

Lipedema: A Current Understanding of its Pathology and Natural History

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Vision

Millions of women around the world live with Lipedema, a chronic, stigmatized, and painful condition. While research is beginning to document the toll Lipedema takes on their lives and relationships, it remains largely unknown in both patient and medical communities. For too many, a diagnosis of Lipedema is ignorantly dismissed as obesity. Lipedema has for 80 years been relegated to a quiet corner of the research community. It is time to bring Lipedema into the open and set forth a roadmap that provides the path to improved recognition and care based on the same standards of evidence that we expect of any serious condition.

Introduction

Despite 80 years of inquiry, Lipedema remains a poorly understood condition. Today, fewer than 250 primary experimental data and case studies characterize the entirety of what is known to the research community. In the absence of high-quality prospective data, the safety and efficacy of many common treatments must be predicted from the experience of individual practitioners or from research successes in related conditions. Thus, in addition to the statistical challenges conferred by perennially low study sizes, Lipedema research is further complicated by limited knowledge in foundational areas. These include lingering questions related to its natural history, diagnosis, and therapeutically important concerns such as appropriateness of endpoints selected for current studies, or adverse events that might specifically be predicted for a Lipedema population.

Many reviews of Lipedema research exist. Indeed, reviews of Lipedema have, at times, outnumbered the primary data reports (Eakin, 2022). As in many fields, the favored works cited by these reviews become canon as a function of merit, but also repetition. The consequence is that older or more peripheral works disappear from citation. This historically facing component of the Roadmap strives to reevaluate these original data wherever possible. In doing so, an attempt has been made to balance modern, technology-rich, insights with an honest examination of historical data otherwise lost to the cycle of review and repetition. The available literature describes an immature field, often characterized by underpowered studies, rare attempts at reproducibility, and substantial challenges to comparability across studies owing to the uncatalogued diversity of the condition and site to site variations in diagnosis and data collection standards. The opinions expressed here are limited by the volume – and often the quality – of available data.

These are challenges, but they are challenges that are consistent with a developing field. While the field of Lipedema research is characterized by less than 300 primary data publications, it should also be realized that half of these have been published in the last four years. This renewed attention is an exciting moment for Lipedema research. The companion effort of this review provides a forward-facing framework by which research initiatives may be prioritized for their potential to support improvements

in the clinical research environment and guide the field towards a future in which well-designed, and appropriately powered clinical research is not only possible, but expected. Finally, the Roadmap is envisioned as a “living” and editable document, that should be reviewed and updated periodically with attention to progress toward goals established here and in future versions. For this reason, it is published to the Lipedema Foundation website, so that its content can be readily edited as new versions become necessary.

Challenges of Lipedema Research

1. Progress is limited by a reliance on a clinical diagnosis for which there is practice-to-practice variation in choice and implementation of available diagnostic criteria. This limits the availability of a confident diagnosis to a limited number of experienced clinicians that is too small to currently address the public health burden of Lipedema. This holds consequence for both the timeliness and availability of a diagnosis for the public, but also limits the access of the research enterprise to adequate numbers of Lipedema patients required for well-powered studies. Likewise, reliance on a clinical diagnosis limits the ability to identify sub-clinical or prodromal Lipedema to complex longitudinal studies.
2. Societal stigma against obesity and gender that manifests at several levels. Stigma is believed to affect availability of care. A tendency to misdiagnose as obesity has the effect of prioritizing behavioral interventions that have little evidence of disease modifying effect. Such stigmas set barriers to accessing care coverage for standard treatments.
3. Lack of research data related to understanding the diversity with which Lipedema presents, and how Lipedema may differ by genetics, race, comorbidities, or sociodemographic factors. Subgroups within Lipedema populations are currently defined narrowly by stage, which does not account for all biological aspects of pathogenesis and symptoms, effects on quality of life, or interplay between these features.
4. Lack of public and professional awareness reduces the available workforce and patient population necessary to recruit and execute large studies.
5. Lack of commitments to research investment from both public and private sources. Consequently, Lipedema research is limited and characterized by
 - a. Small and underpowered studies
 - b. Lack of knowledge of risk factors other than female sex and family history
 - c. Largely undocumented prevalence and burden of illness
 - d. Lack of medical coding facilitating either reimbursement or research
 - e. Variable terminology used to describe Lipedema and its features

The Role of Lipedema Diagnosis in Research

Lipedema is an irreversible, chronic condition first identified as a clinically distinct entity in the mid-20th century (Allen and Hines, 1940; Wold et al., 1951). Lipedema-like features are described in other medical literature sources that predate Allen and Hines (Laignel-Lavastine and Viard, 1912; Lyon, 1910; Moncorps et al., 1940). The organized reporting of Lipedema’s diagnostic features, however, remains credited to Allen, Hines and Wold. The clinical diagnosis of Lipedema has remained relatively consistent

from these first papers and now includes formally developed guidances and consensus statements derived from expert opinion (Alcolea et al., 2018; Bertsch and Erbacher, 2020; Halk and Damstra, 2017; Karen L Herbst et al., 2021; Reich-Schupke et al., 2017; Wounds UK, 2017), including efforts at formalized approaches such as facilitated Delphi (Karen L Herbst et al., 2021) or self-organizing formats such as Open Space Technique (OST) (Bertsch and Erbacher, 2020).

While these publications clearly serve clinical needs, the effect of the reliance on clinical research is worth commenting on because, taken together, these documents form the basis for the diagnostic criteria most frequently cited in published literature. However, no experimental comparisons of different guidances or dissemination and implementation studies of individual guidances have been reported. Each guidance must, therefore, be considered as potentially capable of defining different clinical populations. In the absence of an understanding of implementation, specifically adherence of individual clinicians to a specific guidance, there is little formal ability to predict interrater reliability between individual clinicians, even if ostensibly using the same diagnostic criteria.

Within research manuscripts, the reporting of specific criteria and study inclusion and exclusion criteria is not universal. Together these issues represent a significant barrier to comparison between studies and underscore the need for technologies that assist the clinical diagnosis with well-defined measurements.

Despite these concerns, the available diagnostic strategies have suggested several symptoms and signs that can be associated to Lipedema with varying levels of background evidence. A review of both commonly cited and less frequently discussed features of Lipedema, organized by biological concept, follows.

