintigraphy](#),³⁷ [dual-energy X-ray absorptiometry](#),³⁸ indirect [lymphangiography](#),³⁹ and [ultrasound](#)³⁵ have all been applied to and generated considerable lipedema-specific data, more research is needed to determine whether an individual modality or combination of imaging tests can successfully diagnose the disease.

TYPE AND STAGE OF LIPEDEMA

Nearly 97 percent and 30 percent of women with lipedema present with fat on the legs and arms, respectively.^{4,10,28} Different classification schemes exist, and this report will utilize the Type (I-V) and Stage (1-4) parameters as described by Schmeller and Meier-Vollrath.^{4,6} Other classification systems include those used by clinicians in Australia, United Kingdom and the Netherlands.^{7,11}

Lipedema type describes the areas of the body with fat, while stages indicate the level of the fat accumulation and related comorbidities. It should be noted that a wide variety of disease presentation exists, and it is not fully understood whether each patient progresses through each stage.⁶ The following images are of women with different types and stages of lipedema, and are provided courtesy of the Fat Disorders Research Society. Unfortunately, images of every iteration of Type/Stage (e.g., Type I/Stage 3, Type IVb, Type V) are not available. The full photo essay can be found [here](#).

Lipedema Type: Areas of the body with fat accumulation

Type I: Pelvis, buttocks, and hips

Type II: Buttocks to knees, with formations of folds of fat around the inner side of the knee

Type III: Buttocks to ankles

Type IV a-c: a, Upper arm; b, Lower arm; c, Whole arm

Type V: Knees to ankles

Lipedema Stages: Disease presentation and levels of fat accumulation

Stage 1: Normal skin with enlarged subcutaneous tissue

Stage 2: Uneven skin with indentations in the fat; larger mounds of fat tissue (lipomas) are present

Stage 3: Large extrusions of tissue causing deformations; especially on the thighs and around the knees

Stage 4: Development of lipolymphedema with large overhangs of tissue



Figure 4: Lipedema Type I with Fat Accumulation at the Pelvis, Buttocks, and Hips. (Top) Stage 1; (Bottom) Stage 2, note the presence of indentations in the skin. White arrows indicate ending of lipedema fat above the knees. Images courtesy of the Fat Disorders Research Society.



Figure 5: Lipedema Type II with Fat Accumulation from the Buttocks to Knees, and Formations of Folds of Fat around the Inner Side of the Knee. (Top) Stage 1; (Middle) Stage 2; (Bottom) Stage 3. Images courtesy of the Fat Disorders Research Society.



Figure 6: Lipedema Type III with Fat Accumulation from Buttocks to Ankles. (Top) Stage 1; (Middle) Stage 2; (Bottom) Stage 3, note that this image is not scale with the others because only the lower torso is visualized.

Figure 7: Lipedema Type IV Arm Presentation with Fat Accumulation at the Upper and Lower Arm. (A) Type IVa, Stage 3 side and rear view. (B) Type IVc, Stage 3 side views. Images courtesy of the Fat Disorders Research Society.



Transition of lipedema to lipolymphedema (Stage 4) can occur during stages 2 or 3 and involves development of lymphedema clinical characteristics such as a positive Stemmer's Test, increased fibrosis and stiffening of skin, and swelling and adipose tissue buildup at the hands, feet, trunk, and head.

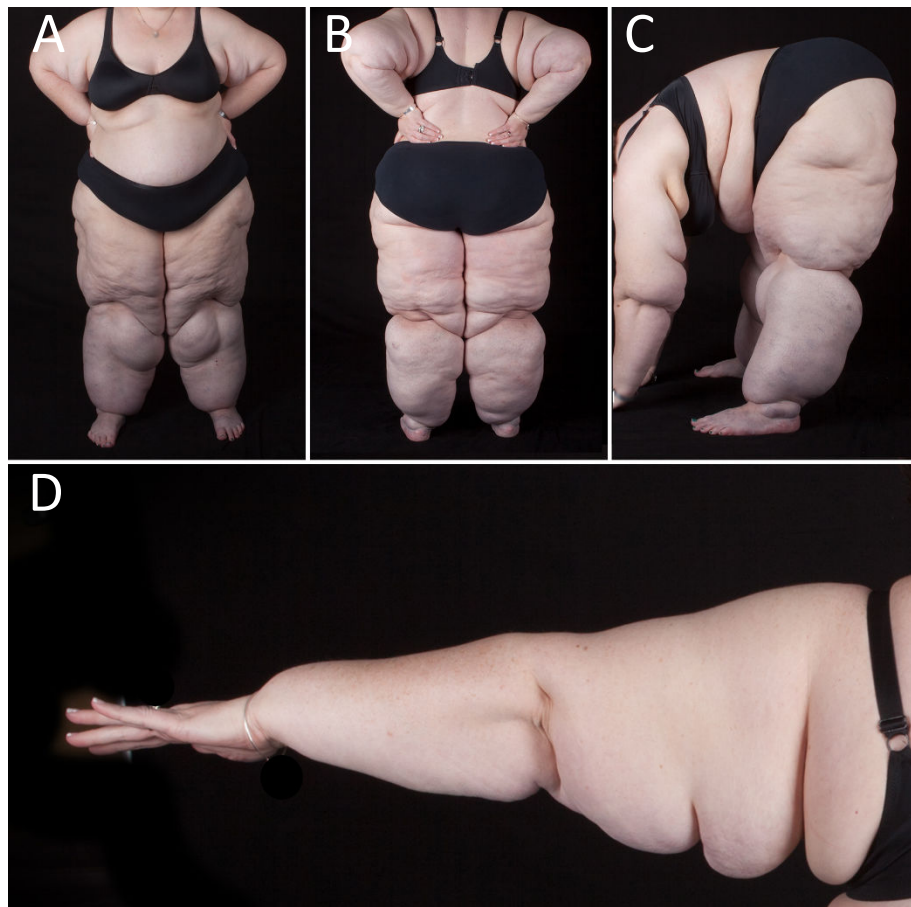


Figure 8: Type III, Stage 4 Lipolymphedema. (A) Front view. (B) Rear view. Please note that for (A) and (B) the patient does not exhibit the characteristic accumulation of fat seen in many Stage 4 patients. (C) Demonstration of hypermobility. (D) Type IVc arm presentation. Images courtesy of the Fat Disorders Research Society.

