AN OVERVIEW FOR CLINICIANS

LIPEDEMA

the DISEASE THEY CALL FAT

Erez Dayan, MD | Harvard Medical School

Julie N. Kim, MD | University of Texas Health Science Center

Mark L. Smith, MD, FACS | Zucker School of Medicine at Hofstra/Northwell

Catherine A. Seo, PhD | The Lipedema Project

Robert J. Damstra, MD, PhD | Nij Smellinghe Hospital

Prof. Wilfried Schmeller, MD | Hanse-Klinik

Yvonne Frambach, MD | Hanse-Klinik

Matthew A. Carmody, MD | Harvard Medical School

Prof. Etelka Földi, MD | Földiklinik for Lymphology

Foreword by Stanley G. Rockson, MD
Stanford University School of Medicine

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An Overview for Clinicians

Lipedema Simplified Publications
The Lipedema Project at The Friedman Center for Lymphedema Research and Treatment
The Center for Advanced Medicine at Northwell Health
Lymphatic Education & Research Network (LE&RN)

AUTHORS
Erez Dayan, Julie N. Kim, Mark L. Smith, Catherine A. Seo
Robert J. Damstra, Wilfried Schmeller, Yvonne Frambach
Matthew A. Carmody, Etelka Földi

LipedemaProject.org

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PUBLISHED BY:
Lipedema Simplified Publications
The Lipedema Project at The Friedman Center for Lymphedema Research and Treatment
in collaboration with Lymphatic Education & Research Network (LE&RN)
The Center for Advanced Medicine at Northwell Health
Boston, Massachusetts 02144
Lake Success, New York 11042
United States
+1-617-721-9463
http://LipedemaProject.org

Citation
APA
Dayan, E., Kim, J. N., Smith M. L., Seo, C. A., Damstra, R. J., Schmeller, W., Frambach, Y., Carmody, M. A., Földi, E., & Rockson, S. G. (2017). *Lipedema - The disease they call FAT: An overview for clinicians*. Boston, MA: Lipedema Simplified Publications, The Friedman Center for Lymphedema Research and Treatment at The Center for Advanced Medicine at Northwell Health in collaboration with Lymphatic Education & Research Network (LE&RN).

AMA
Dayan E, Kim JN, Smith ML, Seo CA, Damstra RJ, Schmeller W, Frambach Y, Carmody MA, Földi E, Rockson SG. *Lipedema - The disease they call FAT: An overview for clinicians.* Boston, MA: Lipedema Simplified Publications, The Friedman Center for Lymphedema Research and Treatment at The Center for Advanced Medicine at Northwell Health in collaboration with Lymphatic Education & Research Network (LE&RN), 2017.

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Layout & Design: MPJ Creative Services (www.mpagejones.com)
Cover photo by Mike Pecci

Editor: Amy Hodson Thompson, PhD, Baltimore, Maryland (www.AmyThompsonPhD.com)

ISBN: 978-0-9989845-0-6 (digital edition)

Library of Congress Control Number: Application in process
Publication date: September 2017
Printed in the United States of America.

Disclaimer: This monograph is intended for informational use and discussion only and does not take the place of advice from a physician. Nothing in this publication is intended as medical advice and is not a substitute for professional medical consultation, diagnosis, or treatment. Always seek the advice of a physician or other qualified health care provider with any questions you have regarding a medical condition, and before undertaking any treatment.

"As a clinician, I expect this will quickly become a 'standard reference' on Lipedema. The clinical information is concise, thorough, and up to date. The monograph is a helpful reference whether checking stages, differential diagnosis or current treatments. It has become a great teaching document in our clinic for therapists, students, and patients alike. It will be a helpful reference to share with physicians as we discuss strategies for care management."

Jean Flanagan Jay, DPT, PT, CLT
Director, Rehabilitation Services
Brigham and Women's Faulkner Hospital
Boston, Massachusetts, USA

"Finally, someone (Doctors Erez Dayan, Mark L. Smith, Catherine A. Seo, and many concerned other experts) comes along to illuminate a disease that has eluded scientific daylight. Patients, plastic surgeons, and everyone who cares about people who are unfortunate enough to be struggling with lipedema owe many congratulations to you.

This monograph on lipedema is a singular achievement. In textbook fashion, it describes the pathogenesis, diagnosis, and treatment of a condition that disables and humiliates but does not kill. Those who suffer from it - until now - have been relegated in many unfortunate instances to second class patients; their doctors do not know, in fact, may never have heard of the disease lipedema, and therefore cannot provide a meaningful treatment, or worse yet, even suggest one.

Advances such as liposuction provide significant long-term improvement for many patients with lipedema; those advances should become part of the body of knowledge that all physicians possess, including those in primary care and family medicine. This comprehensive and clearly written monograph is authored by a group who refused to accept black box status for lipedema any longer. It is just what the medical profession and lipedema patients have sorely needed for many years, and most importantly, it is a testimony to advances in reconstructive surgical techniques and to the perseverance of a determined group of clinicians."

Sumner A. Slavin, M.D.
Clinical Associate Professor of Surgery
Harvard Medical School
Co-Director, The Program for Lymphedema, Boston Children's Hospital
Boston, Massachusetts ,USA

"This comprehensive monograph is the much needed guide that many clinicians have been waiting for. Not only does this work foster enlightened discourse and multidisciplinary collaboration, it highlights how very far we have come in our understanding of lipedema. Even though we still have far to go, this book lights the way by putting everything in a foundation of science and compassion."

Leslyn Keith, OTD, CLT-LANA
Central Coast Lymphedema Therapy
San Luis Obispo, California, USA

"Lipedema - the Disease They Call FAT: An Overview for Clinicians is a truly forward thinking approach to educating clinicians and patients alike of an otherwise often misunderstood disease. The monograph is a much needed, concise, and informative body of work representing the state of the art in current management."

Dhruv Singhal, MD
Director of Lymphatic Surgery
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts, USA

"This is a high-quality, comprehensive summary of the 'State of the Art/Science' relating to lipoedema/lipedema. This disease badly needs attention both from healthcare professionals in order to improve patient care and from scientists to improve our basic understanding of this disease with a view to improved treatment. I am hopeful this monograph will provide the platform for such advances."

Peter Mortimer, MD
Professor of Dermatological Medicine
Molecular and Clinical Sciences Institute (Dermatology Unit)
St. George's, University of London
London, England, UK

"This monograph on lipedema should be required reading for medical students, and residents in all US training programs. Yes, 'obesity' is everywhere but it's clearly not just one disease. We clinicians need to see the shades of grey within our population that appears to be overweight. The phenotype of lipedema is obvious once one learns its characteristics and if one can make the correct diagnosis a whole new world is opened for a patient. So think about the millions of woman who go to their doctor(s) complaining or even just wondering about why their legs look and feel different yet leave with incorrect information. It is up to those of us who know about lipedema to teach those who don't. This monograph is a key part of that process."

S. Scott Tapper, MD, FACS, RPVI
Board Certified Vascular Surgeon
Symmetry Vascular Center
Adjunct Professor of Surgery
Lake Erie College of Medicine
Stuart, Florida, USA

"Understanding lipedema and differentiating it from lipohypertrophy, lymphedema, and general obesity can be very confusing. This monograph for clinicians provides an excellent and well-referenced overview of lipedema, as well as diagnostic and therapeutic approaches currently available. For healthcare providers of various levels, this treatise will bring awareness of a condition that is so very often misunderstood and misdiagnosed, preventing patients from receiving the medical care they deserve."

Guenter Klose
MLD/CDT Certified Instructor; CLT-LANA
Founder, Klose Training & Consulting, LLC
Lafayette, Colorado, USA

"This monograph is a recent summary of what we currently know about the disease of lipedema. It is helpful for doctors and patients alike. The therapeutic recommendations correspond to the state of science and are serious. I will recommend it to my English-speaking patients."

Stefan Rapprich, MD
Dermatologic & Lipedema Surgeon
Phlebology Hautmedizin
Bad Soden, Germany

"Lipedema is a condition that too few know anything about. Research and clinical communities have a long way to go toward appropriately recognizing, diagnosing, and understanding this disease. It is so important to educate us all as we begin to take on and conquer this condition. This reference is a good place to start."

Gwen Randolph, PhD
Professor of Immunobiology
Head, Division of Immunobiology
Washington University in St. Louis
St. Louis, Missouri, USA

"All clinicians working in the best interest of their lipoedema/lipedema patient will find this impressive publication by a collaboration of internationally renowned experts invaluable. Experts with passion, willing to use their skills to develop a far-reaching research agenda for lipoedema and end the decades of misery lipoedema creates for all who suffer from it. My hope is that it will also encourage a wide range of new clinicians to become engaged in the mysteries of lipoedema."

Sharie Fetzer
Chair, Lipoedema UK
LipoedemaUK.org
West Sussex, England, UK

"Despite having a PhD on the topic of adipose tissue remodeling and obesity, prior to meeting Dr. Catherine Seo a few years ago, I had barely come across anything on the topic of lipedema in the research literature. Her passion for bringing new light to this often unrecognized and largely unknown disease shines through in this excellent monograph that brings together the experiences of clinicians, researchers, and patient advocates on the topic of lipedema diagnosis and treatment. It's a must read for patients and health care professionals dealing with untypical cases of obesity."

Ebba Brakenhielm, PhD, Hab. Dr.
Cardiovascular Researcher
Institut National de la Santé et de la Recherche Médicale (INSERM)
Normandy University
Rouen, France

"I've found this monograph very useful for clinicians, a good and complete synthesis of what we know about lipedema."

Isabel Forner-Cordero, MD, PhD
Hospital Universitari i Politecnic La Fe
University of Valencia
Valencia, Spain

THE LIPEDEMA PROJECT AT THE FRIEDMAN CENTER FOR LYMPHEDEMA RESEARCH AND TREATMENT AT THE CENTER FOR ADVANCED MEDICINE AT NORTHWELL HEALTH

The mission of The Lipedema Project is to raise awareness, educate, and support research in all aspects of the fat disorder lipedema, and other related lymphatic disorders, for patients who have the disorder and for healthcare providers.

LYMPHATIC EDUCATION & RESEARCH NETWORK (LE&RN)

Mission: The Lymphatic Education & Research Network (LE&RN) is an internationally recognized non-profit organization founded in 1998 to fight lymphatic diseases and lymphedema through education, research and advocacy. With chapters throughout the world, LE&RN seeks to accelerate the prevention, treatment and cure of these diseases while bringing patients and medical professionals together to address the unmet needs surrounding lymphatic diseases, which include lymphedema and lipedema.

ABOUT THIS MONOGRAPH

There has been very little in the way of lipedema research since Dr. Edgar V. Allen and Dr. Edgar A. Hines first named lipedema at the Mayo Clinic in 1940 at Staff Proceedings.[1] The lack of research and understanding about this fat disorder has contributed to its common misdiagnosis. Interest in lipedema and lymphatic disorders has increased in recent years, and study in these areas is beginning to grow. The Lipedema Think Tank, which took place April 2015 at the *1st International Symposium on Lipedema – Setting the Research Agenda for Lipedema: Steps Towards a Cure* in New York City under the direction of Mark L. Smith, MD, FACS, was critical in establishing a network of professionals who are interested and engaged in this work.

The mission of the Lipedema Project is to raise awareness, educate, and support research in all aspects of the fat disorder lipedema, and other related lymphatic disorders, for patients who have the disorder and for healthcare providers.

The idea of the Think Tank for lipedema was first conceived in conversations between Prof. Etelka Földi, MD, Mark L. Smith, MD, FACS, and Catherine Seo, PhD in Hinterzarten, Germany. Prof. Földi, the world's most prominent expert in lymphology, suggested we...

"invite the experts across many disciplines to come together and discuss the pieces of the very complex puzzle that is lipedema."

The Lipedema Think Tank was a unique opportunity for clinicians, surgeons, researchers, scientists, therapists, patients and advocates across many disciplines to come together to share knowledge, brainstorm, and develop a research agenda to advance our understanding of lipedema. Our goal was met. We established a network of research-oriented individuals who could collaborate to achieve progress in understanding lipedema.

This monograph grew out of this collaboration. We formally began writing this monograph in January 2016. The process has included online and face-to-face working sessions across the US and Europe until its publication September 2017. *Lipedema - The Disease They Call FAT: An Overview for Clinicians* offers a thoughtful and concise overview of this little-known and generally misdiagnosed fat disorder for clinicians, healthcare professionals, and for patients. Our hope is that it furthers the diagnosis, treatment, and management of lipedema.

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Acknowledgements

The authors would like to thank the lipedema patients, their families, friends and supporters worldwide who have courageously approached the challenges of lipedema, lymphedema, and related co-morbidities with determination in working towards diagnosis, treatment, understanding and ultimately healing. We also extend gratitude to the many health care providers, clinicians, surgeons, researchers, scientists, therapists, and advocates who have generously and compassionately worked to bring treatment options to those afflicted with lipedema and related lymphatic and fat disorders. They continue to support awareness and education in the medical community.

We appreciate the work and contributions of those who were instrumental in the editing and design process in creating this monograph. Special thanks to our editor, Amy Hodson Thompson, PhD, for her attention to detail and generous support for this publication; and to M. Page Jones for elegant, clean and Zen-like designs which framed our information in a professional and engaging manner.

FACULTY: LIPEDEMA THINK TANK 2015

We gratefully acknowledge the faculty and participants of the Lipedema Think Tank 2015 at the *1st International Symposium on Lipedema – Setting the Research Agenda for Lipedema: Steps Towards a Cure* for their generous contributions to this field and collaboration in furthering awareness and research about lipedema.

For a complete listing of our faculty please see the back section of this monograph.

Foreword

The body of medical knowledge, hence, its curriculum for medical and post-graduate education, experiences a constant and dynamic evolution. Nevertheless, these changes often occur at a frustratingly slow pace. Thus, it is a great pleasure to witness the birth of this monograph, designed to acquaint the practicing clinician with the extant body of knowledge regarding this important, yet poorly understood, aspect of human disease.

Lipedema first appeared in the medical literature in 1940.[1] As a disease, it was more fully described as a clinical entity in 1951;[2] its clinical descriptors have changed little since that early recognition and classification. This somewhat mysterious entity continues to reflect the interplay of adipose pathology, microlymphatic dysfunction, and inflammation, colored by a perplexing array of genetic and hormonal modulators.[3]

Despite its intriguing biological and pathological attributes, lipedema has been subjected to relative neglect over the many decades that have followed the original publication. Perhaps this reflects under-recognition, but the failure to move forward with lipedema must certainly reflect the absence of either suitable animal models or appropriate substrates for *in vitro* examination. The lack of identified biomarkers for this disease hampers the ability to correctly segregate affected family cohorts for genetic study.

Nevertheless, progress has occurred. Decades of experience with this patient population has sharpened our diagnostic acumen. Surgical interventions have matured, permitting therapeutic decisions that can improve function, appearance, and quality-of-life.

Prevalence estimates, while imprecise, suggest that a sizeable fraction of the adult Western population has lipedema. While we await the exciting investigative insights that will accrue in the coming decade, it behooves practitioners of medicine to recognize this common and important medical condition, so that they are prepared to meet the current needs of their patients. These individuals deserve precise diagnostic evaluations and clear definition from the physician of what can and cannot be achieved in the present moment.