Lipedema Diagnosis – Commonly Cited Features

Family History and Genetics

Since the original descriptions of the condition, a positive family history for similar body shape and symptoms has been linked to Lipedema. In these earlier studies, a positive family history was recorded in 16% of individuals (Allen and Hines, 1940; Wold et al., 1951). More contemporary studies suggest that the range may be higher, with lower estimates ranging 30-50% (Burnand et al., 2011; Crescenzi et al., 2018; Forner-Cordero et al., 2012; Harwood et al., 1996; Ketterings, 1988; Romeijn et al., 2018) and higher estimates ranging from 64-89% (Cornely et al., 2022; Forner-Cordero et al., 2018; I. Forner-Cordero et al., 2021; Ghods et al., 2020; Grigoriadis et al., 2022; Herbst, 2012; Kruppa et al., 2022; Naouri et al., 2010). To date, no single allele has been demonstrated to convey significant risk for Lipedema. Earlier reports of an autosomal dominant inheritance pattern with sex limitation (Child et al., 2010) have largely been replaced with a polygenetic view of Lipedema risk (Grigoriadis et al., 2022; Michelini et al., 2022). Abnormal karyotypes, particularly chromosomal rearrangements at 12q13~15, have been observed in half of non-Lipedema lipomas, but have not been reported in Lipedema affected tissues (PANAGOPOULOS et al., 2015).

It remains unclear what role single allele variants will play in Lipedema risk relative to individuals. A limited number of studies have proposed single locus variations in families with Lipedema, though whether these are causative of the underlying condition is unknown. Two separate whole exome sequencing efforts have been reported as the result of analysis of five (Bendon, 2017) and one

(Michelini et al., 2020) families with Lipedema. Two other case study reports have associated Lipedema with positive candidate gene approach findings for POU1F1/PIT1 (Bano et al., 2010) and NSD1 (Zechner et al., 2009). A subsequent multi-candidate gene association approach surveyed 305 loci with plausible relationships to Lipedema or closely related disorders (Michelini et al., 2022). The study reported 17 predicted deleterious lesions in 21 of the 162 participants with plausibility for a mechanistic relationship to Lipedema. MTHFR polymorphisms have been associated with a greater risk for Lipedema amongst women with Lipedema-like body composition and morphology (Gualtieri et al., 2023). At this time, none of the candidate gene or whole exome data appear strongly associated with Lipedema in GWAS results.

A recent Genome Wide Association Study of 130 individuals identified 6 loci associated with body shape, lipoma formation, adiposity, and sex-hormone biology (Grigoriadis et al., 2022). A complementary study, explored an inferred phenotype in the UK Biobank based on high fat percentage in legs and low waist to hip ratio in 24,450 cases, identified 18 associated loci with similar predicted pathway involvements, and replicating associations for markers near VEGFA and GRB14-COBLL1 (Klimentidis et al., 2022). This is directionally consistent with transcriptomic profiles from other sources suggesting involvement of similar pathways in Lipedema, albeit that transcriptomic profiles more frequently demonstrate immune features e.g. (Felmerer et al., 2020a; Ishaq et al., 2021; Ma et al., 2020; Nankam et al., 2022; Strohmeier et al., 2022). No studies to assess epigenetic contributions to Lipedema are currently available. Little crossover is evident between Lipedema GWAS and associations reported for primary lymphedemas or lipodystrophies. LHFPL6 association has been reported in both Lipedema and in lipoma development (Petit et al., 1999). Yet, associations uncovered through GWAS are correlative and lack functional validation that would support their potential causative role in Lipedema as well as replication in additional cohorts.

No specific early onset variation of Lipedema is known that might represent an early clinical model of Lipedema. Some reports of Lipedema onset in children less than 10 have been reported (Bauer et al., 2019; Herpertz, 2004; Romeijn et al., 2018; Vaquero Ramiro et al., 2021; Wold et al., 1951). A positive family history of Lipedema was also reported for all women who reported onset of symptoms prior to age 10 (Lipedema Foundation, 2022a).

The preponderance of studies reporting a positive family history of Lipedema suggest that studies pursuing a genetic basis for Lipedema are likely to continue to uncover heritable contributions to Lipedema risk. It is likely that Lipedema risk is influenced by many loci, and onset may be triggered by environmental, endocrine, or other complex exposure events. The sensitivity of individuals to these triggers is, itself, likely to be dependent on genetic background. If genetic determinants are confirmed, this would support shifting conceptualization of Lipedema as a syndrome to a disorder of associated molecular pathways. In addition to the need for larger studies, future genetics work will benefit from identification of new and well-characterized cohorts, for which substantial clinical data related to symptoms and comorbidities is available and detailed diagnostic inclusion and exclusion criteria is disclosed.

In addition to advancing discovery in Lipedema research, genetic approaches serve as the basis of biomarker and therapeutic discovery. The multi-factorial and polygenic origins of Lipedema risk suggest both an opportunity and need for rigorously developed risk calculators, that may precede development of diagnostic biomarker or imaging strategies but provide significant utility as screening tools for both clinical decision-making and recruitment to research studies.

Hormonal Change, Age of Onset, and Possible Initiators of Lipedema

The canonical features of Lipedema describe a condition that nearly exclusively affects women, with rare reports of affected males. The age of onset is generally consistent with times of hormonal change, predominantly appearing at puberty (15.7-67.3%), but with substantial numbers of patients describing onset at pregnancy/lactation (9.5-63.1%), menopause (1.9-21%), or in association with supplemental hormones such as oral contraceptives (1.2-3.8%) (Table B1. Lipedema Symptoms and comorbidities reported in primary data). These values are generally consistent with patient reports in online surveys (Fetzer and Fetzer, 2014; Kruppa et al., 2022; Lipedema Foundation, 2022a).

Prepubertal (children less than 10 years) incidence of Lipedema has been reported (Bauer et al., 2019; Lipedema Foundation, 2022a; Schook et al., 2011; Vaquero Ramiro et al., 2021) and may suggest that hormonal changes are sufficient but not necessary to initiate Lipedema. In the Lipedema Foundation Registry, such cases are always associated with a positive family history of Lipedema.