PROGNOSIS OF LIPEDEMA

The prognosis of lipedema is not fully understood.^{4,13} Although the stage of lipedema describes the severity of fat accumulation, some patients may remain at one stage for many years, while others may rapidly progress through stages as a result of stressful events (surgery) or changes in overall weight.^{28,40,41} The occurrence of lipedema from lipohypertrophy or to lipolymphedema and obesity is discussed below:

- **Lipohypertrophy**—The similar physical manifestations of lipohypertrophy and lipedema raise the question of whether the former is an early-stage precursor to the latter. Case reports indicate that patients with lipohypertrophy can develop to lipedema; however, the exact triggers of disease transition are not understood.^{4,9}
- **Lipolymphedema**—Lipedema patients can develop lymphedema suddenly, gradually, or never. The exact drivers of secondary lymphedema is not fully understood; however, development of this comorbidity results in stage 4 lipolymphedema.²⁸ Furthermore, it is poorly understood whether the disease progression is driven by an increase in localized fat or buildup of edema in affected areas that drives degradation of lymphatic function and/or an increase in fibrosis, and thereby results in progression to lipolymphedema.^{4,42}
- **Obesity**—Lipedema patients may also present with obesity. The Földi Clinic reported that the majority of lipedema diagnoses occur in obese individuals.²² However, how disease prognosis changes if obesity or lipedema is the initial insult is not known.²⁰

Overall, more research is needed to understand fully how lipohypertrophy, lymphedema, obesity, and lipedema affect each other's prognosis. Furthermore, lipedema is one of several fat disorders, such as Dercum's disease, Madelung's disease, and lipodystrophy, and exactly how these disorders are similar or differ in their biology is poorly understood.⁶ Increased research and awareness of the medical field of the shared and unique pathways across all the listed conditions would ultimately improve the outlook for all patients affected by these diseases.

Lipohypertrophy is a condition that exhibits a highly similar body shape to early-stage lipedema. Patients with this condition present with fat accumulation in the lower limbs, rarely in the arms, and—critical for a differential diagnosis—do not experience pain or buildup of edema in the affected areas. Although reports indicate that patients with lipohypertrophy have developed lipedema, more research is needed to determine whether the condition serves as a very early stage of lipedema.⁴

Lipohypertrophy is a term more commonly used in Europe. The term is used in the United States, but is unrelated to lipedema, wherein it refers to the build-up of fat at sites of insulin-injection.

Little is known about the basic biology and etiology of lipedema, with most publications focused on the vascular and lymphatic findings of surgeons and physical therapists. The tissue most affected by lipedema is skin, composed of the epidermis, dermis, and hypodermis—and includes the fat that expands in patients. Given the disease's presentation of adipose, lymphatic, and inflammation issues, as well as a potential link to endocrine signaling, it is highly possible that researchers have only just begun to explore the biology underlying the disease.⁴³

ADIPOSE TISSUE

Adipocytes (fat cells) are a part of the endocrine system and are the major component of adipose tissue (body fat). There are several sites of adipose tissue storage, or depots, and they can broadly be divided into visceral (located deep in the abdomen), subcutaneous (located directly below the skin), and ectopic (around organs like the liver, and within muscle fibers) depots.⁴⁴ Subcutaneous depots are present throughout the body, including the face, chest, arms, legs, abdomen, and buttocks. Lipedema can affect the several subcutaneous depots but predominantly impacts the legs and arms.^{4,13}

In subcutaneous adipose tissue, adipocytes are surrounded by fluid that bathes the cells (interstitial fluid), a network of proteins that provide structure and stability (extracellular matrix), as well as other cells important for adipose tissue physiology⁴⁵ (Figure 9). Other adipose tissue cells include adipocyte stem cells (the cell source of adipocytes), immune cells, and tissue and blood lymphatic capillaries composed of endothelial cells.⁴⁶

Depending on disease stage, reports indicate that the feel of lipedema adipose tissue can range from smooth, granular, to nodular.^{1,4,6,28} Furthermore, MRI, CT scans, and tissue biopsies indicate that, in the early stages of lipedema, edema (composed of interstitial fluid) is minimal, and that adipose tissue expansion is likely due to adipose cell enlargement (hypertrophy) and/or an increase in number (hyperplasia).⁴²⁻⁴⁶ Researchers have hypothesized that the edema associated with lipedema may involve impairment of lymphatic vessels due to pressure exerted by fat tissue, which subsequently limits the inward flow of interstitial fluid.^{42,43} Limited research has been performed to assess whether adipose growth and subsequent impairment lymphatic vessels plays a role causative role in lipedema.

Despite the central role of adipocyte expansion in lipedema, little is known about the characteristics of these cells. For example, the mechanisms of hyperplasia and hypertrophy are distinct, with the former driven by cell division, and the latter based in the tissue's need for additional fat storage.^{43,47} Adipocytes, as components of the endocrine system, respond to and release a variety of molecules that may be related to lipedema. These include the key players in hormonal response, levels of inflammation and the resulting pain and tenderness, and metabolism.⁵² To what extent these growth and signaling activities are on/off or impaired is unknown for lipedema.

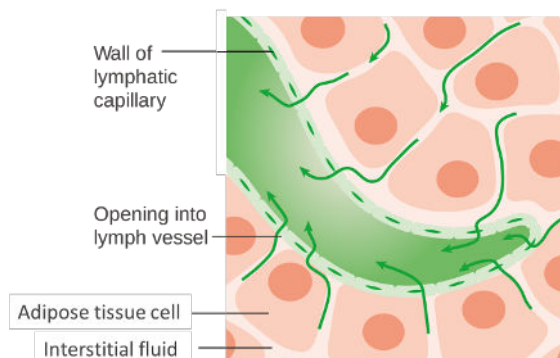


Figure 9: Subcutaneous Adipose Tissue. Pink cells are adipose cells, green is the lymphatic vessel, and light green cells are lymphatic endothelial cells that serve as the wall of the lymphatic capillary. Green arrows indicate the flow of interstitial fluid into the lymphatic vessel. Image modified from Wikimedia Commons.