It is therefore with pride and appreciation that I introduce...

LIPEDEMA - THE DISEASE THEY CALL FAT: AN OVERVIEW FOR CLINICIANS.

Stanley G. Rockson, MD
Allan and Tina Neill Professor of Lymphatic Research and Medicine
Stanford University School of Medicine

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A PCP AND PATIENT–ADVOCATE'S PERSPECTIVES

She presents a striking morphology in fat distribution - a sparse increase in upper body fat, including her waist, and a prolific disproportional fat mass in her lower body including buttocks, hips, and legs which suddenly stops at her ankles. Her granular, bean bag-like fat is painful on palpation and exertion with easy bruisability. Her diet is as disciplined as her swimming and walking is regular.

Is all obesity the same? Does this patient represent a distinct entity? We currently assume that what we say about one obese patient applies to the next. This patient, as well as the array of current obesity research, challenges our assumption of sameness and pushes us to consider the existence of different disorders that influence our work as frontline PCPs treating obesity. This monograph introduces us to the fat disorder called lipedema.

Keeping in mind the idea of distinct obesity types guards us from misunderstanding our patient's needs and creating a feeling represented in this recent email from a patient who wrote to The Lipedema Project seeking help and guidance.

"Dear Catherine, I just went to a new primary care doctor so that she can treat me medically and refer me to a specialist for my lipedema. I left there in tears. She refused to treat me because she's never heard of lipedema. She kept telling me its "lymphedema." I kept telling her it's not and tried showing her pictures and information about lipedema. She said she's the doctor and never heard of it. She looked at me like I was crazy. She was outright unprofessional.

Is there any way of finding a primary care doctor that knows about lipedema?"

There are a few other themes in the many stories of women with lipedema who contact us.

- "My doctor says it's just fat and to lose weight and exercise more."
- "My doctor doesn't believe me and says that I'm making excuses."
- "My doctor says that it's a crazy made-up 'Internet disease'."
- "My doctor won't listen to me."
- And most commonly, "My doctor says that it's my fault."

Unfortunately these narratives have been echoed hundreds of thousands of times by countless women worldwide who futilely seek treatment and help from their clinicians.

In addition to making our practices efficient and effective as well as kind and respectful, it requires that we identify, when we can, this particular type among other fat disorders. Doing so allows that appropriate interventions can be employed.

The authors of this monograph are leading the charge to allow this to happen throughout healthcare. They are from several disciplines encompassing various aspects of care. These clinicians, surgeons, researchers and advocates are laying the groundwork for a humane and skillful response to lipedema.

Matthew A. Carmody, MD
Assistant Professor, Harvard Medical School
Department of Medicine, Mount Auburn Hospital
Boston, Massachusetts, USA

Catherine A. Seo, PhD
Co-Director, The Lipedema Project
Patient Advocate
Boston, Massachusetts, USA

LIPEDEMA
THE DISEASE THEY CALL FAT:
An Overview for Clinicians

I. INTRODUCTION

Confucius once said, *"True wisdom is knowing what you don't know."* For clinicians, a fundamental challenge in clinical diagnosis is recognizing conditions that do not fit into familiar categories. Lipedema is one such condition. First identified in 1940 by Drs. Edgar Allen and Edgar Hines at the Mayo Clinic, lipedema is characterized by abnormal fat deposition in the buttocks and bilateral legs and can be accompanied by orthostatic edema.[1] The pathophysiology of lipedema is poorly understood and since it is not routinely included in medical school curricula, it is frequently misdiagnosed as more familiar conditions, such as obesity or lymphedema.[4, 5] Although first described in the U.S., scientific acknowledgment of lipedema as an independent entity has emerged primarily in Europe, largely due to the work of Professor Michael Földi, MD and Professor Etelka Földi, MD in Germany,[6] and has only recently gained more recognition in the United States.[7] Public awareness of lipedema has increased in recent years in part due to the proliferation of online patient support groups and media awareness about the condition.[8] This monograph is meant as a primer for clinicians and is designed to acquaint them with lipedema, facilitate diagnosis, and provide an overview of current treatments.

II. EPIDEMIOLOGY & CLINICAL FEATURES

The diagnosis of lipedema is made clinically and is typically defined by the disproportionate and symmetrical accumulation of fat in the lower extremities accompanied by complaints of orthostatic edema.[4] The feet are always spared from this enlargement, except in the advanced stage of lipo-lymphedema, where foot swelling occurs secondary to lymphatic insufficiency.[9, 10] The "spared feet" observation is an important sign in distinguishing lipedema from simple obesity. Usually, the upper body is spared until later stages of the disease, although atypical types of lipedema exist that vary from the prototypical lower extremity fat accumulation.[11, 12]

Note: *Lipedema* is the English and *lipoedema* is the European spelling and used interchangeably.

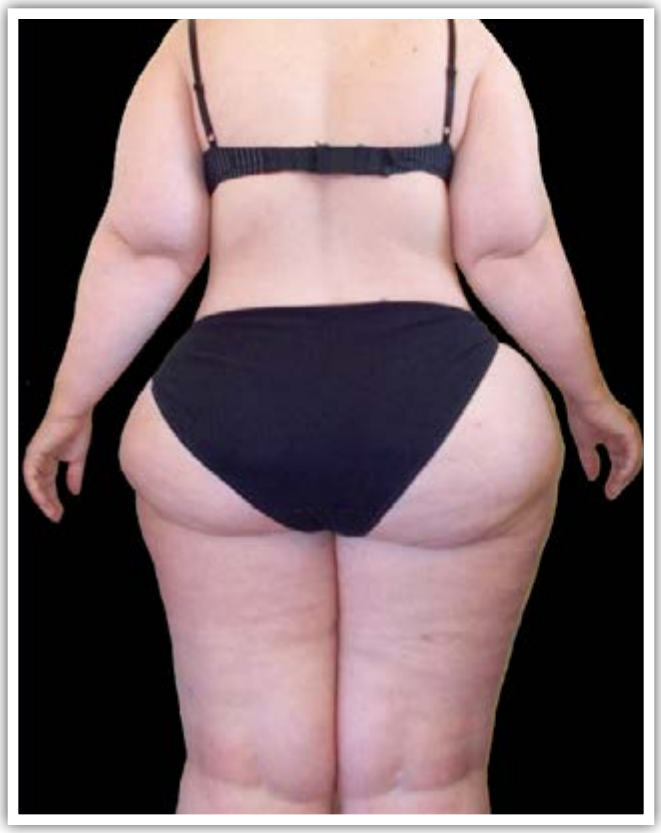


Figure 1: Lipedema Fat Distribution-Disproportional Waist to Hip Ratio (WHR)

LIPEDEMA PRESENTS WITH DISPROPORTIONATE FAT DISTRIBUTION VISIBLE IN WAIST TO HIP RATIO (WHR). ATYPICAL FAT DISTRIBUTION ALSO EXISTS.

There have been cases of upper extremity lipedema reported.[13, 14] In these cases, fat accumulates in the forearms and upper arms, with sparing of the hands, mirroring the appearance of the fat distribution in the legs.[11, 12]

Figure 2: Lipedema Upper Extremity Fat Distribution

FEATURES OF LIPEDEMA INCLUDE THIN HANDS WITH A CUFF AT WRISTS AND INCREASED FAT IN BOTH FOREARMS AND UPPER ARMS.

Areas affected by lipedema often display easy bruising, pain, and tenderness accompanied by complaints of systemic fatigue and loss of physical condition and muscle strength. The onset of symptoms frequently begins during puberty or young adulthood, although some patients may not experience them until later in life after the condition progresses.[4] Progression can occur at times of critical hormonal disturbance such as pregnancy and/or menopause.[6]

Interestingly, as many as 50% of patients with lipedema are also either overweight or obese. This complicates the diagnosis, but doesn't negate the need for diagnosis, as there are important distinctions between the care of patients with general obesity and lipedema.

Lipedema affects women almost exclusively, although there have been several reports of men with the disorder.[2, 4, 15] Conservative estimations of the prevalence of lipedema range from 0.06% to 10.00%.[4] No racial or ethnic group correlations are currently known. Several of the estimates of lipedema prevalence are based on lymphedema clinic patient populations, which contain a subset of misdiagnosed lipedema patients. For instance, Földi & Földi[6] estimated that up to 11% of the female population is affected when they extrapolated their clinic experience to the general population. In another study, Fife et al. found that 10–20% of patients referred to lymphedema clinics were subsequently diagnosed with lipedema.[4] Other reports of percentages of lipedema patients among lymphedema clinic patients range from 8% to 18.8%.[10, 13, 16] Many patients recall other affected female family members, and incidences of familial patterns range from 16-45% in the literature.[2, 4, 17, 18]

Interestingly, as many as 50% of patients with lipedema are also either overweight or obese. This complicates the diagnosis but doesn't negate the need for diagnosis, as there are important distinctions between the care of patients with general obesity and lipedema. It can be difficult to distinguish between lipedema and other physiologic body shapes. The disproportionate fat distribution typical of lipedema can easily be misidentified as disproportionate gynoid or pear-shaped obesity.[19] Obesity is defined medically as a Body Mass Index (BMI) of greater than 30 kg/m^2, therefore many patients with lipedema are considered obese. However, this narrow definition of obesity does not address the ratio of fat to lean body mass or the distribution of fat on the body.[4, 11]

In contrast to generalized obesity, lipedema fat is minimally affected by diet and exercise.[12] In patients with lipedema, treatment aimed at weight reduction can affect the volume and weight of the body but the lipedema disproportion and symptoms typically persist. Because of this important difference in the two conditions, medical care and interventions specific to lipedema are very important to the overall management of the condition, and to prevent further progression of the disease.

A key indicator of lipedema is the classically described "stove-pipe or tree-trunk legs" which increase as the condition progresses. The subcutaneous fat deposits end just above the malleoli, or anklebones, with excess fat deposition in a "pantaloons distribution." The feet being spared causes an abrupt change noticeable at the level of the ankle between the abnormally enlarged legs and the normal-appearing feet. This characteristic is known as the "fat-pad" sign,[4] the "inverse shouldering" or "bracelet effect,"[19] but most commonly is called the "cuff sign."[14] In some cases, this cuffing can be duplicated in the arms, with wrist "cuffs" mirroring the appearance of the fat-cuffs in the ankle region.[11, 12]

ANKLE CUFF ACCOMPANYING LIPEDEMA FAT DISTRIBUTION

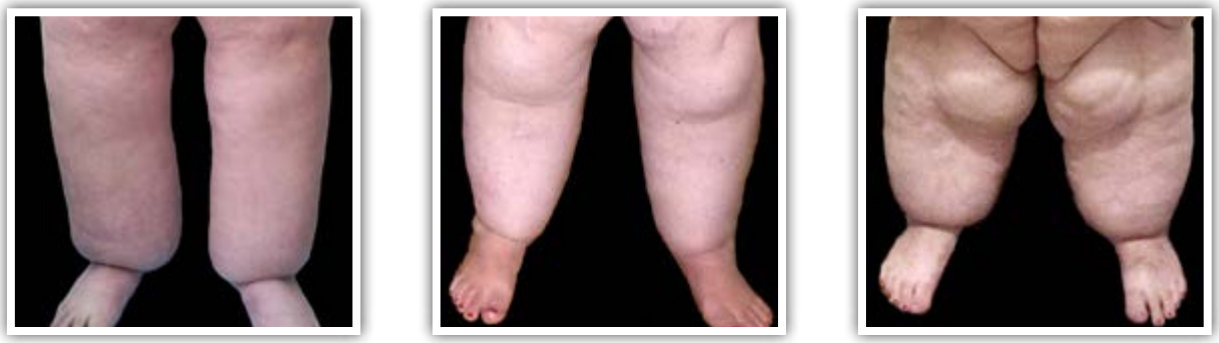


Figure 3: Ankle Cuff Signs of Lipedema

CUFF SIGN WITH ADIPOSE FOLDS CAN BE PRESENT IN DIFFERING STAGES OF LIPEDEMA. WHILE THIS IS A COMMON SIGN, IT IS NOT PRESENT IN ALL TYPES OF LIPEDEMA.

A symptom some patients experience is limb swelling that worsens with orthostasis and warm weather.[2] The skin of the affected areas is usually soft and not discolored, and the edema is typically non-pitting or minimally-pitting.[4] Concurrent findings of erythema, ulcerations, hyperpigmentation, cellulitis, or thickened skin only occur when lipedema is accompanied by lymphedema, venous insufficiency, or stasis dermatitis.[11]

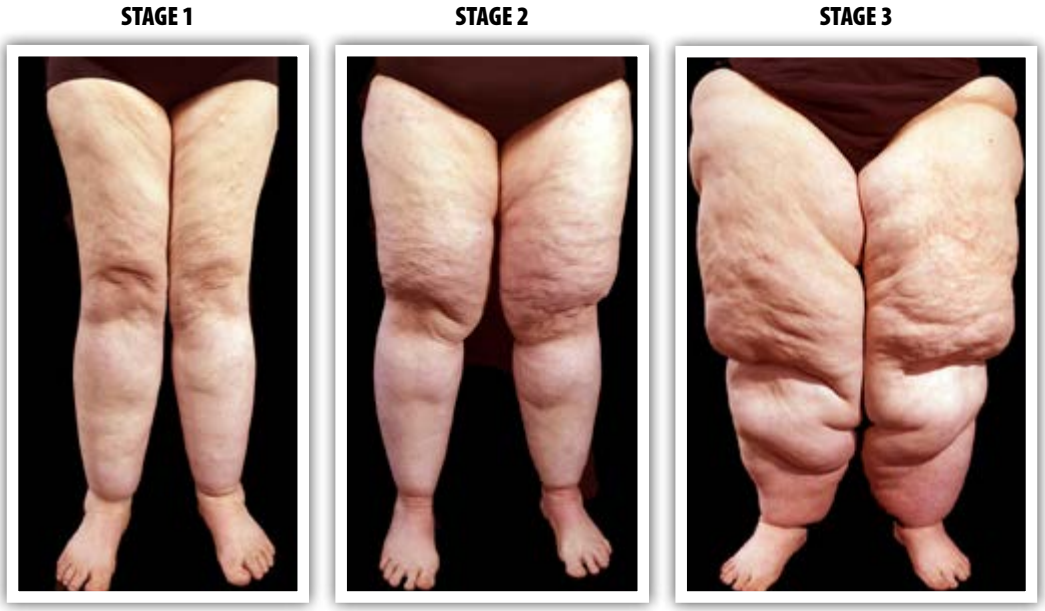
Additional clinical symptoms that are prevalent include pain and easy bruising. The easy bruisability is random with no defined pattern. Lipedema has sometimes been referred to as the "painful fat syndrome"[1, 2] due to the tenderness, pain, and aching that many patients experience upon application of pressure on the affected extremities. The cause and origin of the pain are unknown. Often the more generalized pain has components seen in central sensitization and chronic pain syndrome.[20] As lipedema progresses, the increasing weight of the enlarged lower extremities and fat accumulation or "fat pads" that typically develop at the medial knees, can lead to decreased mobility, gait disturbances and possibly damage to the hips and knees.[12]

Progressive discomfort and disfigurement often lead to physical and psychological suffering. Patients also experience significant frustration from dismissive statements by physicians, such as being told they are "just fat" and to "try harder to diet and exercise." Since lipedema fat is resistant to diet and exercise,[4] in most cases patients have been unsuccessful at losing weight despite repeated attempts that have included diuretics, moderate or extreme weight-loss regimens, regular or rigorous exercise, compression therapies, and even bariatric surgery. Weight loss when it does occur is often predominantly in the upper body, leaving a persistently lipedemic lower body. The lack of improvement after dietary and exercise interventions may also cause a sense of guilt or failure in patients who are led to believe they are not trying hard enough.