In the absence of longitudinal studies, or robust animal models, the role of hormonal change in Lipedema remains fundamentally a patient reported component of the clinical history. As yet, primary research data that demonstrates an association of sex hormones to the patho-etiology of Lipedema has not been published, though possible mechanisms have been recently reviewed (Al-Ghadban et al., 2021; Katzer et al., 2021).

While numerous studies have reported symptoms occurring at times of hormonal change, with estimates ranging from 57-69% (Bauer et al., 2019; Dudek et al., 2016, 2018; Fetzer and Fetzer, 2014; Herpertz, 2004; Kruppa et al., 2022; Lipedema Foundation, 2022a; Romeijn et al., 2018; Vaquero Ramiro et al., 2021), no thorough examination of the role of sex hormones in Lipedema has been completed. To date, only correlative evidence is available to document the relationship of sex hormones to Lipedema. AKR1C1 variance has been reported in three members of a Lipedema affected family where it is hypothesized to interfere with progesterone inactivation (Michelini et al., 2020). CPE, ZNF25 and ZNF33A have also been reported to be associated with Lipedema and estrogen biology by GWAS (Grigoriadis et al., 2022). Recently SVF, endothelial, and PC cells were shown to express ZNF423, which may be regulated by estrogen response elements (Strohmeier et al., 2022). Conference presentation data has also reported mast cells in Lipedema may also express less progesterone receptors (Rosas et al., 2018). Several hypotheses about the role of sex hormones in Lipedema have been recently proposed in literature reviews (Al-Ghadban et al., 2021; Katzer et al., 2021; Szél et al., 2014).

Irrespective of the available hypotheses, no focused studies of menstruation or sex hormone assessments are available in the published Lipedema literature. Indeed, references to simple tests such as urinalysis are exceedingly rare. These are often limited to older literature (Laignel-Lavastine and Viard, 1912; Moncorps et al., 1940), or provided as supportive data related to infectious disease or dietary adherence (Kenani et al., 2008; Sørli et al., 2021). Nevertheless, results of urinalysis or biospecimens related to known Lipedema patients may be available in medical records and amenable to secondary analysis. Urine may be collected as part of clinical care (Foeldi, 2008; Tiwari et al., 2006, 2003), and may also be associated with extant biorepositories (e.g., UK Biobank)(Munguia et al., 2021).

The role of sex hormones could be informed by evaluation of rare cases of Lipedema in men, which are limited to case reports in published literature (Bano et al., 2010; Bertlich et al., 2021; Cadart et al., 2021; Chen et al., 2004; Child et al., 2010; Fife et al., 2010; Herbst et al., 2015; Pereira de Godoy et al., 2022;

Wold et al., 1951). Development of male Lipedema has been attributed to altered sex hormone levels in several reviews (Al-Ghadban et al., 2021; Katzer et al., 2021; Szél et al., 2014). The case reports that support this include citation of unpublished data in a group of four males for whom individuals were reported to show signs of hormonal dysregulation including hypogonadism and gynecomastia. Two individuals from this series were described as ‘testosterone-depleted’ (Child et al., 2010). A separately reported case ascribed “secondary hypogonadism” in a single male (Herbst et al., 2015). However, testosterone and free T4 levels were reported at normal values when measured in a male with Lipedema presumably due to POU1F1/PIT-1 mutation (Bano et al., 2010). Two cases of Lipedema in men with Klinefelter syndrome (XXY) have been reported wherein low testosterone levels were recorded. One case initiated hormone replacement, but no improvement in the Lipedema was seen at one year (Cadart et al., 2021). Lipedema like features may also be evident in both men and women with Williams Syndrome, though an evaluation of hormonal levels has not been reported (Waxler et al., 2017).

Despite the rarity in published research, male Lipedema-like signs and symptoms could be underreported. Because the current diagnostic criteria rely heavily on disproportionate mass accumulation, males with a greater predisposition towards visceral adipose tissue accumulations may be less likely to be identified as Lipedema-like. In the Lipedema Foundation Patient Registry report, 6-7% of women with Lipedema suspect the presence of Lipedema-like features in genetically-related male siblings (Lipedema Foundation, 2022a), though a recent pedigree analysis including fathers and grandfathers did not report similar findings (Hamatschek et al., 2022).

Interventions causing hormonal change have also been implicated in initiating Lipedema. Approximately 2%-4% of patients report onset of symptoms coincident with beginning oral contraceptives (Fetzer and Fetzer, 2014; I. Forner-Cordero et al., 2021; Ghods et al., 2020; Lipedema Foundation, 2022a). Clinical experience linking poor surgical outcomes to hormonal contraceptive use has also been reported (Sandhofer et al., 2017). An unpublished increase in Lipedema after cranial trauma and pituitary adenoma surgical correction has also been reported (Földi and Földi, 2006). Onset of Lipedema following gynecological surgery has been suggested in some cases (Allen et al., 2020; Fetzer and Fetzer, 2014). Despite this, bilateral oophorectomy has been shown to be associated with weight gain, but not increases in Waist to Hip Ratio (WHR) or SAT accumulation (e.g., (McCarthy et al., 2013)). A study of 552 cancer free women following both hysterectomy and oophorectomy, suggested that while increased total fat mass and decreased total lean mass were associated with surgery, these changes were distributed across anatomical areas, though this study was not specific to a Lipedema population (Karia et al., 2021). In addition, the influence of dietary estrogens and phytoestrogens, and any influence of microbiota (Ehrlich et al., 2017) have not been reported in Lipedema.

No Lipedema specific study of adverse events associated with hormonal interventions (e.g., longitudinal studies of oral contraceptive use, or recipients of Gender Affirming Hormonal Therapy (GAHT)) currently exists. Such a study might serve to refine consideration of hormone based triggering events and might predict an initiation cohort of women at artificially higher risk for developing Lipedema.