LYMPHATIC SYSTEM

The lymphatic system is composed of a network of lymphatic vessels, the fluid in the vessels called lymph, and lymph nodes that filter lymph as it passes through them. The system also includes the tonsils, adenoids, spleen, and thymus. Unlike blood, the lymphatic system is not pumped by the heart, but instead relies on the movement of the diaphragm, muscle contraction, skin tension, and the fluid pressures in the blood capillaries, lymphatic capillaries and interstitial space to propel lymph fluid from across body towards the trunk.⁵³ Previously derided as “the body’s sewer system,” the lymphatic system is now understood to be a part of the circulatory system and a vital component of the immune system.

Adipose cells, like any cell in the body, are fed by blood through blood capillaries, and blood returns to main circulation by small veins, or venules.⁴⁵ The interstitial fluid, fluid that leaves the cells, bathes and surrounds the adipose tissue, before flowing into lymph capillaries and eventually into lymphatic vessels, thereby comprising the majority of lymph fluid (Figure 10).

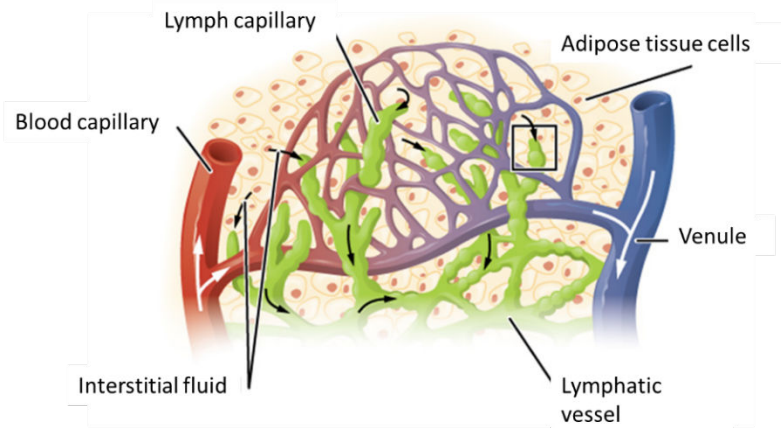


Figure 10: Interstitial Space of Adipose Tissue. The red and transition to blue tubes depicts the transition of blood from the capillary to venule; the yellow cells represent adipose tissue; the green tubes represent the lymphatic capillaries and vessels; and the black arrows show the flow of interstitial fluid into the lymphatic system, and subsequent renaming to lymph fluid. Image modified from Wikimedia Commons.

In lipedema, the edema experienced by patients is primarily composed of interstitial fluid and its components.^{4,42,54} The swelling of lipedema tissue has been found to have an increase in interstitial space, hypothesized to result from the increase in fluid.²⁰ Thus the presence of edema in early stages of lipedema indicates a slight impairment of the lymphatic system’s ability to take up fluid.⁴⁸

Previous work has shown that some lipedema patients present with leaky lymphatic capillaries and vessels, referred to as microaneurysms.^{55,56} As components of the vascular system, spider veins and vascular changes in lipedema patients also suggest a level of microangiopathy (disease of the small blood vessels).⁵⁷ A coupling of these results would suggest that lipedema may be driven by vascular issues that manifest in increased buildup of edema, and subsequent limitations of fluid removal from the interstitial space.⁸

The complex bidirectional relationship between impairment of the lymphatic system and growth/enlargement of adipocytes is a potential driver of lipedema, as late-stage patients demonstrate both. However, to shed light on the initial insult that causes lipedema onset, more research is needed to determine whether lymphatic dysfunction arises from an intrinsic impaired lymphatic and vascular activity or is a secondary manifestation of the disease arising from the pressure exerted by expanded adipocytes on the lymph capillaries and vessels.

PAIN AND INFLAMMATION

The pain and tenderness experienced by lipedema patients suggests an activated state of inflammation within the subcutaneous space (Figure 11). Within the epidermis (dermis and adipose tissue that compose the subcutaneous space), multiple immune cells play a role in activating and mediating an inflammatory response.⁵⁸ Although no research has been performed on whether dendritic cells, T cells, or Langerhans cells play a role in the symptoms of lipedema, activated macrophages were found in a single stage 4 lipolymphedema patient.⁵⁹

Research is needed to determine the role of an activated immune system in lipedema, and its potential impact on the pain associated with the disease. Furthermore, stress is known to play a role in inflammation, and whether the long-term mental health issues experienced by lipedema patients contributes to immune activation is completely unknown.

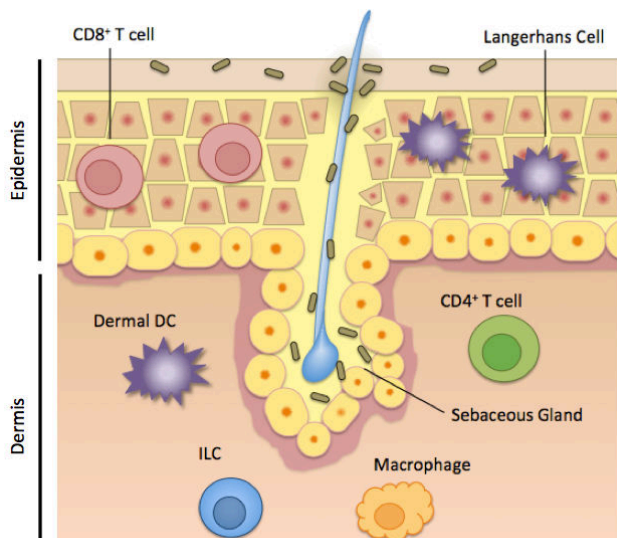


Figure 11: Immune Cells in the Skin Occupy Distinct Locations and Functional Roles. These immune cells include T cells, Langerhans cells, lower layer of skin dendritic cells (dermal DC), innate lymphoid cells (ILC), and macrophages. Figure created by Rachel Cotton, [Just Skin](#). [Deep—Your Immune](#)

ENDOCRINE SIGNALING

The endocrine system is the collection of glands that produce hormones that regulate a host of bodily functions. Given the almost exclusive occurrence in women and disease onset during puberty and periods of hormonal shift, there is a potential role for female-specific hormones in lipedema etiology⁶ (Figure 12). A role for sex-specific hormones is also supported by the rare occurrence of lipedema in men.²

Given the central role of estrogen, its numerous types, receptors, and involvement in many biological processes, research is needed to understand whether disease onset is affected by the estrogen pathway.^{23,60,61} Furthermore, estrogen and its types comprise only a portion of the sex-specific hormones that fluctuate during periods of hormonal shift; thus more research is needed to understand the overall role of hormones in lipedema.