Lipedema is sometimes confused with lymphedema. The lymphatic system in patients with early stage lipedema is typically undisturbed, and lymphoscintigraphy will confirm essentially normal lymphatics, and in some cases, actually increased lymph flow.[17, 21-23] Lipedema has been associated with disturbance of micro-lymphatics, although the cause has not been identified. Secondary lymphedema may develop when the lymphatic system can no longer provide adequate drainage. This progression is known as "lipo-lymphedema" and is diagnosed by the presence of dorsal foot swelling and often results in a positive Stemmer's sign (i.e. the inability to pinch the dorsal skin at the base of the second toe due to thickening of the skin and subcutaneous tissues secondary to lymphedema).[11, 12]

FOUR STAGES OF LIPEDEMA

There are four stages of lipedema, although patients do not necessarily progress through all stages.[4, 24]



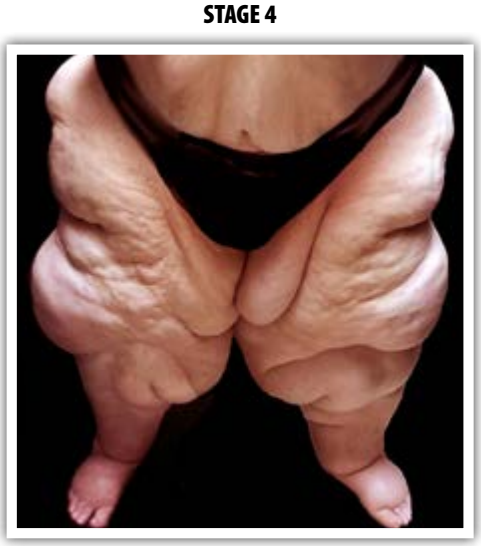


Figure 4: Four Stages of Lipedema

Stages 1 through 4 (left to right). Lipedema is a progressive disorder; when not treated it can progress in severity over the lifetime of a woman.

- Stage I: Normal skin surface with enlarged hypodermis
- Stage II: Uneven skin texture with indentations in the fat, larger mounds of tissue growing as unencapsulated masses.
- Stage III: Thickening and hardening of the subcutis with large nodules and protruding fat pads especially on the thighs and around the knees
- Stage IV: Lipedema with lymphedema (lipo-lymphedema)

FIVE TYPES OF LIPEDEMA

For an animated version of "The Five Types of Lipedema" click HERE.

Table 1: The Five Types of Lipedema

For descriptive purposes only, the disproportionate fat distribution typical with lipedema has been divided into five types, although some patients may fall into more than one type.[24-26]

Type I
Pelvis, buttocks and hips

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

Type III
Buttocks to ankles

Type IV
Arms

Type V
Lower leg

III. ETIOLOGY & PATHOGENESIS

The etiology and pathogenesis of lipedema are not fully understood, but the causes are thought to be multifactorial. Several theories have been offered to explain the development of lipedema. Földi & Földi[6] suggest that microangiopathy, an early histological finding in the affected fatty tissue, causes increased permeability and capillary fragility which leads to leakage of proteins and easy bruising. The fragility of the capillaries is thought to be caused by pathological angiogenesis (abnormal rapid proliferation of blood vessels), which is controlled by several factors including vascular endothelial growth factor (VEGF). Hypoxia (inadequate tissue oxygenation) is also a known inducer of angiogenesis and causes cells to release VEGF, which in turn stimulates the proliferation of new blood vessels to meet tissue demand for oxygen. Siems et al. discovered that lipedema patients had an average VEGF level of 530 pg/ml compared to a normal level of 100-130 pg/ml, suggesting that pathological angiogenesis may play a significant role.[27]

There are significant confusion and under-diagnosis of lipedema due to the lack of availability of a laboratory or genetic diagnosis coupled with the lack of widespread familiarity with the clinical diagnostic criteria for lipedema.

An analysis by Suga et al.[28] found that the size of adipocytes (fat cells) in lipedema tissue were more varied and frequently larger (diameter >150 µm) than that of adipocytes in normal tissue (average diameter of about 100 µm). Through immunohistochemical studies, they observed that necrotic adipocytes in lipedema tissue were surrounded by "crown-like" structures consisting of CD68+ macrophages, which are immune cells which phagocytize, or eat, dead cells. This is also a feature commonly seen in adipose tissue of obese subjects. Immunostaining also showed an increase in cells positive for Ki67, which is associated with cell proliferation, and CD34, a marker of adipose stem/progenitor cells. These two findings suggest that the rapid proliferation of adipocytes results in local hypoxia and adipocyte necrosis, or cell death, and recruitment of macrophages.[4, 11, 28]

The typical onset of lipedema at puberty or other periods of hormonal variation such as pregnancy or menopause suggests a hormonal effect,[29] probably due to estrogen, on the development of lipedema. Rare cases of lipedema affecting males provide further evidence supporting hormones as an important factor, as lipedema tends to occur in men with liver cirrhosis, hypogonadism, depleted testosterone or in men receiving hormonal therapy for prostate cancer. [6, 19, 29-31]

According to Child et al., "frequent observations of mother to daughter inheritance led to the hypothesis that lipedema is a genetic disorder,[19] and in 2011, Online Mendelian Inheritance in Man (OMIM) designated lipedema as a medical condition [OMIM: 614103]. Given the likely hereditary association in lipedema, a genetic connection has also been proposed. Although no study to date has identified a specific gene responsible for the development of lipedema, Bano et al. recently discovered a Pit-1 mutation present in a family with lipedema.[32] Additionally, Child et al. analyzed a series of pedigrees and proposed that lipedema is either an X-linked dominant or autosomal dominant inheritance with sex limitation. They also hypothesized that this gene mutation may lead to failure of male births given the heavy female predominance of the condition.[19]

IV. DIAGNOSIS

There are significant confusion and under-diagnosis of lipedema due to the lack of availability of a laboratory or genetic diagnosis coupled with the lack of widespread familiarity with the clinical diagnostic criteria for lipedema. The potential

for lipedema to masquerade as a number of other conditions (lymphedema, physiologic disproportionate body shape, lipohypertrophy, or gynoid or pear-shaped obesity),[19] can contribute to this confusion and lead to misdiagnosis and under diagnosis. Misdiagnosis in patients with lipedema is concerning, as it can delay appropriate management for the condition and allow the progression of the disease rather than slowing the disease progression via application of appropriate treatment.

CLINICAL DIAGNOSIS OF LIPEDEMA

As mentioned above, lipedema is essentially a clinical diagnosis that relies on the patient's current status and reported history. Key clinical features of lipedema include:

- A disproportionate and symmetrical (bilateral) progressive fatty enlargement of the legs that may include the hips and buttocks, usually with sparing of the feet resulting in a "pantaloon" appearance and known as the "cuff sign" or "fat pad sign."[4, 14, 33, 34]
- The "Stemmer's sign" is negative in pure lipedema patients but may be positive in patients who have a combination of lipedema and lymphedema, referred to as lipo-lymphedema.[11, 12]
- The skin of affected areas usually remains soft, with minimal or no pitting, and normal color and texture.[4, 11, 34]
- Upon palpation, the enlarged subcutis can be either granular to nodular, with descriptions varying from such as "sand grain" texture[35] to "Styrofoam balls,"[4] "round peas in a plastic bag",[25] or a "beanie baby".[25]
- Pain upon pressure and easy bruising, which can appear as petechiae (red, brown or purple spots under the skin surface caused by intradermal hemorrhaging from leaky capillaries) or hematomas.[1, 4, 33]
- Stage 1, stage 2, stage 3, and stage 4 progression as described above, documented via patient history.
- A history of dieting and exercising with no apparent effect on the areas of lipedema fat or worsening of the disproportion.[14]

Lipedema is often misdiagnosed as simple obesity. Additionally, overweightness or obesity can be an accompanying comorbidity in 50% of cases, further complicating the diagnostic process.

DIFFERENTIATION: LIPEDEMA VS. OBESITY

Lipedema is often misdiagnosed as simple obesity.[24, 25] Additionally, overweight or obesity can be an accompanying comorbidity in 50% of cases, further complicating the diagnostic process.[4, 11] Obesity is defined as excess fat mass with an increased body mass index (BMI) of ≥30 kg/m2 or more and increases risks for multiple metabolic diseases, such as type 2 diabetes, cardiovascular diseases and several types of cancer.[36]

FAT DISTRIBUTION AND THE DIFFERENCE BETWEEN ANDROID AND GYNOID OBESITY

The adipose organ includes numerous discrete anatomical depots[37] and the size of fat stores is highly variable, ranging from 5-60 % of total body weight. Women generally have higher adiposity than men. Subcutaneous adipose tissue stores more than 80% of the total fat in the body, and of these subcutaneous depots, the most common and frequently studied are the abdominal, gluteal and femoral depots. The second largest fat depot lies intraperitoneally and retroperitoneally and is called visceral adipose tissue. It comprises 10-20% of total body fat in men and 5-10% in women.[37] In addition, there are other smaller adipose depots, such as epicardial and intermuscular depots. The mechanisms behind adipose tissue distribution are poorly understood,[37] but its distribution seems to be affected by a number of factors. These factors include: sex; race; the sex steroid hormones (estrogen, androgen, testosterone); and age.[38] The fat distribution in obesity typically falls into one of two categories, android and gynoid.

Android fat distribution – also called "apple-shaped" - is characterized by a central fat distribution pattern with an increase of volume mainly in the abdominal area (thus both visceral adipose tissue and subcutaneous tissue). This type of distribution carries an increased health risk compared to the peripheral gynoid type, which seems to be protective.

Gynoid fat distribution – also called "pear-shaped" - leads to a different body appearance with a peripheral increase of volume mainly in the hips, thighs, and buttocks (gluteofemoral region).

Both types can be distinguished by their body appearance and can be determined by using a measuring tape. The circumferences, which are measured just above the navel and above the hips in an upright standing position, are used to calculate the Waist-to-Hip-Ratio (WHR). In obese males the WHR is >1: in females a ratio > 0.85 characterizes obesity. Another important ratio for the determination of obesity is the waist-to-height-ratio (WHtR). A person's WHtR is defined as their waist circumference divided by their height. Both the WHR and the WHtR are better predictors of the risk of heart attack, stroke or death due to obesity than BMI alone. Lipedema patients, when obese, typically have gynoid distribution with additional fat in the extremities.

LIPEDEMA VS. OBESITY

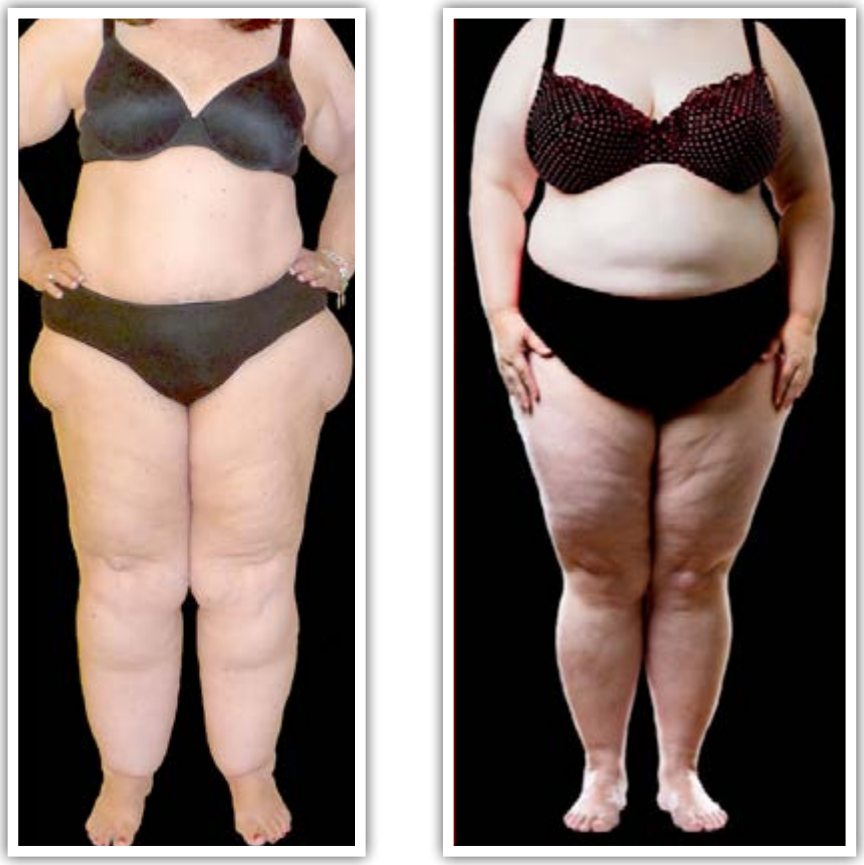


Figure 5: Lipedema (left) vs. Obesity (right).

LIPEDEMA (LEFT) IS OFTEN MISDIAGNOSED AS OBESITY. ON CLOSER EXAMINATION AND HISTORY, LIPEDEMA'S DISTINCTIVE SIGNS AND SYMPTOMS CAN BE DIFFERENTIATED FROM GENERALIZED OBESITY (RIGHT).

The morphology of gynoid obesity (pear-shaped increase of volume) in particular and lipedema (slim upper body, big lower body with an increase of volume in the lower extremities) may look similar. In this case, we need the typical symptoms of orthostatic edema, spontaneous pain, tenderness on palpation and easy bruising to differentiate these two entities. But it is important to know that obesity can aggravate the symptoms of lipedema. Additionally, with higher grades of obesity, and especially in women during or after menopause, we can often find a combination of both types of fat distribution - both central and peripheral. These are the patients who have been typically misdiagnosed for years as having obesity only.

So it is very important to check for the typical clinical symptoms of lipedema and to ask for the historical timing of symptom development and fat distribution of the legs (e.g. after puberty, pregnancy or menopause). Strict differentiation between gynoid obesity and lipedema is often very difficult because features of each can be present in a patient.