Adipose and the Development of Nodules and Textural Changes

Lipedema appears as a bilateral and symmetric accumulation of mass, that generally appears disproportionately distributed to the lower half of the body, though many women with Lipedema will show overt evidence of upper arm involvement, variously reported as 24-90% (Ghods et al., 2020;

Herbst, 2012; Herbst et al., 2015; Herpertz, 1997; Kruppa et al., 2022; Lipedema Foundation, 2022a; Wollina and Heinig, 2019). Lipedema, in the absence of comorbidity, is generally described as sparing of the hands and feet (Wold et al., 1951) which can result in a cuff or collar appearance at the ankle and wrist (Brunner, 1969; Schmitz, 1980). Evidence exists in both patient report (Lipedema Foundation, 2022a) and medical literature (Herbst et al., 2015) documenting Lipedema-like signs and symptoms, especially nodular structures, in all areas of the body, albeit at considerably lower frequencies than found in thigh, buttocks, and upper arms. While the systemic impacts of Lipedema has not been thoroughly evaluated, the recent observation of increased preadipocyte determination factor, ZNF423, has been reported in abdominal endothelial cells derived from people with Lipedema (Strohmeier et al., 2022).

Accumulation at specific sites has also been demonstrated as prominent malleolar fat-pads or a loss of sulci lateral to the Achilles tendon (Marshall and Schwahn-Schreiber, 2011; Rudkin and Miller, 1994; Wold et al., 1951; Wounds UK, 2017). Accumulation of adipose in the medio-posterior knee has also been demonstrated to associate with Lipedema (Brunner, 1982; Stallworth, 1974; Unlu and Kartal, 2018; Wollina et al., 2014; Wounds UK, 2017) and may be specifically associated with pain on palpation (Stallworth, 1974).

Since its earliest description, Lipedema has been associated with changes in the subcutaneous adipose tissue (SAT) (Allen and Hines, 1940; Rank and Wong, 1966; Wold et al., 1951), which is generally considered less associated with hypertension and insulin resistance risk than accumulation of visceral adipose tissue (VAT) (Fox et al., 2007; Scheuer et al., 2015). SAT accumulation is, however, associated with adipose disorders involving pain (Foeldi and Foeldi, 2010; Herbst, 2019; Lemaitre et al., 2021). And more generally, Lipedema affected adipose has been described as bloodier than unaffected adipose depots (Ishaq et al., 2021), which may account, in part, for anecdotal descriptions of distinct odors to Lipedema adipose apparent during surgery.

Most, but not all, diagnostic criteria and studies addressing weight loss report a resistance to dietary and exercise interventions. Similarly, outcomes of bariatric surgery may demonstrate reduction of total fat mass, but this loss of mass is less likely to reduce volume in affected areas, or other symptoms such as pain (Bast et al., 2016; Cornely et al., 2022; Wounds UK, 2017).

Those that caveat these observations may attribute successful weight loss to the loss of otherwise normal excess adipose (e.g., obesity) (Bertsch and Erbacher, 2020; Reich-Schupke et al., 2017). An understanding of the pathophysiological differences between tissue with lipedema and otherwise healthy adipose remains a significant gap in our research understanding, despite recent progress characterizing the molecular and cellular differences between the two tissue types (Al-Ghadban et al., 2019; Felmerer et al., 2020a).

Imaging studies demonstrate enlargement of the SAT and thickened skin in affected areas. More recent work has provided more detailed understanding of the manner by which distribution of adipose differs from that of Body Mass Index (BMI)-matched controls, revealing highest SAT volume to muscle volume ratios in the mid-thigh (Crescenzi et al., 2020, 2018; Taylor et al., 2023) and (Åström et al., 2001) – unavailable for review). Body composition measurements of android to gynoid fat mass, and leg to trunk fat mass have been evaluated by dual-energy X-ray absorptiometry (DEXA). In a study of 49 women with Lipedema, significant differences relative to BMI matched controls were reported for low BMI individuals (Dietzel et al., 2015). A separate study of 74 women with Lipedema, suggested exclusion of

Lipedema from consideration in differential diagnosis may be supported at high sensitivity the ratio of leg fat mass to total fat mass calculated from DEXA is less than 0.38 (Buso et al., 2022). Stromal Vascular Fraction (SVF) yield following liposuction has also been reported to be greater in people with Lipedema than control populations (Priglinger et al., 2017).

In healthy tissue, adipose cells are arranged in lobules, and delineated from other lobules by collagen-rich and elastin-rich fibrous septa, with fibrogenic and adipogenic progenitor cells distributed through both the somatic and septal compartments (Estève et al., 2019). Subcutaneous adipose tissue (SAT) is likely to contain fewer cells, and is less enervated than Visceral Adipose Tissue (VAT), but may be more densely populated by capillaries and exhibit greater potential for vascular remodeling (Gealekman et al., 2011; Redondo et al., 2020). The lymphatic network accompanying lobules may display depot specific architecture. SAT has been reported to be sparsely populated with lymphatic capillaries with little continuity to the more developed lymphatic network of the adjacent dermis (Redondo et al., 2020).

The histology of Lipedema-affected adipose is relatively limited. Lipedema adipose is generally described as fibrotic masses consisting of hypertrophic adipocytes that may show signs of infiltration by numerous capillaries, monocytes, and tissue mast-cells (Table B2. Histology Characterization in Lipedema).

Several specific questions complicate the interpretation of this literature. While some recent studies have provided high quality experimental data, many of the frequently cited works are single patient case reports, or individual panels used for illustrative purposes in literature reviews. In many cases the reports lack description of anatomical position, or the depth of the biopsy (see Figure A1 for tissue architecture).

These concerns aside, a limited number of publications offer perspective on the tissue architecture, details of which are presented in Table B2 and summarized as a thickening of both the dermis and the SAT along with increased fibrosis. The expansion of the SAT is typically reported as influenced by hypertrophic increases in cell diameter in both SAT and VAT (see, in particular, Al-Ghadban et al., 2019; Felmerer et al., 2020a; Von Atzigen et al., 2023; Wolf et al., 2021). Adipogenesis may also contribute to mass increases, based on direct visualization of increased adipose progenitor markers and cell cycle regulators such as CD34, ZNF423, ZIC1, UGT1A7, GREM1, TRIM67, Bub1 in biopsied tissue and SVF (Ishaq et al., 2021; Strohmeier et al., 2022). Adipose Stem Cell (ASC) derived from the thighs and abdomens from study participants with Lipedema (Al-Ghadban et al., 2020; Priglinger et al., 2017) have also been demonstrated to have higher proliferations rates than those derived from controls (Al-Ghadban et al., 2020). Such differences may be evident even in ASC derived from lean women with Lipedema (Ernst et al., 2023). Similar ASC reports have implicated increases in the cell cycle regulator, BUB1, as a potentially contributor to pathologic adipogenesis (Ishaq et al., 2021). An important consideration of such a proliferative environment would be to examine the developmental plasticity of resident cells. Evidence of calcium deposition has been reported (Ignjatović and Cerović, 1999; Pavlov-Dolijanovic et al., 2014; Taylor et al., 2004), and might suggest the possibility of a previously unknown osteosis phenotype in Lipedema affected adipose. Such a phenotype would be consistent with consideration of Lipedema affected adipose as a benign tumor and might inspire biomarker approaches ranging from cell cycle regulators as described above to telomere length testing.