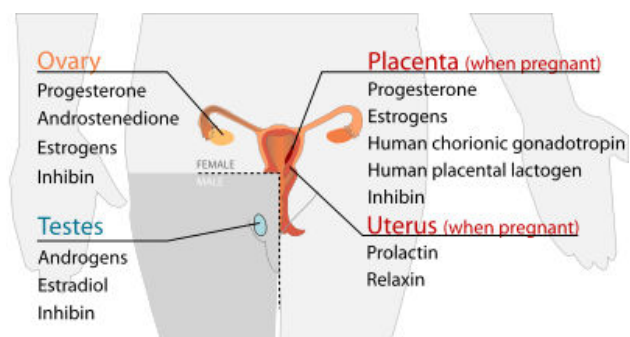


Figure 12: Sex-specific Hormones Produced by Reproductive Endocrine Organs. Image courtesy of Wikimedia Commons.

TREATMENTS

Lipedema is a chronic disease with limited therapeutic options. Because the causes or drivers of disease onset remain unknown, currently available therapies are geared toward ameliorating symptoms and preserving patient health. The Dutch Lipedema Guidelines also developed clinimetrics to assess the health profiles of patients undergoing therapy for lipedema. These measurements include circumference of lipedema affected areas, mobility, strength, pain via the VAS, fatigue, weight, levels of activity, condition and walking capacity, and quality of life.^{7,17}

CONSERVATIVE THERAPY

The goal of conservative therapy is to aid in disease management and address the symptoms associated with lipedema.⁷ The [Fat Disorders Research Society provides videos](#) that comprehensively describe treatment options. It is critical to note that although the treatments below are what patients and caregivers employ to address lipedema, limited research is available to understand why certain treatments are effective or ineffective for patients.

Exercise is a key component of conservative therapy and serves to reduce or stabilize weight, strengthen muscles, improve blood and lymph flow, and boost mental health.^{5,16,17,62} Commonly used exercises include low-impact workouts such as walking, lymphatic yoga, rebounding, cycling, and Pilates. Aquatic exercise involves submersion in a pool to perform low-impact exercises.^{5,63}

Healthy eating, such as the Rare Adipose Diet, Paleo Diet, and Anti-inflammatory Diet, is a strategy that has been used by the patient community. Although the effects and success of specific diets differ from patient to patient, regular exercise and proper nutrition will affect body fat, thereby improving a patient's well-being.^{16,64}

Psychosocial counseling and support groups are important due to the mental health issues associated with lipedema. Patients are encouraged to participate in support groups, engage their friends and family, and seek the aid of mental health professionals to support disease management.^{5,30,62}

Locomotion (orthopedic) problems and lack of proper shoe wear are very common in patients with lipedema and leg lymphedema. This issue negatively impacts upward transport of fluid from the legs, thereby contributing to the buildup and progression of edema. Flat feet should be analyzed and treated with adequate shoes. Mechanical hindrance due to enlarged fat deposits on the inner and upper thighs should be treated as possible, as this can directly impact patient mobility and health.^{65,66}

Compression therapy involves garments that can be fitted to specific areas affected by lipedema. These include bandaging with garments with inelastic systems, and wraps with Velcro attachments to allow for easy wear and adjustment. These garments work by applying pressure to the affected limbs to keep lymph moving from the tissues into the vessels and are useful for patients who experience edema buildup, and have been reported to reduce pain.^{5,16,17}

Manual lymphatic drainage (MLD), sometimes called manual lymphatic therapy, is a specific type of massage designed to move excess interstitial fluid out of the tissues and into the lymphatic vessels. The goal of MLD is to increase the flow of lymph, thereby generating a suction effect and driving lymph from a fluid-rich area to a fluid-poor area.^{5,16,30,67} Although MLD is standard therapy for lymphedema, its success for treating lipedema is considered unproven.¹⁷

Complete decongestive therapy (CDT), also called complex decongestive therapy and decongestive lymphatic therapy, is a program that combines multiple treatment approaches to reduce the swelling and edema-related symptoms of lipedema. Tailored to the individual, CDT initially involves regular sessions with a physical therapist involving MLD or intermittent pneumatic compression, use of bandaging and compression garments, and therapeutic exercises.⁵⁷ Once the swelling is reduced, patient self-management involves application their own bandaging, compression, and exercise in an effort to maintain the reduction in swelling.^{5,16} CDT and MLD have been shown to reduce capillary fragility in lipedema patients, but to what extent this impacts the disease long-term is not fully understood.⁵⁷

Deep breathing is beneficial as it activates the diaphragm and promotes lymphatic pumping.⁶³

Supplements such as Butcher's Broom and selenium have been used by patients with isolated and anecdotal reports of improvement of lymphatic flow and limb reduction.⁶⁸

LIPOSUCTION AND REDUCTIVE SURGERY

Surgery is the only available technique to correct abnormal adipose tissue. Two types of surgery have been used in lipedema treatment, liposuction and reductive surgery.

Liposuction is a surgical treatment that involves application of general or local (tumescent and water-assisted) anesthesia, and subsequent removal of adipose tissue through a straw-like device called a cannula.⁴² One end of the cannula is connected to a vacuum device, and the other end is inserted through a small incision of the skin and removes fat via aspiration.