DIFFERENTIATION: LIPEDEMA VS. LYMPHEDEMA

Lipedema primarily seems to be a disease of the subcutaneous fatty tissue. Lymphedema, on the other hand, is primarily a disease of impaired lymphatic transport resulting from injury, infection, obstruction or congenital defects of the lymphatic system. Lymphedema leads to stasis of protein rich interstitial fluid resulting in chronic inflammation, adipose deposition, and tissue fibrosis.[39]
There are a number of key diagnostic differences between lipedema and lymphedema. Lipedema always affects both sides of the body, while lymphedema in most cases is asymmetric. Lipedema of the legs does not affect the feet, there is a negative Stemmer's sign (in early stages), and lipedema of the arms does not affect the hands. In lipedema, there is soft pliable skin, although later some elasticity may be lost.

In contrast, in Stage I lymphedema, or spontaneously reversible lymphedema, patients have a pitting edema. Stage II lymphedema, or persistent lymphedema, is described as swelling of the limb that does not go away with elevation. The skin is harder and may be thickened due to the edema-induced fibrosis and adipose deposition. This results in a positive Stemmer's sign, thickening of skin folds, a convex dorsum of the foot and an increased amount of fat and connective tissue in the peri-malleolar region. Stage III, the most advanced stage of lymphedema, is characterized by significant non-pitting swelling, fibro-adipose deposition, increased skin thickness, and hyperkeratosis.[40]

Strict differentiation between gynoid obesity and lipedema is often very difficult, because features of each can be present in a patient.

Also, while the tissue in lipedema tends to be painful upon application of pressure, in lymphedema it is not. Bruising after minimal trauma, a common phenomenon in lipedema does not often occur in lymphedema.

LIPEDEMA VS. LYMPHEDEMA

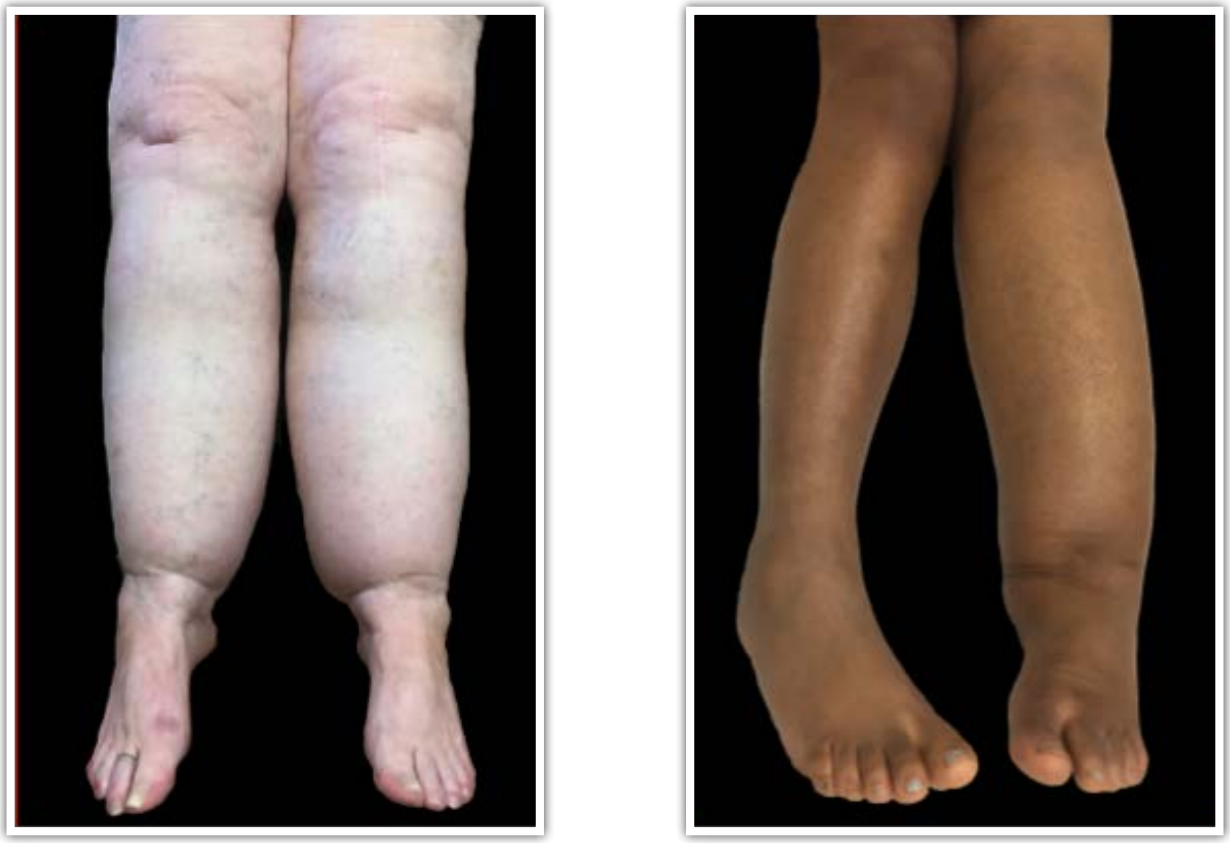


Figure 6: Lipedema vs. Lymphedema

LIPEDEMA (LEFT) IS BILATERAL AND THE FEET ARE SPARED. LYMPHEDEMA (RIGHT) GENERALLY AFFECTS ONE LIMB AND INCLUDES PITTING EDEMA OF THE FOOT.

Some factors, however, can make the distinction between lipedema and lymphedema less clear, particular in patients who are also obese, and in those with the more advanced stages of lipedema. Lymphatic overload (high output failure) can occur secondary to lipedema. In morbid obesity, dependent edema may also be seen. In addition, obese patients are prone to venous insufficiency, which may also contribute to leg edema.[41, 42]

Therefore, obesity may worsen both lipedema and chronic edema. This form of chronic edema is due to the long-lasting overload of the lymphatics. The increase of fat tissue, as it appears in obesity but also in lipedema, has been shown to decrease lymphatic function by decreased pump function and increased interstitial filtration; though lymphatic impairment in obesity seems to be reversible.[43] Furthermore, the lymphatic fluid has been shown to increase adipocyte proliferation and differentiation, revealing the two-way relationship between obesity and lymphatic function and the importance of treating both the edema and concomitant obesity.[44]

DIFFERENTIATION: LIPEDEMA VS. DERCUM DISEASE

Dercum disease (adiposis dolorosa) is characterized by multiple, painful lipomas (adipose tissue tumors) that typically can be distributed throughout the trunk and extremities. Nodules in Dercum disease are often tender to pressure, while in lipedema, tenderness is often more diffuse.[45] Since lipedema and Dercum disease can present with a similar complaint of tender fatty tissue, clinical history and physical examination is essential in order to obtain a correct diagnosis. The characteristic symmetric enlargement and fatty hypertrophy extending from the hips to the ankles seen in lipedema are not specifically associated with Dercum disease.[45, 46]

Both conditions are characterized by a similar distribution of excess, painful nodular subcutaneous adipose tissue (SAT). However, SAT in women with Dercum disease causes more systemic complaints when compared to patients with lipedema, including higher levels of pain, specific abdominal pain, shortness of breath, fibromyalgia, and migraines.[47] Also, patients with lipedema have nodular subcutaneous adipose tissue more prevalent in the lower body (gynoid distribution) than patients with Dercum disease.

Table 2. Lipedema vs. Dercum Disease[47]

DERCUM DISEASE	LIPEDEMA
Greater pain: average >/= 6	Less pain: average </= 6
Fibromyalgia	Easy bruising
Lipomas	Nodule fat on hands/feet
Migraine Headaches	Fibrotic tissue areas
Greater likelihood to have diabetes	Gynoid distribution

The differentiation between Dercum disease and lipedema includes considering the location of fat and presence of lipomas/fatty tumors, the higher average daily pain in Dercum disease patients, and the presence of other painful comorbidities.[47]

DIAGNOSTIC SUMMARY OF LIPEDEMA

Wold et al. studied 119 cases in 1951 and outlined the diagnostic criteria of lipedema:[2, 24]

1. Almost exclusive occurrence in women developing by the third decade of life;
2. Bilateral and symmetrical fat deposits downward from the hips with usual sparing of the feet;
3. Non-pitting or minimally-pitting edema;
4. Pain and tenderness of affected subcutaneous regions;
5. Persistent enlargement despite elevation of the extremities or weight loss;
6. Increased vascular fragility; easy bruising.

Additionally, a characteristic texture of the subcutis has been reported in the literature:

7. Upon palpation, the enlarged subcutis can be either granular to palpation, with a "sand grain" texture[35] or contain nodules that have been described as "Styrofoam balls"[4] or round peas in a plastic bag,"[25] or a "beanie baby".[25]

Table 3. Features of Lipedema vs. Chronic Lymphedema vs. Obesity

	LIPEDEMA	LYMPHEDEMA	OBESITY
Gender	Almost exclusively in females; seen only in males with feminizing endocrine status	Female and Male	Female and Male
Location	Hips, buttocks and legs, can affect upper extremities	Upper or lower extremities; can occur anywhere in the body	Whole body
Feet involvement	No (except in lipo-lymphedema)	Yes	Not usually, though sometimes
Side	Bilateral	Usually unilateral, if bilateral, asymmetrical	Bilateral
Pain	Yes	No, not usually	No
Skin changes	No	Yes, in later stages	No
Stemmer's sign	Negative	Positive	Negative
Edema	Non-pitting or mildly pitting	Pitting in Stage I and II, non-pitting in Stage III	Usually not present

Table 3 shows the typical characteristics and differences of lipedema, lymphedema, and obesity. While there are currently no specific diagnostic tests for lipedema, there are some tests and radiological exams that may help differentiate lipedema from other pathological conditions. It is also imperative that other more common etiologies, systemic diseases, and localized causes are first ruled out with a comprehensive history, physical exam, blood tests, and necessary studies. Interstitial fluid volume is affected not only by lymphatic transport but also by fluid production, which can be affected by venous pressure, oncotic pressure and capillary leakiness. Congestive heart failure, medications, myxedema, and renal or hepatic insufficiency are other medical conditions that can cause lower extremity edema and have to be considered in the differential diagnosis.

Imaging tests can be performed that may assist in differentiating lipedema from other conditions. Naouri et al. used high-resolution cutaneous ultrasound to distinguish lipedema from lymphedema. They found that dermal thickness and echogenicity in lipedema patients were normal with an increased subcutaneous layer and no true edema. In contrast, there was increased dermal thickness and decreased echogenicity with dermal edema in patients with lymphedema.[48]

A duplex ultrasound examination can also measure venous flow and will show if there is venous insufficiency or obstruction that may be contributing to symptoms or causing swelling. However, edema seen on ultrasound may or may not be related to lymphatic insufficiency. To visualize lymphatic flow and areas of lymphatic stasis or reflux and assess for lymphatic insufficiency, lymphoscintigraphy or another form of lymphangiography, such as near-infrared fluorescent lymphangiography with indocyanine green is helpful.[49]

LYMPHANGIOGRAPHY IMAGES OF LYMPHATIC FLOW OF THE FOOT

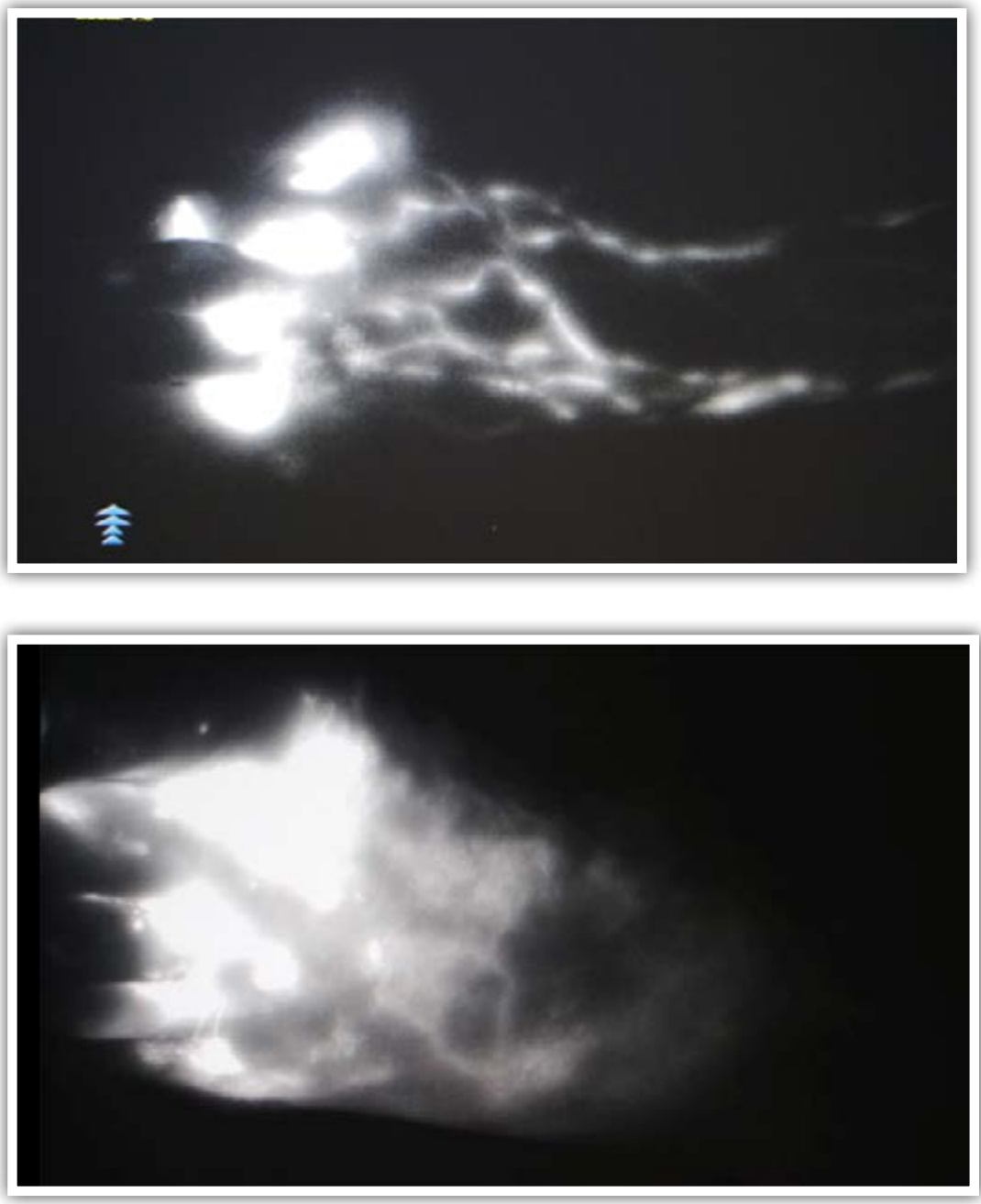


Figure 7: Lymphangiography with Indocyanine Green Images of the Foot

DEMONSTRATION OF NORMAL LYMPHATIC DRAINAGE OF PATIENT'S FOOT (TOP). ABNORMAL PATHWAYS (STARDUST PATTERN) OF LYMPHATIC FLOW INDICATES LYMPHATIC OBSTRUCTION AND DIAGNOSIS OF LYMPHEDEMA (BOTTOM).

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are additional noninvasive imaging studies that have been used to evaluate patients with enlarged extremities.