Ongoing work to study the relative contributions of hypertrophy and hyperplasia in vivo, are likely to help clarify this aspect of Lipedema pathology and may suggest exploitable mechanisms for future therapeutics.

Many lingering questions remain. The degree to which sex hormone influences on Lipedema initiation affect adipose is unknown (Reviewed in Al-Ghadban et al., 2021; Katzer et al., 2021; Szél et al., 2014). One suggested hypothesis is that normal healthy adipose is mechanically constrained by fibrous septa. Fibrolytic pathways dependent on both estrogen receptor alpha (ER- α) and matrix metalloproteinase 14 might be perturbed in Lipedema, causing remodeling of the septa and providing a model for hormone influenced adipose tissue hypertrophy (Kruglikov et al., 2020). A common sign of Lipedema is occurrence of rigid nodular structures, described more fully in other portions of this document. A significant gap in the available literature is the lack of systematic attention paid to characterizing these prominent features both in terms of their frequency with SAT or DAT, and histological and molecular descriptions. Similar descriptions of intramuscular or perivascular adipose are not well-characterized in the literature in either the leg or in other areas of the body.

While immunohistochemical approaches to documenting candidate molecules will continue to play a role in characterizing Lipedema specimens, there is a strong need for unbiased assessments. Approaches such as single cell transcriptomics may pay significant dividends in cataloging types and activities of cells found in affected adipose.

Immune Influences on Symptoms

Immune contributions to Lipedema are relatively unclear, though implicated by observations such as increased tissue sodium (Crescenzi et al., 2020, 2018), and immune-related common comorbidities. Several studies have demonstrated macrophages resident to Lipedema affected adipose (Al-Ghadban et al., 2019; Felmerer et al., 2020b; Ishaq et al., 2021; Strößenreuther and Baumeister, 2001), and possibly proximal to areas of adipose necrosis (Suga et al., 2009). In one study, macrophages were not broadly distributed, but may have increased presence proximal to blood vessels, consistent with a leaky vessel hypothesis (Strohmeier et al., 2022). Increased expression of CD163 in Lipedema samples suggests polarization of macrophages to an M2 phenotype and a role in hemoglobin scavenging, which is consistent with increased vascular permeability, and release of anti-inflammatory cytokines (Felmerer et al., 2020b). A single report of a foamy lymph node, proximal to Lipedema affected adipose, is similarly suggestive of mobilization of macrophages (Ketterings, 1988).

Mast cell involvement in Lipedema has been observed by histology (Strößenreuther and Baumeister, 2001), including as CD117 positive cells in biopsied SAT (Al-Ghadban et al., 2019). A functional role for mast cells is speculative, but may be related to angiogenesis and remodeling of adipose (Divoux et al., 2012). As mast cells are typically responsive to bacterial infection, the recent hypothesis that bacteria derived lipopolysaccharides (LPS) in gluteofemoral white adipose tissue might stimulate a range of features consistent with Lipedema, including fibrosis and adipogenesis would also be consistent with mast cell recruitment to the same area (Kruglikov and Scherer, 2022). Lower levels of progesterone receptors on tissue resident mast cells in Lipedema have been observed, prompting a hypothesis that histamine release could affect local vascular permeability (Rosas et al., 2018)

Edema and Symptoms Related to Swelling

The role of the lymphatic system has proven challenging to understand as it relates to Lipedema. Various signs and symptoms associated with edema are widely reported both in LF's patient registry, surveys, and in research studies (Table B1).

Clinically, a positive Stemmer sign has been associated with lymphedema (Stemmer, 1976). In this test, an inability to pinch the dorsum of the second or third toe is associated with lymphedema. A negative Stemmer sign is associated with a sparing of symptoms from the hands and feet and is frequently observed in association with Lipedema, though increased adiposity, fibrosis, and consequent lymphostasis may result in development of a positive Stemmer sign in later stage Lipedema patients (Földi et al., 1983), reviewed in (Kruppa et al., 2020).

The association of edema itself to Lipedema was documented in the original description of the condition (Allen and Hines, 1940), which placed enough importance on association to orthostatic edema as to warrant inclusion of this symptom in the title of the original paper. At the time of the original characterization of Lipedema, orthostatic edema was defined without reference to origin of fluid accumulation, and was considered related to a broader class of physiologic edema such as those related to venous compression during pregnancy as well as occlusive arterial diseases (Casanueva del Campo, 1950; Fairbairn, 1963). Streeten tests for edema due to capillary permeability have reported fluid retention in all stages of Lipedema, consistent with orthostatic edema (Foeldi, 2008; Forner-Cordero et al., 2012; Streeten, 1995; Szolnoky, 2011). Analysis of orthostatic edema with comparison between upper and lower extremities has not been reported in a Lipedema population.

Today, the presence or absence of edema in Lipedema is routinely debated. Some nuances of this debate may reflect semantic differences. Some authors may consider clinically significant fluid accumulation as the threshold for edema classification. This is in contrast to the pathogenetic perspective that any noteworthy accumulation of fluid should be considered as edema, whether or not it represents an indication for clinical intervention. This is tacitly acknowledged in one German language clinical review, that specifies that “[Leg swelling that does not present accumulation of water in the strict sense of the definition of edema is Lipedema]” (Ludwig and Vetter, 1989). Similarly, specificity of whether fluid accumulation may be a consequence of failures of capillary hydrostatic pressure, lymphatic function, or permeability-related edema (Scallan et al., 2010) may help to provide common ground to this debate. Finally, specificity between dermal and adipose confined edema represents a third axis by which this debate should be considered. For the purposes of this review, any ectopic fluid of any origin in proximity to Lipedema-affected adipose depots is considered worthy of remark and may support future hypothesis driven inquiry.