- **Tumescent liposuction** involves introduction of large volumes of tumescent solution into the subcutaneous space to tumesce (swell) the area. The solution contains an anesthetic, which induces local numbing; epinephrine, which causes constriction of blood vessels to reduce bleeding; and saline, which causes swelling of the adipose tissue. The solution is allowed to infiltrate the tissue, and its high salinity causes the adipose tissue and cells to swell and separate from the connective tissue, at which point the cannula is used to aspirate the fat.^{14,20,69,70}
- **Water-assisted liposuction** does not involve over-swelling of the adipose tissue. Instead, small amounts of tumescent solution and water are introduced into the adipose tissue. Once sufficient numbing occurs, a modified cannula with an attached fan-shaped water jet is inserted into the subcutaneous space and applied to separate the adipose cells from the tissue, while simultaneously aspirating the solution and detached cells.⁷¹

Although liposuction has been more commonly used to treat lipedema, the Dutch lipedema guidelines state that *"[liposuction] is only the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative therapy. Before using [liposuction], associated deteriorating components such as edema, obesity, unhealthy lifestyle, lack of physical activity, lack of knowledge about the disease, and psychosocial distress should be addressed. Moreover, even after liposuction, women generally require conservative therapy, and weight normalization should remain a goal."*¹⁷

Reductive surgery, also called excision and resection, is a more invasive procedure that involves excision of large localized deposits of lipedematous tissue, or lumps, possibly including the surrounding skin. Development of these lumps can cause the knees to twist outward (valgus deformity) or droop to the side of the leg (ptosis) and, in serious cases, lead to the inability to walk, thereby dramatically impacting the patient's life.

CLINICAL PIPELINE

Clinical research is a branch of biomedical research that involves human subjects. The goal of clinical research is to understand better the health outcomes of participants and to evaluate the safety and efficacy of therapy, drugs, medical devices, or diagnostics intended for use in humans. These studies can also be used to collect specimens from human subjects for further research. There are two key types of clinical studies: observational, and interventional (see box).

Importantly, information on potential side effects of interventions are gathered during the study and weighed against the potential therapeutic benefit of the treatment under investigation.

Observational Studies

In this type of clinical study, investigators assess the health outcomes in groups of participants according to a research protocol without any specific medical intervention.

Interventional Study (or Clinical Trial)

In this type of clinical study, participants are assigned to receive an intervention/therapy so that researchers can evaluate the effect of the intervention on health-related outcomes according to a research protocol. Participants may receive diagnostic, therapy, or drug interventions.

LIPDEMA CLINICAL STUDIES

As of January 2017, only four clinical studies have been conducted in lipedema.

Observational Studies

[Insight Into Subcutaneous Adipose Tissue Disorders \(INSIGHT\)](#)—This study aims to understand the observable physical characteristics of a person that results from the interaction of his or her genetic makeup with the environment. This type of interaction is called a phenotype. More specifically, this study focuses on understanding the phenotypes of individuals with subcutaneous adipose tissue disorders such as lipedema and Dercum's disease. This study is currently recruiting participants.

[Imaging Lymphatic Function in Normal Subjects and in Persons with Lymphatic Disorders](#)—This study aims to understand the potential applicability of near-infrared fluorescence lymphatic imaging as a diagnostic assay of lymphatic flow in participants with lymphedema, lymphatic disorders, vascular disorders, or lipedema. This study is enrolling participants by invitation only.

Interventional Studies

[Physical Condition in Lipedema and Obesity](#)—Because lipedema and obesity are often misdiagnosed for each other, the primary aim of this study is to understand whether there is a difference in muscle strength between women with lipedema and women with obesity. This study has been completed and contributed data to the Dutch Lipedema Guidelines.¹⁷

[Quadrivas Therapy to Reduce Lipedema Subcutaneous Adipose Tissue](#)—Quadrivas is an intensive massage therapy for different tissues. This study aims to understand whether the therapy can reduce subcutaneous adipose tissue in participants with lipedema. This study is ongoing but is not recruiting participants.

RESEARCH CHALLENGES AND PHILANTHROPIC OPPORTUNITIES

The little that is known about the etiology of lipedema and its holistic effect on patients is based on isolated clinical case reports and limited research studies. Research efforts are complicated by a subjective clinical diagnosis process that faces scalability and standardization issues. Discussions before, during, and after the 2016 Lipedema Scientific Retreat revealed several research challenges and philanthropic opportunities, which, if addressed, will help to define and develop the lipedema research field.

Lipedema Basic Biology and Genetics

To define lipedema and develop treatments for patients, research tools such as cell lines, mouse models, and an understanding of the aberrant cells and physiological processes that drive the disease are required. Given the multiple diseases that require differential diagnosis from lipedema, it is likely that expansion of lipedema research will contribute to the understanding of lymphedema, obesity, Dercum's disease, lipohypertrophy, and other fat disorders. Furthermore, development of multidisciplinary teams that span research fields (adipose, lymphatic, metabolic, etc.) and disciplines (academics, clinicians, surgeons, etc.) would be the ideal approach to address the key unmet research needs of the disease.

Development of local surgeon-researcher teams

- **Research Challenge:** Access to fresh research samples and their sharing/storage at biobanks are complicated by processing challenges for researchers and few incentives for liposuction surgeons to participate in research efforts.
- **Research Opportunity:** A potential approach is to leverage the desire of lipedema patients to receive liposuction surgery by developing local surgeon-researcher teams, which will facilitate access to fresh patient samples while maintaining and expanding a biorepository's tissue bank.

RNA sequencing of lipedema patient samples such as blood, adipose tissue, and exosomes

- **Research Challenge:** The transcriptional (gene expression levels) differences in the genes transcribed into RNA, or between normal and lipedema fat, remain unknown.
- **Research Opportunity:** In an unbiased manner, this effort has the potential to determine the genes that are differentially expressed between lipedema tissue and non-lipedema tissue from the same patient, as well as by affected and unaffected family members.

Histology, morphology, and immunostaining of lipedema tissue

- **Research Challenge:** To date, lipedema publications offer two to three case reports with the occasional hematoxylin and eosin staining of patient biopsies to visualize cellular structures.
- **Research Opportunity:** If performed in a concerted and collaborative manner, this effort has the potential to visualize aberrant cellular structures and processes of lipedema tissue.