Monnin-Delhom et al.[50] determined that CT was 95% sensitive and 100% specific for the diagnosis of lipedema, 93% sensitive and 100% specific for lymphedema, and 91% sensitive and 99% specific for DVT. On CT imaging, lymphedema patients had thickened skin with subcutaneous edema in a honeycomb pattern, DVT patients had muscle enlargement and subcutaneous edema without the honeycomb appearance associated with lymphedema, and lipedema patients had homogeneous enlargement of the soft tissues but without any skin thickening, subcutaneous edema, or muscle hypertrophy. [50-52]

MRI IMAGES – FAT-FILLED VS. FLUID-FILLED

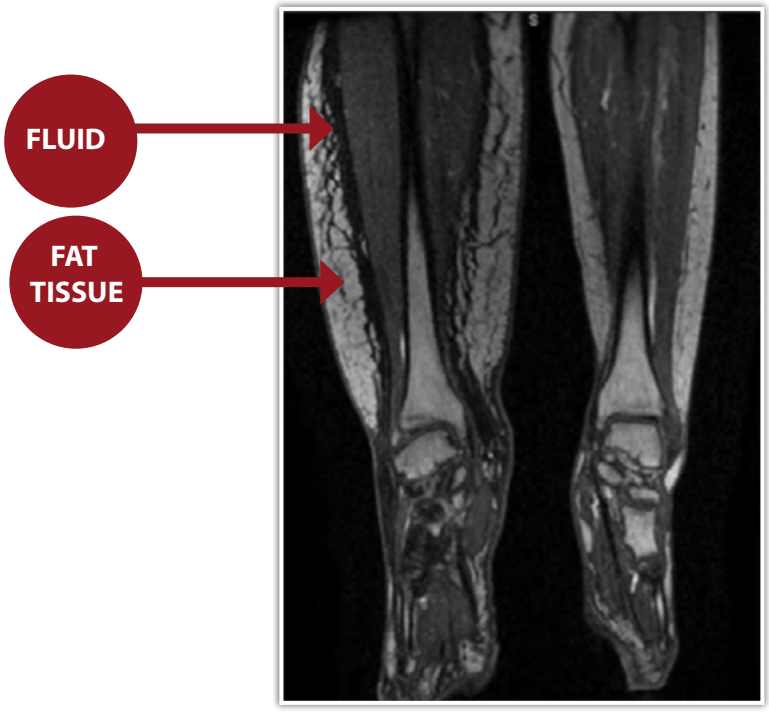


Figure 8: MRI-Differentiation of Fat-filled vs. Fluid-filled Extremities

MRI IMAGING CAN BE USED TO DIFFERENTIATE FAT (WHITE) VS. FLUID (BLACK) CONTENT OF THE EXTREMITY

MRI findings are similar to those of CT. Some centers use MRL, a modified form of an MRI that requires an injection of a contrast agent into the skin of the forefoot in order to evaluate the lymphatic circulation.[30] Using MRL, Lohrmann et al. found that while there was no lymphedema present in pure lipedema patients, some of the patients had enlarged lymphatic vessels up to 2mm in diameter, which was thought to be an indication of a subclinical status of lymphedema.[30]

Lymphoscintigraphy, which is the gold standard for evaluating the lymphatics and diagnosing lymphedema, is a helpful radiological study to exclude lymphatic dysfunction when assessing leg edema or enlargement.[12, 49]

LYMPHOSCINTIGRAPHY CAMERA

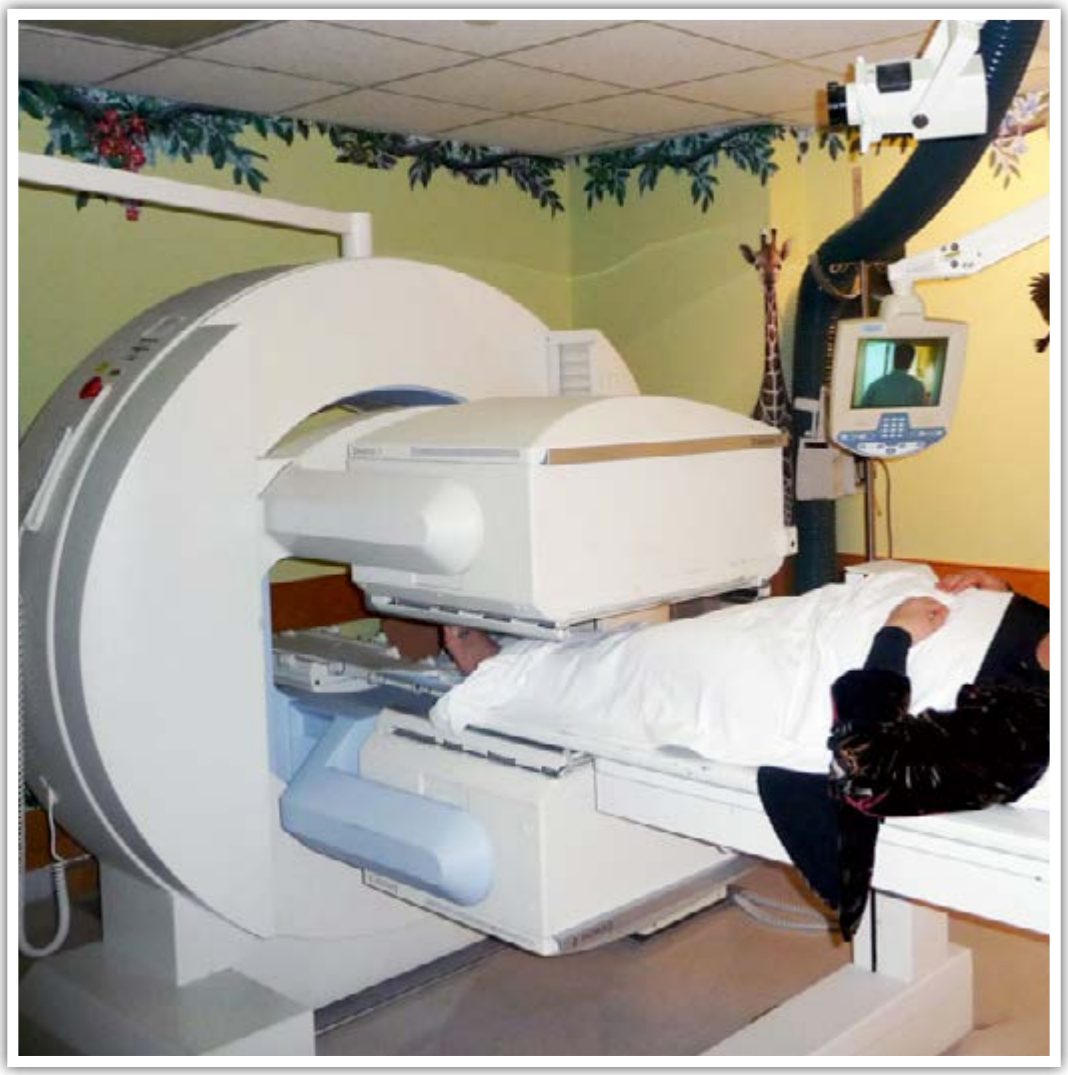


Figure 9: Lymphoscintigraphy Camera

LYMPHOSCINTIGRAPHY CAN BE USED TO MAP THE LYMPHATIC PATHWAYS USING A RADIOACTIVE TRACER (TECHNITIUM 99)

Technitium 99, a medical radioisotope, is injected into web spaces of the hand or foot and is normally taken up by lymphatics. These lymphatics drain into lymph node basins where Technitium 99 is concentrated in the lymph nodes, which appear on the scan as black circles. In patients with abnormal lymphatic function, lymph transport and uptake are diminished or absent. The Tc99 dye either remains in the hand or foot or may be seen refluxing into the tissues of the extremity through incompetent lymphatic valves as seen in Figure 10 on the next page. In lipedema, lymphoscintigraphy will usually show normal lymphatic flow and uptake but may be slower overall compared to that of normal individuals.[17, 21]

LYMPHOSCINTIGRAPHY IMAGE

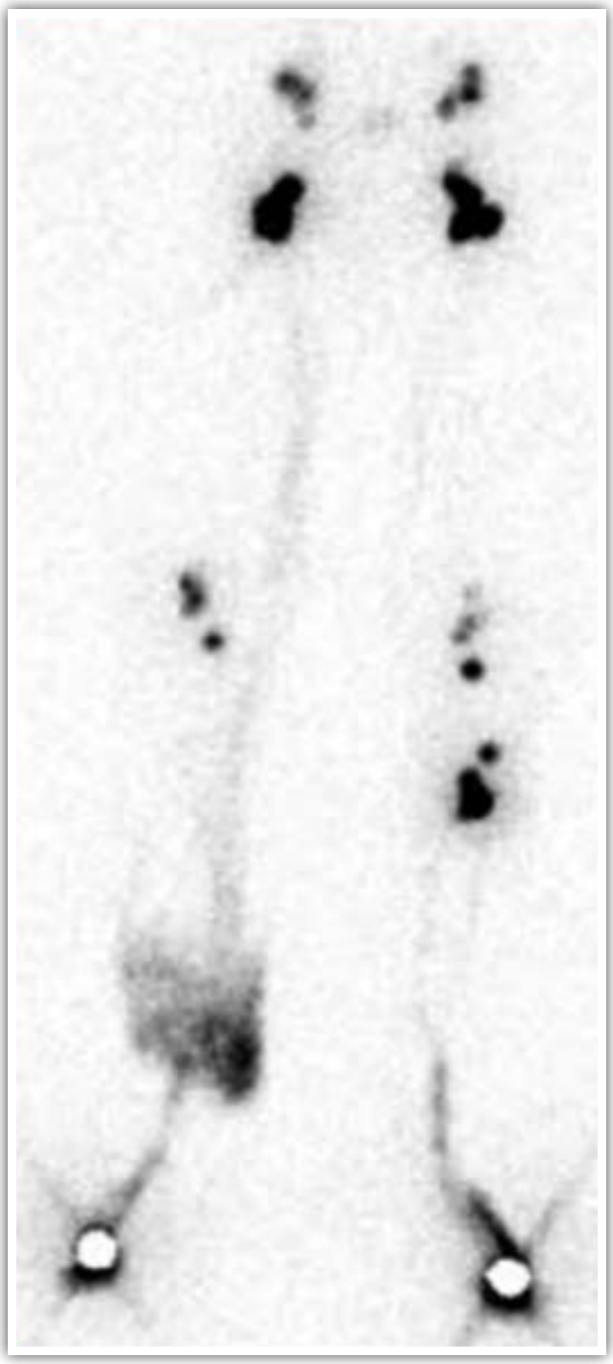


Figure 10: Lymphoscintigraphy Image

IMAGE OF LYMPHATIC PATHWAYS SHOWS THE TRACER TRAVELING FROM FOOT TO LYMPHATIC BASINS PROXIMALLY.

Table 4 summarizes various imaging technologies and their characteristics that can be helpful in differentiating lipedema from lymphedema and other pathologies.

Table 4: Radiological Differentiation of Lipedema from Lymphedema

	LIPEDEMA	LYMPHEDEMA
Duplex ultrasound/ Doppler measuring venous flow/ High-resolution cutaneous ultrasound	Increased subcutaneous layer with normal echogenicity[12]	Increased dermal thickness and subcutaneous layer with decreased echogenicity indicating the presence of fluid[12, 46]
Computed Tomography (CT)	Homogeneous increased subcutaneous layer, but without any skin thickening, subcutaneous edema, or muscle hypertrophy[48]	Increased dermal thickness with subcutaneous edema in a honeycomb pattern
Magnetic Resonance Imaging (MRI)	Significantly increased subcutaneous layer, normal lymphatic vessels, normal venous system, and no excess fluid or edema	Classic honeycomb pattern of the thickened, edematous subcutaneous fat without muscle edema[49]
Lymphangiography (MRL)	Some patients can have normal flow but enlarged lymphatic vessels up to 2mm in diameter[30]	Functional or anatomic obstruction of the lymphatic system is apparent[46]
Lymphoscintigraphy	Typically normal[17]	Abnormal results, indicating a functional or anatomic obstruction of the lymphatic system

CLASSIFYING PATIENTS WITH THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY, AND HEALTH (ICF)

Because the diagnosis of lipedema is very complex and is subjectively made by a healthcare professional, the Netherlands has chosen to use the ICF bio-psycho-social model advocated by the World Health Organization (WHO)[53] for their 2014 guidelines for the diagnosis of lipedema.[54, 55] This model offers a more holistic approach towards the patient and is already used in many other chronic conditions such as rheumatoid arthritis, Parkinson's disease, and multiple sclerosis.

The framework advocates the following measurements in lipedema patients: waist and limb circumference taken as a repeated measure, BMI, scoring of daily activity levels, pain assessment, and quality of life assessment. It also recommends diagnosis and treatment of psychosocial issues and any additional coexisting disorders. By classifying the patients in terms of the ICF model and the use of validated measurements, a dedicated treatment program can be designed.

V. TREATMENT

While there is currently no cure for lipedema, there are treatment options available. Treatment consists of four main therapies that can be combined to address clinical symptoms: 1) complex physical therapy (manual lymphatic drainage, compression therapy, exercise therapy, and skin care), 2) diet and physical activity, 3) surgical treatment of liposuction and plastic surgery, and 4) psychological support as needed.[56] Conservative treatment serves to manage any secondary edema, while medically-accepted surgical treatment options are available to debulk the abnormal adipose tissue.

The goals of treatment are threefold:
1. To relieve or lessen symptoms, improving the quality of life
2. To slow the progression of the disease
3. To prevent complications, including the development of lipo-lymphedema

It is essential that the patient and physician set realistic expectations and simultaneously address the psychological and emotional issues associated with lipedema.[10, 57-60]

CONSERVATIVE TREATMENT: COMPLEX PHYSICAL THERAPY

Complete (Complex or Combined) decongestive therapy (CDT), also known as Decongestive lymphatic therapy (DLT) is useful in managing secondary edema or lipo-lymphedema. However, this type of therapy is generally unhelpful in pure lipedema where the problem is excess fat accumulation rather than excess fluid or lymphatic dysfunction.[4] CDT consists of manual lymphatic drainage (MLD), compression, decongestive exercise and skin care.[55]

LYMPHATIC DRAINAGE: REDUCTION OF FLUID

Manual lymphatic drainage (MLD) is a specialized massage technique that gently directs fluid away from the swollen areas of the body or extremities and decreases lymphostasis. MLD should be accompanied by compressive therapy to maintain the decongestive results. Bandaging or wrapping can be effective in reducing fluid and can be maintained at home with the use of an intermittent pneumatic compression pump (IPC), although some lipedema patients may not be able to tolerate the bandaging or IPC due to pain. IPC, which improves venous flow and reduces the amount of fluid escaping into the tissue, cannot alone reduce the volume of fatty tissue, however, it is helpful in reducing the edema and decreasing the pressure, thereby alleviating some of the pain and improving mobility.[10, 11, 61]

COMPRESSION GARMENTS FOR LIPEDEMA

As fat is not reducible by compression, the garments are meant to avoid the accumulation of fluid in order to prevent swelling and possible progression to lymphatic insufficiency (Figure 11). Patients without signs or symptoms of edema may not experience much benefit from continuous CDT. In the first stages of lipedema, class 2 circular knit garments are enough to help to drain the edema and improve the heaviness symptoms. At this stage, since feet are spared and full pantyhose including the feet are not easy to tolerate, footless leggings can be a good option to be worn during the day, especially during summertime and during exercise (Figure 12a). When the disease advances, a class 2 circular knit full pantyhose is recommended during the whole day (Figure 12b), except in cases with deformity of the limbs that may need a flat-knitted garment. Compression in two pieces, such as a capri garment combined with knee-length compression socks, can improve the doff-and-donning difficulty in older patients that need a flat-knitted garment and have osteoarthritis of the hands (Figure 12c).[10]

COMPRESSION GARMENTS

Figure 11: Conservative Therapy: Compression Garments

COMPRESSION GARMENTS ARE USEFUL IN SUPPORTING THE ADIPOSE TISSUE AS WELL AS MINIMIZING LYMPHATIC FLUID ACCUMULATION IN THE INTERSTITIAL SPACE. PICTURED WITH BARE LEGS (LEFT) AND THEN WITH COMPRESSION GARMENTS (RIGHT).