Clinical signs of edema in the context of Lipedema make reference to non-pitting edema (Allen and Hines, 1940; Wold et al., 1951), or use terms like “jelly-like/ sulzige Lipödem” (Ludwig and Vetter, 1989) to distinguish Lipedema fluid exam from that of lymphedema. Importantly, most of the frequently cited criteria for the Lipedema diagnosis allow for “minimal pitting edema” (Allen and Hines, 1940; Buck and Herbst, 2016; Halk and Damstra, 2017; Karen L Herbst et al., 2021; Reich-Schupke et al., 2017; Wold et al., 1951; Wounds UK, 2017). Guidelines that do not allow for any edema suggest that the presence of any edema is likely (Alcolea et al., 2018) or exclusively (Bertsch and Erbacher, 2020) comorbid and not associated with the “pure” Lipedema diagnosis. Patients commonly report a sensation of swelling and heaviness (reviewed below) that has been suggested as supportive of an underlying edema. This was recently compared to clinical measurements of thigh circumferences, in which the study authors failed to demonstrate statistical correlation between patient report and measurement (Erbacher et al., 2022). In this study, the relationship of circumference to circle area would suggest that the 11% variance in circumferential measurements would minimally imply that the study would have difficulty detecting

volume changes less than approximately 30%. It remains uncertain what change in limb volume is necessary to evoke sensations of swelling.

The existence of edema would suggest a mechanism for progression of Lipedema. In this scenario, a primary insult resulting in either adipose proliferation or lymphatic deficits would support a positive feedback loop whereby excess lymphatic fluid induces adipose remodeling that further perturbs local lymphatic structure (Kataru et al., 2020; Zampell et al., 2012), and has been suggested in Lipedema literature, for example (Földi and Földi, 1984; Herpertz, 1995). Alternative hypotheses have proposed that mechanical forces imposed by increased adipose volume may cause mechanical restriction of existing lymphatics (Damstra, 2013; Langendoen et al., 2009; Shin et al., 2011). Such stochastic events might contribute to the explanation of phenomenon in which the bilaterally symmetric accumulation of adipose might allow for asymmetric development of lymphatic abnormalities (e.g., Bilancini et al., 1995; Gould et al., 2020; Kinmonth, 1982). More recently, evidence of local inflammation in Lipedema affected adipose offer plausible scenarios under which tissue destruction and fluid accumulation might occur (Al-Ghadban et al., 2019; Felmerer et al., 2020b, 2020a; Ishaq et al., 2021; Strohmeier et al., 2022; Strößenreuther and Baumeister, 2001).

Evaluations of the lymphatic structure and function have been equivocating as to whether detectable changes should be considered incidental or intrinsic to the pathogenesis of Lipedema (Table B3. Structure and Function of Lymphatic Involvement in Lipedema). The preponderance of studies, however, suggests the possibility of an edema phenotype associated with Lipedema either as a primary or secondary effect.

Structurally, a recent retrospective study of ICG lymphangiographic images representing 40 women with Lipedema returned no significant structural finding in 85% of cases (Mackie et al., 2023). However, recent MR lymphangiographic data is consistent with the presence of edema in Lipedema-affected thighs and demonstrates patterns of accumulation that may be distinct from morbid obesity or lower extremity lymphedema secondary to oncology treatments. Recent blinded analysis of MR lymphangiography data reported characteristic hyperintense signals in the SAT of Lipedema patients as compared to females without lipedema (controls), including lymphedema. These results were similar in both women with and without a lymphedema diagnosis, suggesting a profile of subcutaneous edema that is unique to Lipedema (Crescenzi et al., 2022). This technique has advantages over traditional lymphangiographic techniques in that it is less susceptible to signal attenuation in deep tissues. This technique is less reliant on tracer perfusion, and not subject to toxicities or venous leakage that complicate usage of tracers such as gadolinium (Mazzei et al., 2017).

Histological assessment of lymphatic structure has inconsistently correlated perturbations of microvascular and lymphatic structure to Lipedema. Early evidence suggested dilation of vascular structures and localized fibrosis (Curri, 1984; Curri and Merlen, 1986). Recent immunohistochemical approaches have been inconsistent in replicating these findings. Demonstration of increased lymphatic vessel diameter, hypervascularity and dilatation of blood vessels infiltrating Lipedema affected adipose (Al-Ghadban et al., 2019; Allen et al., 2020) was not reported in similar analyses of vessel number and area (Felmerer et al., 2020b; Strohmeier et al., 2022; Von Atzigen et al., 2023). These latter reports were, however, suggestive of increased endothelial permeability, as evidenced by macrophage infiltration and morphological and functional changes to endothelial junctions. Conditioned media from Lipedema stromal vascular fraction has, additionally, been shown capable of inducing remodeling of

endothelial junctions (Strohmeier et al., 2022). Enlarged interfibrillar spaces have also been used as a proxy measurement for interstitial fluid accumulation and reported to be of larger volume in women with Lipedema compared to non-Lipedema controls (Allen et al., 2020). This has contributed to the hypothesis that edematous fluid from leaking capillaries may be ionically bound to glycosaminoglycans in the interstitial space, though this has not yet been experimentally tested, but should be amenable to many approaches including mass spectrometry (Herbst, 2020).

Analysis of human Lipedema tissues revealed a reduction of superficial lymphatics with the presence of deep lymphatic vessels surrounding the infiltrating fat in the dermis. The reduction of superficial lymphatics was associated with a reduction of Notch4 expression in the dermal lymphatics (Muley et al., 2021 and unpublished data). The suggestion of Platelet Factor 4 expression in people with Lipedema independent of comorbid obesity, though complicated by comparison to male controls, is also consistent with the presence of lymphatic impairments and deserving of follow-up (Ma et al., 2020). Characterization of lymphatic endothelial junctional connections has not been reported, but perturbation of zipper and button architecture is known to be associated with lymphatic impairment mouse models and human disease (Baluk and McDonald, 2022; Hägerling et al., 2018; Zhang et al., 2020), and may be suggested by studies of HUVEC cells exposed to Lipedema SVF conditioned media (Strohmeier et al., 2022). The cytokine rich environment of inflamed adipose is, likewise, consistent with expansion of local lymphatic network (Chakraborty et al., 2020).