Molecular profiling of lipedema adipose stem cells

- **Research Challenge:** It is unknown whether adipose stem cells drive the expansion and growth of lipedema tissue.
- **Research Opportunity:** This effort has the potential to determine the current proteomic (protein expression levels), transcriptomic (gene expression levels), and metabolic state of lipedema adipose stem cells, and whether key pathways are altered in these cells. Furthermore, these research efforts can be applied to other potential cells of interest in lipedema tissue, such as lymphatic endothelial cells, differentiated adipose cells, and skeletal muscle.

Assessment of circulating and local cytokine and hormone levels of lipedema patients

- **Research Challenge:** Although standard panels have been performed on lipedema patient blood samples, these efforts have been neither comprehensive in their testing of all known cytokines/hormones, nor indicative of the local levels of cytokines/hormones in lipedema tissue.
- **Research Opportunity:**
 - Cytokine-focused efforts may determine what drives the inflammatory and pain component of lipedema.
 - Hormone-focused efforts may shed light on what drives onset and exacerbation of the disease.

Lipedema symptoms-based mouse studies

- **Research Challenge:** In the absence of known genetic mutations and altered cells/signaling pathways, the relevant mouse models for lipedema are unknown.
- **Research Opportunity:** A potential approach is to study the symptoms of lipedema patients in currently available mouse models. This effort would expand the network of animal model researchers, and potentially the range of diseases and research fields related to lipedema.

Determine the genetic markers and drivers of lipedema

- **Research Challenge:** Because the genetic architecture of lipedema is currently unknown, the heritability component and genetic markers and drivers of the disease are poorly understood.
- **Research Opportunity:** Understanding of the genes that underlie development of lipedema could serve as a potential diagnostic tool that would inform basic biology studies. These efforts would benefit from multiple, well-phenotyped cohorts to facilitate data comparison and reproducibility.

Lipedema Diagnosis and Epidemiology

The epidemiology of lipedema is unknown, and available studies are restricted by small sample sizes and comparison difficulties. To increase awareness and acceptance of lipedema as a disease, accurate values of incidence/prevalence are needed. Collection of data to determine incidence/prevalence would increase clinical, research, and industry interest in the field. Furthermore, tools to facilitate patient identification and engagement are essential to performing epidemiological studies.

Development of lipedema-specific diagnostic tools

- **Research Challenge:** Currently available imaging and diagnostic assays are not approved to serve as a primary test to diagnose lipedema or as confirmation of a clinical diagnosis of lipedema.
- **Research Opportunity:** Development of novel diagnostic tools or improved application of currently available tools to better diagnose lipedema would be a critical advancement for the field.
 - A potential approach is to explore the value and applicability of novel imaging techniques such as sodium-based MRI or near-infrared fluorescence lymphatic imaging.
 - Another approach is to expand and improve the use of currently available imaging techniques such as MRI, CT, ultrasound, and dual-energy x-ray absorptiometry scans to determine whether a combination of imaging tests might generate lipedema-specific parameters able to differentially diagnose the disease.

Development of consensus and scalable solutions for lipedema diagnosis and epidemiology

- **Research Challenge:** An accurate and scalable diagnostic procedure for lipedema is a clear unmet need. However, the exact process for addressing this need remains undefined.
- **Research Opportunity:** A potential approach is to form a working group focused on developing a standard, minimal survey/questionnaire that would be applicable for patient registry intake questions; an epidemiological incidence and prevalence study; and general practitioners and centers that see potentially undiagnosed individuals with lipedema.

Development and launch of a patient registry

- **Research Challenge:** Lipedema patients are highly interested in participating in research, and their participation is central to leveraging the basic biology, genetic, and epidemiological opportunities. However, converting patient interest into engagement requires the return of results to study participants, as well as the sharing of results with the broader lipedema research field.
- **Research Opportunity:** A potential approach is to develop a well-curated lipedema patient registry connected to an existing biorepository. Such an effort would facilitate
 - Assessment of diagnosis and epidemiology studies
 - Patient recruitment into basic biology, genetic, and diagnostic research studies
 - Development of a long-term natural history study that captures disease progression, symptoms, and treatment history of lipedema patients; followed by dissemination of results to all participants and patient networks

NONPROFIT ORGANIZATIONS INVOLVED IN LIPEDEMA

RESEARCH-FUNDING FOUNDATIONS

[Lipedema Foundation](#)—This foundation was founded in 2015 with the mission of defining, diagnosing, and developing treatments for lipedema. To date, the Foundation has committed more than \$2.9 million towards lipedema research, including genetic studies, support for postdoctoral fellows, mouse model research, and launch of the University of Arizona Treatment, Research, Education, Adipose Tissue (TREAT) program and tissue biorepository.

[Fat Disorders Society \(FDRS\)](#)—As a funding organization and patient support and advocacy group, this U.S.-based society was founded in 2009 and is dedicated to improving the quality of life for all people affected by adipose tissue disorders through research, education, advocacy, and collaboration. The society also holds annual conferences that bring together patients, clinicians, therapists, caregivers, and researchers to discuss key issues facing the field.

[Lymphatic Education and Research Network \(LE&RN\)](#)—Founded in 1998 as the Lymphatic Research Foundation, LE&RN's mission is to fight lymphatic disease and lymphedema through education, research, and advocacy. With financial support from the Fat Disorders Research Society, LE&RN facilitated the awarding of three lipedema postdoctoral fellowships in 2015.

PATIENT SUPPORT AND ADVOCACY GROUPS

[Lipoedema UK](#)—This United Kingdom-based charitable organization was founded in 2012 by women with lipedema and the Lymphoedema Service at St. George's Hospital in London. Its focus is to educate doctors, health professionals, and the public about lipedema and its symptoms to facilitate diagnosis and earlier treatment.

[Talk Lipoedema](#)—This United Kingdom-based charitable organization provides support to people with lipedema and their families and caregivers. The organization supports efforts that will improve the accuracy of lipedema diagnosis, development of individual patient care plans, and patient access to services and self-support management.

[Lipoedema Ladies](#)—The mission of this United Kingdom-based nonprofit organization is to support women with lipedema, raise awareness about the disease as well as treatment and management options, and contribute to the overall body of knowledge and understanding for lipedema.