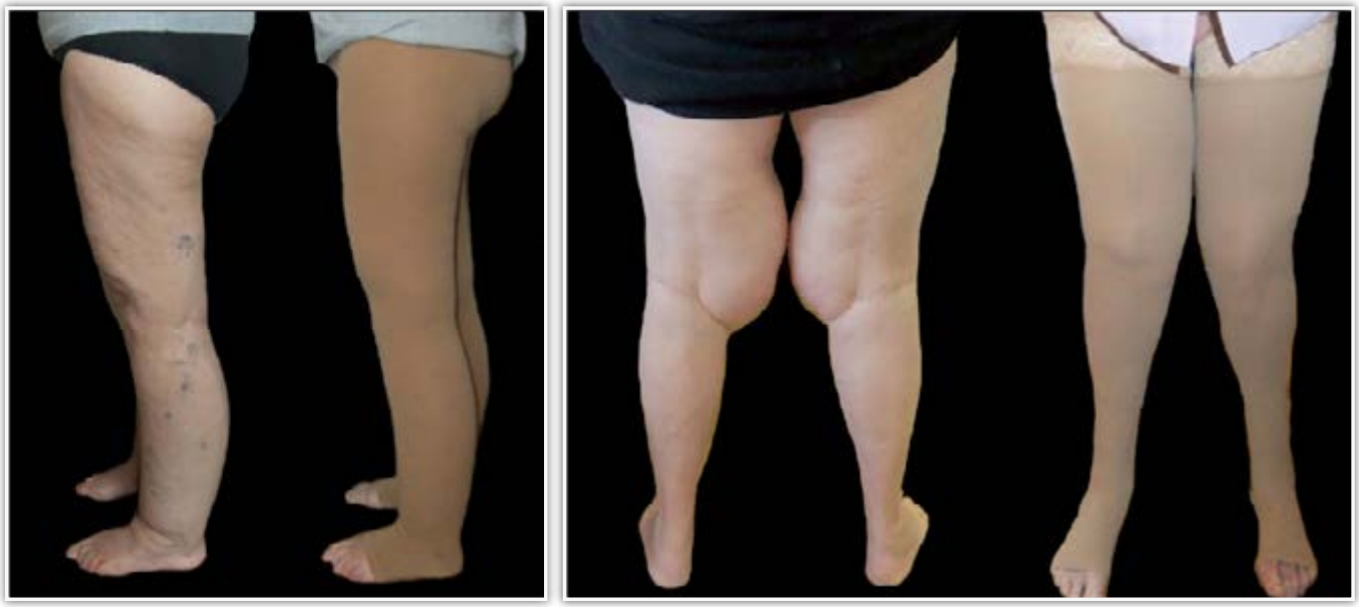


Figure 12: Compression Garments Variations

VARIOUS COMPRESSION GARMENTS BASED ON STAGE AND SEVERITY OF SYMPTOMS

FIGURE 12a

FIGURE 12b

FIGURE 12c

Szolnoky et al. found that CDT in a group of patients with lipedema (MLD, IPC, and multilayered short-stretch bandaging) resulted in a significant reduction in pain intensity, a decrease in leg volume and a decrease in capillary fragility as evidenced by less bruising and petechiae.[57] In another study, Szolnoky et al. determined that although IPC is a safe treatment and both CDT alone and CDT with IPC produced a significant reduction in average leg volume, the inclusion of IPC in the CDT bundle did not provide any added benefit.[61]

Despite the fact that weight loss has not proven to significantly affect the lipedema fat deposition, and may even accentuate the disproportional features as weight is lost from the upper body, the overall prognosis is improved when concurrent obesity is addressed.

CONSERVATIVE TREATMENT: DIET AND PHYSICAL ACTIVITY

Despite the fact that weight loss has not proven to significantly affect the lipedema fat deposition, and may even accentuate the disproportional features as weight is lost from the upper body, the overall prognosis is improved when concurrent obesity is addressed.[11, 33]

DIET FOR LIPEDEMA

Unlike obesity, lipedema fat is resistant to diet and exercise or bariatric surgery.[4, 35] In a survey conducted in the UK in 2014, a significant number of patients (95%) reported that they failed to lose weight in areas affected by lipedema, despite rigorous measures with successful outcomes in other areas of the body.[58] While calorie restriction has proven unsuccessful, current research on low carbohydrate/moderate protein/high fat (LCHF) has shown promise for weight and symptom management in lymphedema[62] and lipedema.

PHYSICAL ACTIVITY/EXERCISE FOR LIPEDEMA

Exercise and physical therapy are other important components of conservative therapy in lipedema patients. Activities that utilize the leg and calf muscles help to increase lymphatic drainage and venous flow, thereby reducing or preventing edema.[11] In some cases, exercise can assist with general weight loss and either prevent or reduce obesity. Suggestions for low impact exercises that can support the lymphatic system while minimizing excessive pressure on ankles and knees include lymphatic yoga, pilates, yoga, rebounding, swimming or aquatic exercises, use of a vibration plate, deep breathing, and stretching.[63, 64]

AQUATIC THERAPY

Aquatic therapy has been found helpful for lipedema patients, in particular for those in more advanced stages who have limited mobility. Responses from 79% of patients surveyed in the UK described reductions in limb size and relief at the "freedom of movement and weightlessness that the water provides.[58] Either swimming or walking in water exerts hydrostatic pressure on the body which "aids blood circulation, helps prevent blood pooling, and improves blood return from the extremities, which means kidneys will work more efficiently during exercise."[58, 63] This pressure helps the circulation and reduces fluid in the legs.[62]

Aquatic lymphatic therapy (ALT) is a specialized form of self-therapy that combines the CDT exercises of the Casley-Smith Method with water exercises. Developed by Dorit Tidhar,[65] ALT is a a full program of exercises which incorporates self-massage, generally performed in a pool, to complement CDT for ongoing improvement and maintenance of lymphedema and lymphatic disorders. This form of treatment is designed to maximize the effectiveness of self-massage using the natural viscose properties of the water. Based on the anatomical principles of the lymphatic system, the limb movements enhanced by the hydrostatic pressure of the water can promote strengthening,

AQUATIC THERAPY

Figure 13: Therapeutic Swimming

SWIMMING AND WATER EXERCISES AIDS IN CIRCULATION AND FLUID REDUCTION.

improve pumping of the lymphatic vessels, and increase the reduction of lymphatic fluid volume in the limbs.[66]

PHYSIOTHERAPEUTIC APPROACH

After measuring weight, volume, body strength, physical condition, type and origin of the fatigue, quality of life and caloric balance (the difference between caloric intake and burn), a treatment program can be proposed. Weight control is important to the extent that increasing weight tends to worsen symptoms. Exercise not only aids in weight control and conditioning but is also important in activating the calf muscle's pumping action on the venous and lymphatic vessels, decreasing venous stasis and increasing lymphatic drainage. Combined with compression therapy on the lower leg, this further stimulates venous and lymphatic transport.

SURGICAL TREATMENT: LIPOSUCTION AND PLASTIC SURGERY

Historically, lipedema was treated with the conservative therapies listed above. Recently, medical experts are employing surgical management more frequently with conservative measures being an important component of pre- and post-op care. Reconstructive lymph-sparing liposuction (removal of fat via suction cannulas) is the standard procedure. Liposuction or lipectomy is not a cure for lipedema and patients typically still require adjunct therapies, including compression therapy and/or MLD.[11]

TUMESCENT LIPOSUCTION FOR LIPEDEMA

When liposuction was first introduced in the early 1990's, larger cannulas were used with a "dry technique" without infiltrating the subcutaneous tissues with a liquid solution before suctioning out the fat.[22, 65] As a result, there were reports of complications including swelling from mechanical damage to the lymphatics and bleeding/hematomas from injury to the blood vessels, causing some critics to recommend against liposuction therapy.[4, 6, 31, 67]

With the advances in liposuction such as the use of tumescent local anesthetics and vibrating blunt microcannulas (smaller cannulas that are 2mm-4mm in diameter), as well as the utilization of proper methods by experienced surgeons, the risk of complications is much lower.[67]

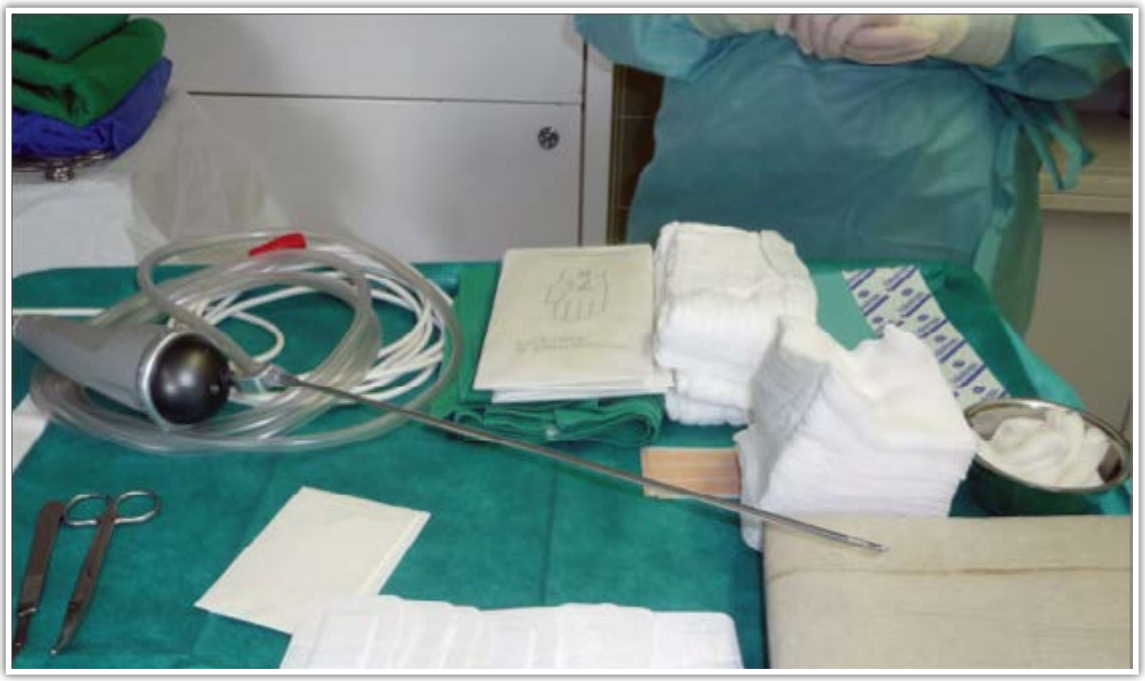


Figure 14: Vibrating Microcannula Set up for Surgery

POWER ASSISTED LIPOSUCTION MICROCANNULA SET UP FOR SURGERY

TUMESCENT LIPOSUCTION WITH VIBRATING MICROCANNULA

Tumescent liposuction, also known as the "wet technique," involves the subcutaneous infiltration of a large volume of a solution usually containing local anesthetics, saline, sodium bicarbonate, and epinephrine, followed by suctioning of the fat through cannulas.[4,7] This technique has improved the results of liposuction by increasing tissue turgor to facilitate fat removal, vasoconstricting the blood vessels with the epinephrine to reduce bleeding, and increasing postoperative pain control via the local anesthetic.[67]

Schmeller et al. performed tumescent liposuction with vibrating microcannulas on a group of patients with lipedema and evaluated their results after an average of 12.2 months, publishing in 2006.[7] They found that the patients reported an overall improvement in their appearance, reduction or complete resolution of pain, diminishment or complete resolution of bruising, and decreased need for physical therapy. The patients experienced no major complications from the procedure, and all significantly increased their quality of life.[7]

Rapprich et al.[22] also studied a group of patients who underwent tumescent liposuction and found that quality of life was increased, symptoms were improved and patients could tolerate longer periods without conservative treatment, though the follow-up period was shorter in this study (6 months). In addition, they concluded that results were better for younger patients in earlier stages of lipedema compared to older patients in later stages.[22] Several other studies have reported similar benefits using other forms of liposuction. [68-70]

Figure 15: Water Jet-assisted Liposuction (WAL) for Lipedema

WATER JET-ASSISTED LIPOSUCTION IS A COMMONLY UTILIZED SURGICAL TECHNIQUE FOR PATIENTS WITH LIPEDEMA.

WATER JET-ASSISTED LIPOSUCTION (WAL) FOR LIPEDEMA

Water jet-assisted liposuction (WAL) is another version of liposuction which has been used successfully since the early 2000s in Germany and more recently more widely adopted in the USA, Europe, and the UK. WAL consists of a "fan-shaped water jet" which immediately separates the fat cells from the rest of the tissue while simultaneously suctioning this fat along with the tumescent fluid mixture. WAL differs from tumescent liposuction in that less fluid is injected initially (i.e. just enough to anesthetize the area to be suctioned) and then large volumes of fluid are pulsed in and out during the suctioning. Since fluid is simultaneously injected and suctioned out with the fat, the tissues do not become fully tumesced (i.e. distended) with fluid, making it easier to assess the contour of the limb during suctioning. A study by Stutz and Krahl[71] analyzed the aspirated fat cells with immunohistochemistry and found that there was minimal presence of lymphatic vessels in the lipoaspirates. They concluded that there was minimal, if any, damage to lymphatic structures during WAL and that WAL is a viable option with aesthetic results similar to that of tumescent liposuction.[71]

COMBINED SURGICAL THERAPY

There have been reports of combination therapies consisting of both liposuction and lipectomy (surgical excision of skin and subcutaneous/fat tissue). Rudkin[18] describes suction lipectomy with limited skin and subcutaneous tissue excision in four patients with successful improvement in contour and size of the affected extremities. Peled et al.[72] reported a successful case using suction-assisted lipectomy in a lipedema patient

with improvement in aesthetic results that was maintained even four years postoperatively and caused no changes in lymphatic function as confirmed on lymphoscintigraphy. They also concluded that removing the excess fat in lipedema significantly reduced the mechanical strain on the lymphatic structures enabling patients to no longer need compression therapy beyond the immediate postoperative phase.