Additional indirect evidence of fluid accumulation is implied by evidence of tissue sodium accumulation in calf skin and muscle in a manner correlated to pain and Lipedema stage (Crescenzi et al., 2020, 2018). Bioimpedance studies have also suggested that water content in legs with lipedema increases with Lipedema stage, and differs from water content in other adipose disorders (Dercum's disease) (Crescenzi et al., 2019). While it remains unclear what role or marker function might be suggested by elevated sodium, the demonstration of elevated sodium is evocative of patient observations that high sodium meals can lead to temporary exacerbation of symptoms. If supported by further research, therapeutic management of sodium offers an exciting hypothesis for study, as pharmacological and behavioral interventions are well-established, as are novel and minimally invasive opportunities for continuous monitoring of sodium (Bandodkar et al., 2014).

Taken together, these findings are evocative of the prelymphatic collector deficits and hyperpermeability of capillaries suggested in earlier works. Under this hypothesis, microstructural pathologies might increase fluid volume in the prelymphatic space, exceeding the capacity for local drainage (Brauer and Brauer, 2005; Curri and Merlen, 1986; Földi et al., 1983; Lohrmann et al., 2009; Partsch et al., 1988). To date, however, the only published Genome Wide Association Study (GWAS) for Lipedema, did not suggest association of any loci clearly suggestive of a primary role for the lymphatic system in Lipedema.

Lymphatic function has been separately addressed (Table B3) by numerous studies. Recent near infrared fluorescence lymphatic imaging (NIRFLI) of upper and lower limbs reported dilation of lymphatic vessels, and significantly higher lymphatic pumping rates than matched controls (Rasmussen et al., 2022), reminiscent of higher lymph flow reported in early studies (Ketterings, 1988). Radiographic evidence consistent with a Tertiary Lymphatic Organ (TLO), and similar to those seen in rheumatic conditions, was also reported in the NIRFLI study. These results suggest the possibility of compensatory changes to lymphatic function in early-stage Lipedema. Further exploration of these findings across Lipedema

stages is likely warranted, as therapeutic modifiers of lymphatic function are currently being developed. If lymphatic function is affected in a stage dependent manner, the safety of such therapies would be informed by these studies.

Additional alternative hypotheses also leave the door open for further study of edema in Lipedema. As tracer-based imaging modalities require injection of tracer, often to the foot, consideration of the location and depth of the injection is worthwhile. Interdigital injections have been reported to preferentially drain to anteromedial vessels. These vessels may be different in size, and be subject to differential utilization dependent on fluid loading (Shinaoka et al., 2020, 2019). Similarly, depth of injection may result in differential routing of tracer. Thus, the most common tools for clinical study of lymphatic structure and function may exhibit 'blind spots', especially in posterior and deeper lymphatics that may not be connected to the superficial lymphatic system (Barbieux et al., 2019). Though requiring replication, it is noteworthy that a single Lipedema cadaver study reported enlarged short saphenous vein and increased perivascular adipose (Caggiati, 2001; presented by Simarro, 2022). Because Lipedema is generally characterized as preferentially sparing of hands and feet, how differential utilization of lymphatic drainage pathways might account for this phenomenon is unreported in primary data.

The issue today is likely not to involve the question of whether lymphatic perturbation is associated with Lipedema, as the weight of the data emerging from prospective and statistically robust studies suggests this association strongly. More important to future therapeutics will be the answer to whether that disturbance is primary or secondary to the as-yet unknown mechanisms that initiate or maintain Lipedema. If primary, it will be important to consider potential systemic effects that might account for common comorbidities. Such future studies will need to pay careful attention to the above issues to allow comparison between studies. Recommendations in this include specific attention to the location and time to observation of tracer studies, and controls for both Lipedema stage and participant age. Future functional studies are also warranted and may help to understand whether measures of pump strength, synchrony, or other measures of lymphatic function might reveal distinct Lipedema-associated patterns.

Neural Involvement and Pain

Pain is not required in most published diagnostic criteria, though it is emphasized above other symptoms in some (Damstra et al., 2014; Lipedema Foundation, 2022b). Some contemporary clinical practices do require pain upon palpation of the thigh or inner knee for a Lipedema diagnosis. In other practices, pain is usually, but not always, associated with Lipedema, unlike obesity and lymphedema. For purposes of this review, pain is not considered a requirement for the Lipedema diagnosis, due to the variability of reporting of pain in the available literature, and the semantic conundrum imposed when pain is therapeutically remedied (i.e., if a non-disease modifying treatment eliminates pain, is Lipedema therefore cured?)

Onset of pain is poorly understood and complicated by varying terminology. In some literature, lipohypertrophy is considered a related or pre-Lipedema state in which adipose proliferates symmetrically, but is not associated with edema or pain (Bertsch and Erbacher, 2020; Brenner, 2005; Cornely, 2006; Herpertz, 1993; Von Atzigen et al., 2023). Recent reports that lipohypertrophic tissue has a different lymphatic and immune profile to Lipedema led authors to suggest that lipohypertrophy may be a clinically distinct entity from Lipedema (Von Atzigen et al., 2023). Adding to confusion, some

subtypes of lipohypertrophy have been described as associated with pain (Szolnoky, 2011). Other literature does not make the distinction of a pain free prodromal stage (Karen L Herbst et al., 2021). The disparity between these two schools of thought is likely to diminish by the introduction of robust screening or diagnostic biomarkers, which may transform future approaches to Lipedema staging.

Estimations of the penetrance of the pain phenotype ranges dramatically. Original descriptions documented pain in 40% of patients (Wold et al., 1951) while more recent evaluations detected pain in up to 92% of patients (Forner-Cordero et al., 2018; Isabel Forner-Cordero et al., 2021; Herbst et al., 2015) (Table B1). More than half of patients categorized pain as severe or extremely severe in one study of Lipedema symptoms (Dudek et al., 2016). Prevalence of pain increases with disease stage, severity, or age (Allen and Hines, 1940; Chakraborty et al., 2022; Falck et al., 2022; Herbst et al., 2015), which could explain failure to detect pain in some study populations.