[Lipoedema Australia Support Society \(LASS\)](#)—This Australia-based society aims to raise disease awareness through patient support and advocacy. The association was formed to involve and educate sufferers, as well as to facilitate coordination of the different medical areas necessary for ongoing management of lipedema.

[Lipoedem Hilfe \(Lipoedema Help\)](#)—This Germany-based organization was founded in 2011 with the goal of increasing general awareness and recognition of lipedema as a chronic disease. The organization aims to improve patient access to treatments by fostering closer cooperation among doctors, health insurers, hospitals, authorities, and politicians.

[Nederlands Netwerk voor Lymfoedeem & Lipoedeem \(Dutch Lymphedema and Lipoedema Network\)](#)—

Founded in 2006, this Netherlands-based foundation is focused on helping individuals affected by lymphedema and lipedema. The network's goals are to develop an independent platform for scientific knowledge, through the development of national and international guidelines, and to serve as a resource for patients, patient organizations, and caregivers.

[Stichting Nederlandse Lipoedeemdag \(Dutch Lipoedema Foundation\)](#)—This Netherlands-based foundation has the goal of raising regional, national, and international awareness of the disease. The foundation convenes an annual symposium for patients, partners, physical therapists, and medical practitioners to share best practices and recent developments in lipedema.

GLOSSARY

adenoids	Also known as a pharyngeal tonsil or nasopharyngeal tonsil, it is a mass of lymphatic tissue situated where the nose blends into the throat.
adipocyte stem cells	The cell population from which mature adipocytes arise from.
adipocytes	Also known as fat cells, they are the primary components of adipose tissue and specialize in storing energy as fat.
adipose tissue	Fat; a loose connective tissue primarily made up of adipocytes.
adiposis dolorosa	Also known as Dercum's disease or Anders disease, it is a rare condition characterized by generalized obesity and fatty tumors in the adipose tissue. The tumors are normally painful and found in multiples on the extremities. The understanding of the cause and mechanism of Dercum's disease remains unknown.
anesthetic	A drug given to a patient to prevent pain during surgery.
angiolipoma	A benign mass of fat tissue and blood vessels. They often appear at multiple sites and occur as painful subcutaneous nodules.
autosomal dominant inheritance with sex limitation	An inherited genetic condition wherein the only one copy of the mutant gene is needed to present the phenotype. The sex limitation component indicates that phenotype is only expressed in one sex. For lipedema, it may be an indicator of why the disease occurs almost exclusively in women.
cellulitis	A common, potentially serious bacterial skin infection. It appears as a swollen, red area of skin that feels hot and tender, and can spread rapidly to other parts of the body.
chronic venous insufficiency	A condition that occurs when the venous wall and/or valves in the leg veins are not working effectively, making it difficult for blood to return to the heart from the legs, thereby causing blood to "pool" or collect in these veins. This pooling is called stasis.
circulatory system	Also called the cardiovascular system or the vascular system, is an organ system that circulates blood, facilitating the transportation of nutrients, oxygen, carbon dioxide, hormones, and blood cells to and from the cells.
clinimetrics	The practice of assessing or describing symptoms, signs, and laboratory findings by means of scales, indices, and other quantitative instruments.
computed tomography	An imaging procedure that uses special x-ray equipment to create detailed pictures, or scans, of areas inside the body. It is also called computerized tomography and computerized axial tomography (CAT) scans.
connective tissue	Tissue that connects, supports, binds, or separates other tissues or organs, typically composed of collagen or other fibers, and including cartilaginous, fatty, and elastic tissues.
cytokines	Any of a number of substances, such as interferon, interleukin, and growth factors secreted by certain cells of the immune system and have an effect on other cells.
dendritic cells	Antigen-presenting cells (also known as accessory cells) of the mammalian immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. They act as messengers between the innate and the adaptive immune systems.
Dercum's disease	Also known as adiposis dolorosa or Morbid Dercums, is a rare condition characterized by generalized obesity and fat masses, or lipomas in the adipose tissue. The lipomas can be painful and found in multiples on the extremities. The understanding of the cause and mechanism of Dercum's disease remains unknown.
dermis	The layer of tissue below the epidermis containing blood capillaries, nerve endings, sweat glands, hair follicles, and other structures.
diabetes	A disease in which the body's ability to produce or respond to the hormone insulin is impaired, resulting in abnormal metabolism of carbohydrates and elevated levels of glucose in the blood and urine.

diaphragm	A sheet of internal skeletal muscle that extends across the bottom of the thoracic cavity. The diaphragm separates the thoracic cavity, containing the heart and lungs, from the abdominal cavity. During respiration, as the diaphragm contracts, the volume of the thoracic cavity increases and air is drawn into the lungs.
dual-energy X-ray absorptiometry	DXA, previously DEXA, is a means of measuring bone mineral density (BMD). Two X-ray beams, with different energy levels, are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone. Although widely used to assess BMD, DXA has been used to measure soft tissue mass and adiposity.
ectopic fat	Ectopic means "not where it's supposed to be". Ectopic fat is non-normal accumulation of fat in areas such as the abdominal region (beer belly), liver, muscle tissue including the heart, pancreas, and perhaps in lipid-rich deposits in the arteries.
eczema	Also known as dermatitis, eczema is a group of diseases that results in skin inflammation. These diseases are characterized by itchiness, red skin, and a rash, with the area of skin involved varying from small to the entire body.
edema	The medical term for swelling, which may be caused by trapped fluid, inflammation, and other causes.
endocrine system	The collection of glands that produce hormones that regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep, and mood.
endothelial cells	These cells make up the endothelium, which is a type of tissue that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall.
epidemiology	The branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health.
epidermis	The outer layer of cells that overlays the dermis.
epinephrine	A hormone, neurotransmitter and medication. During surgical procedures it used as a medication that facilitates constriction of blood vessels.
estrogen	The primary female sex hormone which is responsible for the development and regulation of the female reproductive system and secondary sex characteristics.
etiology	The cause, set of causes, or manner of causation of a disease or condition.
exosomes	Cell-derived vesicles that are present in many and perhaps all eukaryotic fluids, including blood, urine, and cultured medium of cell cultures. Research has shown that these small vesicles play a role in cell-to-cell signaling and can serve as disease biomarkers.
extracellular matrix	A collection of molecules on the outside of cells, and which are secreted by cells to provide structural and biochemical support.
fibrosis	The thickening and scarring of connective tissue, usually as a result of injury.
genotype	The genetic constitution of an individual.
genetic architecture	Refers to the underlying genetic basis of a trait or disease, and describes whether the genotype connected to the phenotype occurs rarely, or is common, and whether its effect is highly penetrant, moderate or minimal.
hematoxylin and eosin	One of the principal stains in histology and is the most widely used stain in medical diagnosis. The hematoxylin stain nuclei, while the eosin stains proteins inside and outside of the cells.
hormones	Any member of a class of signaling molecules produced by glands in multicellular organisms. They are transported by the circulatory system to target distant organs to regulate physiology and behavior.
hypermobility	Joints that are more flexible than normal or that move in excess of a normal range of motion are considered hypermobile. When generalized, hypermobility occurs with symptoms such as muscle or joint pain without systemic disease, and is called - hypermobility syndrome or joint hypermobility syndrome.