Given the complexity of the issues of body image dissatisfaction for women in general and as a result of the disfigurement caused by lipedema, self-compassion practices were found to increase self-acceptance, self-support and QOL.

Another combination therapy has been described by Wollina et al. in elderly patients with advanced lipedema. This therapy consisted of laser-assisted tumescent liposuction followed by a subsequent modified medial thigh lift with lower partial abdominoplasty.[73] All excision procedures must be carefully performed to avoid injuring the lymphatic system and causing iatrogenic lymphedema and should be done by a surgeon who has had training and experience with lipedema patients.

Typically, experienced surgeons recommend that surgery be combined with aftercare that includes compression garments and MLD as well as active movement such as walking, yoga, swimming, and bouncing on a rebounder/trampoline. This supports the resolution of postoperative swelling and offers continued support for the lymphatic system.

PSYCHOLOGICAL SUPPORT: QUALITY OF LIFE

Psychological factors have a significant impact for patients with lipedema. Most overweight or obese patients report experiencing some form of anti-fat bias in seeking diagnosis and treatment from clinicians.[74] Referrals for psychological counseling are rare even though 85% of women with lipedema report that it impacts their mental health, daily functioning, and quality of life.[58] In addition to the pain, swelling, futile attempts at management through diet and exercise, patients with lipedema experience visible disfigurement even with successful conservative and/or surgical treatment.[58, 63, 64] Psychological support becomes paramount.

ANTI-FAT BIAS IN HEALTHCARE: THE IMPACT OF THE CLINICIAN/PATIENT RELATIONSHIP

Healthcare professionals are exposed to the same social messages about obese persons as is the general population and are even more aware of the negative health consequences of obesity.[74] Evidence in various studies suggested that negative attitudes expressed by medical professionals, often lacking empathy and rapport,[75] are directed not just toward obesity as a health condition, but also against people who are obese.[74, 76] This corroborates the underlying discomfort, shame, and blame reported by patients in interacting with their medical professionals. This is particularly problematic for those with lipedema since the appearance of obesity is a medically-based condition that has been historically under-recognized. Overweight and obese women report being treated disrespectfully by medical professionals because of their weight. One study found that 53% of overweight and obese women reported receiving inappropriate comments about weight from their doctors.[76] This seems to be even more prevalent in those with lipedema.

PSYCHOLOGICAL SKILLS FOR THE LIPEDEMA PATIENT

A personal communication from a lipedema patient to one of the co-authors expresses the sense of loss associated with the physical and emotional burden of lipedema:

> *"Grief. Do you battle with it? For what this disease has robbed you of? For all the things you wanted but can't have because of it? Is anger a problem*

for you? Depression? It seems to me this disease in its advanced stages takes such a terrible emotional toll on us, not just physical. We have such a hard road to hoe do we not? We're so often isolated, judged, vilified and so on just because of what some people see on the outside, so very often some of us don't have a lot of support. How do you cope with being so misunderstood so much of the time?"

A study conducted in 2016 of 120 lipedema patients indicated that two factors, psychological flexibility and social connectedness, contributed to a better quality of life (QOL).[59, 60] A third factor, self-compassion, was reported to ameliorate the suffering accompanying the deep discrediting of the body from the disfigurement typically accompanying lipedema.[60, 77]

Dudek et al. reported that women who developed higher levels of psychological flexibility were more open to experience, more present with their experiences, both pleasant and painful, and more engaged in their lives. Patients also described a higher frequency of self-care actions such as being able to go to the swimming pool despite body image dissatisfaction, better adherence to treatment such as regularly engaging in CDT, acceptance of difficult emotions, and engagement in values-based behaviors.[59]

Social connectedness was found to be another important element that resulted in a higher QOL. As they developed greater levels of social connectedness, they reported the experience of coming together with others, interacting, and developing a sense of intimacy that led to greater mental and physical health, functioning, longevity, and well-being.[60]

Given the complexity of the issues of body image dissatisfaction for women in general[77] and as a result of the disfigurement caused by lipedema, self-compassion practices were found to increase self-acceptance, self-support and QOL. Studies found that meditation was well suited to address the kind of suffering that many women experience in regards to their body image.[60, 77] Research conducted on self-compassion meditation demonstrated a decrease in negative body image, anxiety, depression, and low self-esteem and an increase in positive body image, psychological health, higher levels of well-being and self-compassion.[77]

VI. PROGNOSIS

Lipedema is a progressive condition that if left untreated may progress, worsen, and give rise to secondary problems. Conservative therapy may decrease symptoms of swelling and heaviness and offer a lifestyle change. Those patients who can remain compliant with conservative therapies, maintain a normal weight, and who have fewer comorbidities have a better prognosis and usually a milder disease course than those who do not.[11] Complications of lipedema, most importantly the progression to lipo-lymphedema, can be prevented or minimized by early diagnosis and treatment. Surgical treatment of lipedema is promising and has been shown to be effective in not only reducing symptoms and improving mobility but also in significantly improving the quality of life in patients suffering from this disfiguring and disabling condition.[16]

Note:
The Lipedema Project Directory at http://lipedemaproject.org/lipedema-lipoedema-lipodem-provider-directory/ lists clinicians, surgeons, and therapists who provide healthcare specific to lipedema, lipo-lymphedema, and lymphedema.

If you are a provider who is diagnosing, treating, or caring for lipedema patients, and would like to be added to the directory, please contact: providerdirectory@lipedemaproject.org.

VII. ICD, MESH, AND OTHER CODES

INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) CODES

List of ICD-10 codes that apply to lipedema and relevant co-morbidities.

Lipedema, Lymphedema, Edemas

R60.9 Edema, Unspecified (can be used for lipedema)
http://www.icd10data.com/ICD10CM/Codes/R00-R99/R50-R69/R60-/R60.9

Q82.0 Hereditary Lymphedema
http://www.icd10data.com/ICD10CM/Codes/Q00-Q99/Q80-Q89/Q82-/Q82.0

I89.0 Lymphedema, not elsewhere classified
http://www.icd10data.com/ICD10CM/Codes/I00-I99/I80-I89/I89-/I89.0

I97.2 Postmastectomy lymphedema syndrome
http://www.icd10data.com/ICD10CM/Codes/I00-I99/I95-I99/I97-/I97.2

Obesity and Other Fat Disorders

R63.5 Abnormal weight gain
http://www.icd10data.com/ICD10CM/Codes/R00-R99/R50-R69/R63-/R63.5

E65 Localized adiposity
http://www.icd10data.com/ICD10CM/Codes/E00-E89/E65-E68/E65-/E65

E66.8 Other obesity
http://www.icd10data.com/ICD10CM/Codes/E00-E89/E65-E68/E66-/E66.8

E66.9 Obesity, unspecified
http://www.icd10data.com/ICD10CM/Codes/E00-E89/E65-E68/E66-/E66.9

E88.2 Lipomatosis Dolorosa, not elsewhere classified (Dercum disease)
http://www.icd10data.com/ICD10CM/Codes/E00-E89/E70-E88/E88-/E88.2

Vascular and Skin Issues

I87.2 Venous insufficiency (chronic) (peripheral)
http://www.icd10data.com/ICD10CM/Codes/I00-I99/I80-I89/I87-/I87.2

R20.8 Other disturbances of skin sensation
http://www.icd10data.com/ICD10CM/Codes/R00-R99/R20-R23/R20-/R20.8

Functionality: Gait and Mobility Issues
L98.7 Excessive and redundant skin and subcutaneous tissue
http://www.icd10data.com/ICD10CM/Codes/L00-L99/L80-L99/L98-/L98.7

R26.89 Other abnormalities of gait and mobility
http://www.icd10data.com/ICD10CM/Codes/R00-R99/R25-R29/R26-/R26.89

R29.8 Other symptoms and signs involving the nervous and musculoskeletal systems
http://www.icd10data.com/ICD10CM/Codes/R00-R99/R25-R29/R29-/R29.8

German ICD-10 Codes for Lipoedema/Lipedema
https://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2017/block-e70-e90.htm

- E88.20 Lipoedema, Stage 1
- E88.21 Lipoedema, Stage 2
- E88.22 Lipoedema, Stage 3
- E88.28 Other or unspecified lipoedema

ICD-11 CODES BETA DRAFT - WORLD HEALTH ORGANIZATION (WHO)

Lipoedema/Lipedema
Category 14: Diseases of the skin
Diseases of the skin: Disorders of subcutaneous fat

EK54 Lipoedema

http://apps.who.int/classifications/icd11/browse/l-m/en#!http%3A%2F%2Fid.who.int%2Ficd%2Fentity%2F1172950828

Lipo-lymphedema
Category 11: Diseases of the circulatory system
Disorders of lymphatic vessels or lymph nodes

BC63.1Y Lymphoedema secondary to other specified cause
Used for lipo-lymphedema

http://apps.who.int/classifications/icd11/browse/l-m/en#http%3a%2f%2fid.who.int%2ficd%2fentity%2f643334575%2fmorbidity%2fother

OTHER CODES

MeSH (Medical Subject Heading)
MeSH identification number (DUI or Descriptor Unique Identifier) in the National Library of Medicine (NLM)
MeSH code for lipedema: MeSH D065134
https://meshb.nlm.nih.gov/record/ui?ui=D065134

OMIM (Online Mendelian Inheritance in Man®)
OMIM® is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily.
OMIM code for lipedema: OMIM 614103
http://www.omim.org/entry/614103

ORPHA (Rare diseases and orphan drugs)
ORPHA Net is a portal for rare diseases and orphan drugs.
ORPHA code for lipedema: 77243
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=77243

VIII. RESOURCES

There are multiple resources available in various domains by many contributors to this field. In order to keep most up-to-date you can find these resources online. These resources are updated on a continuing basis.

- Educational Resources available online at http://lipedemaproject.org/lipedema-education/
- Medical Resources available online at http://lipedemaproject.org/resources/
- Social Resources available online at http://lipedemaproject.org/social-resources/

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Setting the Research Agenda for Lipedema

Steps Towards a Cure

A Continuing Medical Education (CME) Course for Physicians

This CME course reviews the diagnostic criteria, work up and differential diagnosis for patients with lipedema. Surgical and non-surgical treatment options are discussed. The physiology and pathophysiology of fat metabolism, lipedema research opportunities and obstacles to patient care are reviewed.

FREE CME Course

For more information and registration

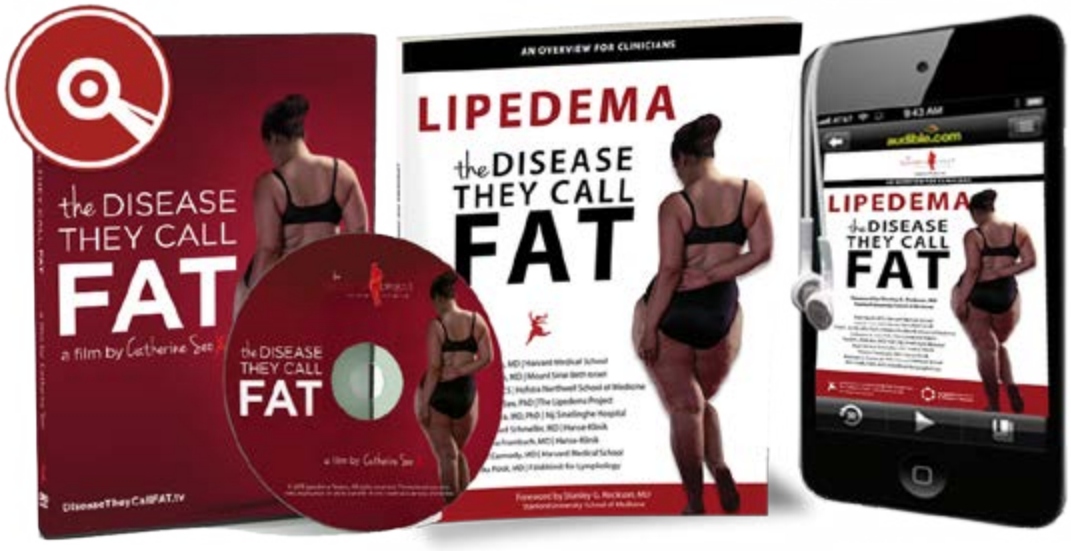
https://LipedemaProject.org/cme-setting-the-research-agenda-for-lipedema/

This enduring material online course is designated for a maximum of 5.5 AMA PRA Category 1 Credits TM.

ACCREDITATION: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint providership of Mount Sinai Beth Israel and The Friedman Center for Lymphedema Research & Treatment. Mount Sinai Health System Hospitals: Mount Sinai Beth Israel, Mount Sinai St Luke's and Mount Sinai West, are accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Disease They Call FAT DVD

There are an estimated 17 million women in the USA that have the fat disorder lipedema and don't know it. Filmmaker and patient Catherine Seo brings us on a journey of discovery, as she explores this misunderstood and commonly misdiagnosed disease.