hyperplasia	In fat cells, this process refers to an increase in the rate of cellular reproduction
hypertension	Abnormally high blood pressure.
hypertrophy	In fat cells, this process refers to an increase in the size of cells
hypodermis	The innermost and thickest layer of skin, which is primarily composed of adipocytes.
immune system	A network of cells, tissues, and organs that work together to defend the body against attacks by “foreign” invaders. These are primarily microbes—tiny organisms such as bacteria, parasites, and fungi, that can cause infections.
incidence	The occurrence, rate, or frequency of a disease.
indirect lymphangiography	An X-ray based assay used to visualize and delineate lymphatic vessels. The indirect aspect of the assay refers to administration of contrast agents to image, or “light up” vessels.
inflammation	A component of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, and is a protective response involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. The classical signs of inflammation are heat, pain, redness, swelling, and loss of function.
interstitial fluid	The fluid released by cells and that bathes the surrounding cells and tissue.
Langerhans cells	Dendritic cells that are present in the skin and mucosa.
lipedema	A chronic disease that occurs almost exclusively in women. It presents as symmetrical accumulation of fat in the subcutaneous tissue of the limbs. The affected areas are also painful, easy to bruise, with the fat tissue demonstrating limited response to weight loss strategies.
lipodystrophy	A condition characterized by abnormal or degenerative conditions in adipose tissue.
lipohypertrophy	A term more commonly used in Europe, it refers to the symmetrical accumulation of fat in the legs that do not present with pain.
lipolymphedema	The late stage of lipedema, wherein the increased fat accumulation and strain in the lymphatic system results in lymphedema as well.
lipomas	Masses of fat tissue that expand under the skin.
lymph	The fluid inside of lymph vessels, which is composed of immune cells, proteins, and lipids.
lymph node	An organ of the lymphatic system present widely throughout the body. They act as filters for the lymph that passes through them.
lymphangiography	An X-ray based assay used to visualize lymph nodes and lymph vessels.
lymphatic capillaries	A small network of thin-walled vessels that collect the interstitial fluid and allows them to flow into the lymphatic system, becoming lymph.
lymphatic vessels	The larger network of vessels that collect lymph fluid, passes it through lymph nodes, and towards the trunk.
lymphedema	A disease that presents with buildup of the fluid surrounding tissues, or interstitial fluid, in the muscle and skin leading to increased fat deposition. The disease can be hereditary (primary lymphedema) or arise from damage to the lymphatic system from different insults such as cancer, surgery, radiation therapy, trauma, or infection (secondary lymphedema).
lymphoscintigraphy	An imaging procedure that allows visualization of lymph nodes through the use of injected contrast agents.
macrophages	A large cell found in stationary form in the tissues or as a mobile white blood cell, especially at sites of infection. It is characterized by its phagocytic, or sampling, capacity of its extracellular surroundings.
Madelung’s disease	Also known as benign symmetric lipomatosis, it is a condition characterized by

	extensive fat deposits in the head, neck, and should girdle area.
magnetic resonance imaging	A form of medical imaging that measures the response of the atomic nuclei of body tissues to high-frequency radio waves when placed in a strong magnetic field, and that produces images of the internal organs.
metabolic biology or metabolism	The sum of all chemical reactions in an organism by which digestion of food is turned into and stored as energy.
microaneurysms	With respect to lipedema, this refers to the enlargement and dilation of a vessel wall.
microangiopathy	A vascular condition wherein the vessels appear smaller than normal.
obesity	The condition of having excessive body fat, with its related comorbidities that increase the risk of health problems.
phenotype	The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.
phlebedema	Edema or swelling that is the result of venous insufficiency.
prevalence	The commonness of a disease or trait in a population.
prognosis	The likely course of a disease or ailment.
proteomic studies	Research that focuses on the amount, types, and function of generated proteins.
spleen	An abdominal organ involved in the production and removal of blood cells in most vertebrates and a component of the immune system.
spider veins	Small red, purple, and blue veins that twist and turn and are easily visible through the skin, also called venulectasia.
T cells	A lymphocyte produced or processed by the thymus gland, and plays an active in the immune response.
telangiectasia	A condition in which there are visible small linear red blood vessels (broken capillaries) on the skin, also called telangiectases.
thymus	A lymphoid organ situated in the neck of vertebrates that produces T cells for the immune system. The human thymus becomes much smaller at the approach of puberty.
tonsils	Either of two small masses of lymphoid tissue in the throat, one on each side of the root of the tongue.
transcriptomic studies	Research that focuses on the amount, types, and function of generated RNA transcripts.
ultrasound	A medical imaging assay that uses sounds or vibrations at an ultrasonic frequency to generate and image.
visceral fat	Depots of fat tissue located deep in the abdomen.
X-linked dominant inheritance	X-linked dominant inheritance, sometimes referred to as X-linked dominance, is a mode of genetic inheritance by which a dominant gene is carried on the X chromosome.

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