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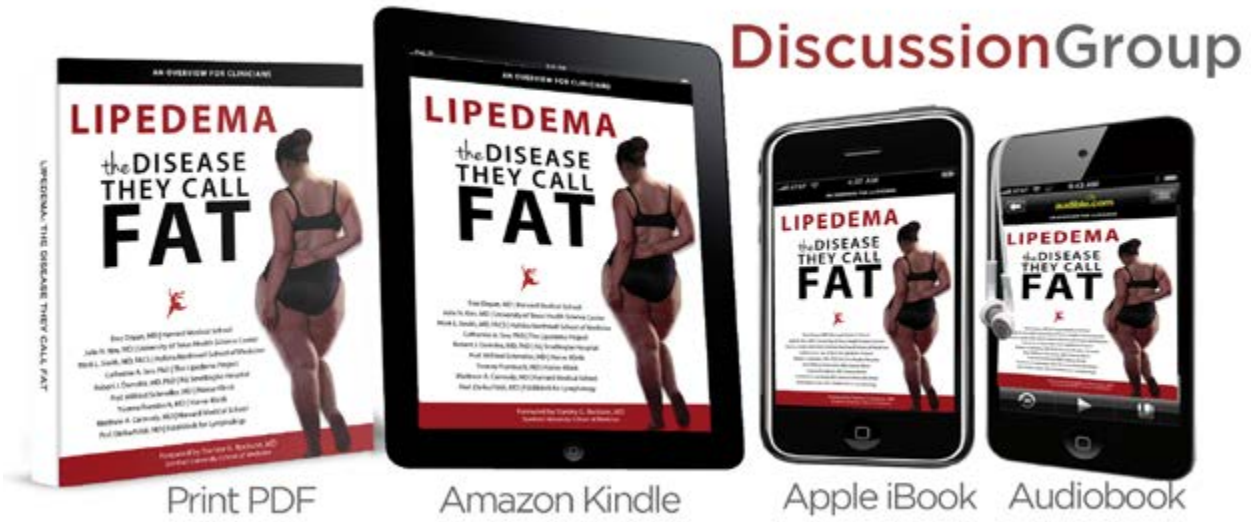

We hope that this monograph has generated questions and comments to begin a conversation. Join us for a discussion on Facebook.

https://www.facebook.com/groups/lipedemabookdiscussion/

TITLES COMING SOON FROM THE LIPEDEMA PROJECT

Other Titles in the Monograph Series

LE: Lymphedema for Healthcare Professionals and Patients
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Publications in Process

The Lipedema Sourcebook:
Stories, Education, and Tools for the Disease They Call FAT

Weight Loss for Lymphatic Disorders: Breaking the Cycle

Unstoppable: Lipedema, Fat, and Finding Freedom

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Michael Alatriste, LMT, CLT
Co-Founder and Clinical Director
Lymphedema Alliance of New York
Educational Director
TAM-Lymphedema Management Certification
New York, New York, USA

Jeanine Albu, MD
Chief, Interim and Fellowship Program Director; Division of Endocrinology, Diabetes and Nutrition; Mount Sinai, St. Luke's and Mount Sinai Roosevelt Hospitals; Professor of Medicine, Icahn School of Medicine at Mount Sinai
New York, New York, USA

Polly Armour
Patient Advocate
Executive Assistant
Stutz Lipedema Services LLC
Gardiner, New York
Schwarzenbach am Wald, Germany

Sarah Bramblette, MS Health Law
Patient Advocate
Born2lbFat Blog
Vice Chair Lymphedema Treatment Act
Biscayne Park, Florida USA

Donald W. Buck II
Assistant Professor, Surgery
Associate Program Director
Division of Plastic and Reconstructive Surgery
Washington University School of Medicine in St. Louis.
St. Louis, Missouri, USA

Christoph Buettner, MD, PhD
Professor, Medicine, Endocrinology, Diabetes and Metabolism and Bone Disease
Icahn School of Medicine at Mount Sinai
New York, New York, USA

Matthew Carmody, MD
Primary Care Physician
Department of Medicine
Mt Auburn Hospital
Assistant Professor,
Harvard Medical School
Cambridge, Massachusetts, USA

Felicitie Daftuar, MBA
Founder and Executive Director
Lipedema Foundation
Greenwich, Connecticut, USA

Jens Diedrichson, MD
Plastische Chirurgie im Medienhafen
Consultant, Clinic for Plastic and Cosmetic Surgery
Florence Nightingale Hospital
Board Member, German Board of Plastic and Aesthetic Surgery
European Board of Plastic Reconstructive and Aesthetic Surgery
Düsseldorf, Germany

Heather Ferguson
Founder, Executive Director
Lymphedema Advocacy Group
Advocate and leader in passing
The Lymphedema Treatment Act
Charlotte, North Carolina, USA

Professor Etelka Földi, MD
Physician-in-Chief
Földiklinik Clinic, Special Clinic for Lymphology
Hinterzarten, Germany
Founder, Földiklinik College, Teaching Institute
for Manual Lymph Drainage,
Complete Physical Therapy
Freiburg, Germany

Harriet Forman, EdD, RN
Patient Advocate
Independent Healthcare Consultant and Author
New York, New York, USA

Kathleen Francis, MD
Physiatrist, Rehabilitation Medicine
Medical Director, Lymphedema Treatment Center
RWJ Barnabas Health Ambulatory Care Center
Medical Director, Klose Training and Consulting
Steering Committee, American Lymphedema Framework Project
Livingston, New Jersey, USA

Susan K. Fried, PhD
Professor, Department of Medicine, Division of Endocrinology, Diabetes and Bones Diseases
Director, Translational Adipose Biology and Obesity
Diabetes, Obesity and Metabolism Institute
Icahn School of Medicine at Mount Sinai
New York, New York, USA

Kimberly Gudzune, MD, MPH
Assistant Professor of Medicine
Division of General Internal Medicine
Johns Hopkins University School of Medicine
Core Faculty,
Welch Center for Prevention, Epidemiology, and Clinical Research
Baltimore, Maryland, USA

Donna Haynes
Patient Advocate
Orlando, Florida, USA

Falk-Christian Heck, MD
Orthopedic and Plastic Surgeon
Praxis für Lipödem-Chirurgie
Essen, Germany

Robert Heinzman
Change Leadership Expert
Senior Partner
Growth River
Lee, Massachusetts, USA

Karen Herbst, PhD, MD
Associate Professor
University of Arizona College of Medicine
Director, Treatment, Research, Education of Adipose Tissue Program (TREAT)
Tucson, Arizona, USA

William B. Inabnet III, MD
Chairman, Department of Surgery
The Eugene W. Friedman, MD, Professor of Surgery
Surgical Director of the Diabetes, Obesity and Metabolism Institute
Icahn School of Medicine at Mount Sinai
Director of Endocrine Surgery Quality
Mount Sinai Beth Israel Health System
New York, New York, USA

Cheri Hoskins, CLT, CCT
President and CEO
Compression Done Right, Inc.
Dallas, Texas, USA

Jean Flanagan Jay, DPT, PT, CLT
Director, Rehabilitation Services
Brigham and Women's Faulkner Hospital
Boston, Massachusetts, USA

Guenter Klose, MLD/CDT
Founder, Klose Training & Consulting, LLC.
Lafayette, Colorado, USA

Ruth Loos, PhD
Professor, Icahn School of Medicine at Mount Sinai, Director of the Genetics of Obesity and Related Metabolic Traits Program, Charles Bronfman Institute of Personalized Medicine
New York, New York, USA

April Gilliam Pope, PA-C
Patient Advocate
Associate Professor/Clinical Coordinator
Physician Assistant Program
Campbell University
Buies Creek, North Carolina, USA

Gwendalyn J. Randolph, PhD
Emil R. Unanue Distinguished Professor
Dept of Pathology & Immunology
Head, Division of Immunobiology
Washington University School of Medicine
Washington University in St. Louis
St. Louis, Missouri, USA

Stefan Rapprich, MD
Dermatologist and Surgeon
Facharzt für Dermatologie
Hautmedizin Bad Soden
Dermatologische BAG PartG
Frankfurt, Germany

William Repicci
President and CEO
Lymphatic Education & Research Network (LE&RN)
New York, New York, USA

Stanley G. Rockson, MD
Cardiovascular Medicine,
Allan and Tina Neill Professor of Lymphatic Research and Medicine
Director, Center for Lymphatic and Venous Disorders
Stanford University School of Medicine
Stanford, California, USA

Catherine Seo, PhD
Co-Director, The Lipedema Project
Director & Producer, *The Disease They Call FAT* documentary
Founder & Director,
Lipedema Simplified, LLC
Boston, Massachusetts, USA

Nadiv Shapira, MD, FACS, FACPh
Surgeon
First State Lipedema
Wilmington, Delaware, USA

Tilly Smidt
Patient Advocate
Founder, Dutch (National) Lipoedema Patients Association (LIPV)
Owner, www.lipv.nl
Amsterdam, The Netherlands

Mark L. Smith, MD, FACS
Professor, Department of Surgery
Hofstra Northwell School of Medicine
System Vice-Chair, Department of Surgery
Northwell Health System
Director, The Friedman Center for Lymphedema
Research and Treatment
Co-Director, The Lipedema Project
Lake Success, New York, USA

Jennifer Svahn, MD, FACS
Vascular Surgeon
Director, Vein Surgery at Union Square
Northwell Health Physician Partners
Assistant Professor of Surgery,
Hofstra Northwell School of Medicine
New York, New York, USA

Melody Swartz, PhD
Professor and William B. Ogden Chair
Institute for Molecular Engineering
Ben May Department for Cancer Research
University of Chicago
Chicago, Illinois, USA

Jay Vogt, MA
Facilitator & Consultant
Peoplesworth
Concord, Massachusetts, USA

Jane Wigg, RGN, MSc
Director, LymphVision
Director, Lymphoedema Training Academy
Staffordshire, UK

Christine Wise, BSc in Advanced Nursing Practice
Lymphoedema Nurse Specialist
St. George's Hospital
Joint Nurse Advisor, Lipoedema UK
London, UK

FOR MORE INFORMATION ABOUT OUR COLLABORATORS:

THE LIPEDEMA PROJECT THINK TANK

Our Authors

Erez Dayan, MD

Department of Plastic and Reconstructive Surgery, Brigham and Women's Hospital - Harvard Medical School, Boston, Massachusetts, USA

Dr. Erez Dayan is from the Harvard Plastic Surgery Program in Boston, Massachusetts. He has been actively involved in seminal research related to surgical treatments for lymphedema and new technology and imaging modalities for assessing fluid and fat content of various body parts. He has lectured and published on these topics on over 100 occasions nationally and internationally.

Julie N. Kim, MD

Division of Plastic and Reconstructive Surgery, University of Texas Health Science Center, San Antonio, Texas, USA

Dr. Julie N. Kim is in her first year of residency in Plastic and Reconstructive Surgery at the University of Texas Health Science Center at San Antonio. She recently completed her residency in General Surgery at Mount Sinai Beth Israel in New York City. At MSBI she was fortunate to work with both Dr. Mark Smith and Dr. Erez Dayan who introduced her to the intricacies of both lymphedema and lipedema.

Mark L. Smith, MD, FACS

Department of Surgery, Zucker School of Medicine at Hofstra/Northwell, The Lipedema Project, The Friedman Center for Lymphedema Research and Treatment at The Center for Advanced Medicine at Northwell Health, New York, USA

Dr. Mark L. Smith is Professor and System Vice-Chairman of the Department of Surgery at Zucker School of Medicine at Hofstra/Northwell and Director of Reconstructive Oncology for Northwell Cancer Institute. He is also Director of the Friedman Center for Lymphedema Research and Treatment and Co-Director of the Lipedema Project. He is an expert in the field of cancer reconstruction and lymphatic surgery.

Catherine A. Seo, PhD

The Lipedema Project, The Friedman Center for Lymphedema Research and Treatment at The Center for Advanced Medicine at Northwell Health, Boston, Massachusetts, USA

Dr. Catherine Seo is Co-Director of The Lipedema Project and Founder and Director of Lipedema Simplified, LLC. She produced and directed the documentary *The Disease They Call FAT*. She holds a doctorate in Media Psychology. She has developed online courses on lipedema for patients and healthcare professionals as well as multi-media learning tools.

Robert J. Damstra, MD, PhD

Department of Dermatology and Dutch Expert Center for Lympho-Vascular Medicine, Nij Smellinghe Hospital, Drachten, the Netherlands

Dr. Robert J. Damstra is a dermatologist at the Nij Smellinghe Hospital in Drachten, the Netherlands. He co-founded the Drachten Working Group on Lymphedema in 1995, expanding the hospital's reach to include a specialized expertise center for the diagnosis and treatment of lymphedema and lipedema. The Center collaborates with many national and international groups to put lipedema on the agenda and to create more awareness and recognition of this disease.

Prof. Wilfried Schmeller, MD

Hanse-Klinik, Lübeck, Germany

Professor Dr. Wilfried Schmeller is a dermatologic surgeon with expertise in phlebology and lymphology. His background includes the Department of Dermatology at the University of Lübeck, the Vein Clinic in Bad Bertrich, and the Rosenpark-Klinik in Darmstadt. He founded the Hanse-Klinik in Lübeck in 2002 to treat patients with lipedema with liposuction. He has published many scientific articles on this topic. Prof. Schmeller is head of the working group Operative Lymphology of the German Society of Lymphology and has been participating in the new German Guidelines for Lipoedema/Lipedema.

Yvonne Frambach, MD

Hanse-Klinik, Lübeck, Germany

Dr. Yvonne Frambach is a board certified dermatologist who specializes in allergology and medicinal tumor therapy. She has treated chronically ill patients, particularly those suffering from inflammatory diseases and tumours, as well as those with lipedema and lymphedema. She has been a physician at the Hanse-Klinik since 2014.

Matthew A. Carmody, MD

Department of Medicine, Mount Auburn Hospital, Cambridge - Harvard Medical School, Boston, Massachusetts, USA

Dr. Matthew Carmody is Assistant Professor of Medicine at Harvard Medical School and an internist affiliated with Mount Auburn Hospital. He specializes in Internal Medicine and has been instrumental implementing Patient–Centered Medical Home (PCMH), a team-based health care delivery model led by a health care provider that is intended to provide comprehensive and continuous medical care to patients with the goal of obtaining maximized health outcomes.

Prof. Etelka Földi, MD

Földiklinik, Specializing in Lymphology, Hinterzarten, Black Forest, Germany

Professor Dr. Etelka Földi is one of the world's foremost authorities on the lymphatic system. She and her husband, Professor Michael Földi, MD founded the Society of German Lymphologists in 1969. Their seminal textbook on lymphology, *Földi's Textbook of Lymphology: for Physicians and Lymphedema Therapists* is currently in its third edition and has become a classic treatise on the management of lymphedema and other disorders of the lymphatic system.

Stanley G. Rockson, MD

Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA

Dr. Stanley G. Rockson is the Allan and Tina Neill Professor of Lymphatic Research and Medicine at Stanford University and directs the Stanford Center for Lymphatic and Venous Disorders, where he conducts basic and clinical research in lymphatic disorders, including lipedema. He is the Founding Chair of the LE&RN Scientific and Medical Advisory Committee. Dr. Rockson has authored more than 150 scientific papers, reviews, book chapters, and books devoted to various aspects of lymphatic biology and disease, vascular biology, and cardiovascular medicine.

"The Lipedema Think Tank was a unique opportunity for clinicians, surgeons, researchers, scientists, therapists, patients and advocates across many disciplines to come together to share knowledge, brainstorm,
and develop a research agenda to advance our understanding of lipedema."

LIPEDEMA

THE DISEASE THEY CALL FAT:
An Overview for Clinicians

Lipedema – The Disease They Call FAT: An Overview for Clinicians is a monograph that provides a clinical synopsis of lipedema, a fat disorder, that is often mistaken for simple obesity, that affects an estimated 11% of post-pubertal women (17 million women in the USA alone). Written with the clinician in mind, it is a practical overview of the condition and provides important information for healthcare providers who treat women.

Experts are saying...

"This is a high-quality, comprehensive summary of the 'State of the Art/Science' relating to lipoedema/ lipedema. This disease badly needs attention both from healthcare professionals in order to improve patient care, and from scientists to improve our basic understanding of this disease with a view to improved treatment. I am hopeful this monograph will provide the platform for such advances."

Peter Mortimer, MD
Professor of Dermatological Medicine
Molecular and Clinical Sciences Institute (Dermatology Unit)
St. George's, University of London
London, England, UK

"As a clinician, I expect this will quickly become a 'standard reference' on Lipedema. The clinical information is concise, thorough, and up to date. The monograph is a helpful reference whether checking stages, differential diagnosis or current treatments. It has become a great teaching document in our clinic for therapists, students, and patients alike. It will be a helpful reference to share with physicians as we discuss strategies for care management."

Jean Flanagan Jay, DPT, PT, CLT
Director, Rehabilitation Services
Brigham and Women's Faulkner Hospital
Boston, Massachusetts, USA

"I've found this monograph very useful for clinicians,
a good and complete synthesis of what we know about lipedema."

Isabel Forner-Cordero, MD, PhD
Hospital Universitari i Politecnic La Fe
University of Valencia
Valencia, Spain

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