Lipedema associated pain is typically reported by patients as a function of intensity using Visual Analogue Scale (VAS) or similar unidimensional measurements. Some use of pain specific instruments has been reported (Chakraborty et al., 2022). Several reports have provided narrative descriptions of pain which confirm Lipedema pain as a multi-dimensional construct. Pain quality may differ by patient or over time (Melander et al., 2021; Schmeller and Meier-Vollrath, 2008). Multiple efforts have cataloged various descriptions of pain highlighting sensations such as “dull”, “pressing”, “throbbing”, “tearing” or “nagging” as being most applicable, but with many patients describing their pain as sharp or piercing as well (Gensior and Cornely, 2019; Schmeller and Meier-Vollrath, 2008). Such descriptors may vary by stage or duration of disease, with radiating pain, stinging sensations, and allodynia described as temperature sensitivity or sensitivity to light touch being less common in earlier stages (Chakraborty et al., 2022). Pain perception may change throughout the day, has been reported to peak in evenings (Gensior and Cornely, 2019), and bears similarity to other chronic neuropathic pain conditions (Angst et al., 2020a; Grigoriadis et al., 2022)

Understanding of how pain is perceived in terms of intensity or quality, and how it interferes in patient lives, may help bring greater clarity to the utility in using pain as clinical endpoints in future research studies.

When present, pain may allow differentiation of Lipedema from other conditions. Cross-sectional validity of Patient Reported Outcomes Measures (PROM) designed to broadly address many domains of health-related quality of life (hrQOL) have been reported and have reported discriminant validity for pain relative to other conditions like lymphedema. These include the FLQA-LS physical complaints construct and SF-36 bodily pain construct (Angst et al., 2020b). Such results may not be as robust in other practices, as the authors' Lipedema diagnosis appears to have required pain. Dutch language versions of Rand-36 and EQ-5D-3L have separately been observed to differentiate between the general Dutch female population and Dutch women with Lipedema (Romeijn et al., 2018). An evaluation of this approach in a population diagnosed under other diagnostic criteria, or supported by a future biomarker, represents a gap in the available literature.

To date, no PROM for pain has been examined specifically in a Lipedema population, nor have minimal clinically important differences (MCID) been defined. Such studies would be important to allow interpretation of pain related PROM data in current and future Lipedema clinical studies.

Understanding the biological origin of pain in Lipedema is fundamental to providing therapies that durably control this symptom. Dermal neuronal loss has been reported in the abdomen of people with Lipedema, along with a progressive decrease in neuropeptides CGRP and NGF independent of BMI in thighs and abdomen (Chakraborty et al., 2022). Follow-up experiments in the same study, observed stage dependent mechanical allodynia in calves, arms, and thighs and were suggestive of a systemic Lipedema phenotype. A single study of three related women diagnosed with a pain-free Lipedema, has been reported, and identified an AKR1C1 mutation associated with the women, hypothesizing a GABAergic analgesic effect (Michelini et al., 2020).

Nerve conductance tests have not been systematically evaluated, but are provided in two case studies which reported a reduced amplitude of motor nerve action potentials in the sural and peroneal nerves, but no deficit in nerve conduction velocity or latency (Shin et al., 2011). From this a A β and CT-fiber mediated pain phenotype has been hypothesized (Brenner, 2017). A mechanical origin of pain in which nerve fibers become compressed by swelling or fibrosis remains attractive, but difficult to reconcile with the lack of pain in other adipose disorders. (Langendoen et al., 2009).

An inflammatory influence on pain has been frequently suggested, though until recently had been considered largely speculative. Identification of both pain dependent increases in tissue sodium, and decreases in specific neuropeptides involved in neuroinflammation have now been reported (Chakraborty et al., 2022; Crescenzi et al., 2020, 2018) and offer indirect support of an immune origin to nociceptive hypersensitization phenotype in Lipedema.

Therapeutic reduction of pain has been reported following conservative treatments including manual lymphatic drainage (Atan and Bahar-Özdemir, 2021; Donahue et al., 2022; Herbst et al., 2017; Schneider, 2020; Stallworth, 1974; Szolnoky et al., 2011; Volkan-Yazıcı et al., 2021), liposuction (Baumgartner et al., 2020, 2016; Dadras et al., 2017; Rapprich et al., 2011; Schmeller et al., 2012; Wollina and Heinig, 2019), and dietary interventions (Apkhanova et al., 2021; Cannataro et al., 2021; Di Renzo et al., 2021; Sørliie et al., 2021).

Biological Drivers of Tissue Textural and Elasticity Changes

Guidelines for clinical diagnosis frequently evoke clinically observable tissue texture changes as a common sign and symptom of Lipedema. Though original publications did not directly address deep 'nodular' textures, they reported a 'soft and pliable' quality to the skin (Allen and Hines, 1940). Later, descriptors such as translucency and "pseudo-peau d'orange" (Rank and Wong, 1966) or even "pig skin appearance" (Stallworth, 1974) were used to describe the surface appearance of patients' skin. These terms formed the original basis for a staging system relating severity of the condition to the size of subsurface textural irregularities (described below). The term 'nodule' may be misleading, as the term is often used to describe lipomas which, while similarly formed from expansion of adipose, are generally encapsulated. Although Lipedema 'nodules' have not been thoroughly examined histologically and molecularly, observations suggest there is no encapsulation of Lipedema 'nodules'.

To date, no study has precisely associated a "nodule" known to the patient and clinician by palpation, with a specific structure visible by typical imaging modalities or histology. Thus, a precise description of nodules is largely unknown, despite being a prominent feature for many women.

Tissue texture is related to the extracellular environment, including fascia. The effect of Lipedema on superficial and deep fascial organization is not published, but some ultrasound evidence has suggested that fascia may be discontinuous (Cestari, 2023; Iker, 2022) or dysmorphic (Sandhofer et al., 2017).

Various changes to the skin have been reported including translucency (Rank and Wong, 1966), thickening (e.g., Amato et al., 2021; Iker et al., 2019; Naouri et al., 2010; Unlu and Kartal, 2018; Von Atzigen et al., 2023) or increases in skin elasticity (Jagtman et al., 1984; Stallworth, 1974). More recent skin durometry tests in a mixed stage cohort have not replicated these findings (Zaleska et al., 2022), and the observation of skin thickening would seem at odds with reduced tone or translucency, and indeed was not found in one histological report (Strohmeier et al., 2022).

Proximity to dermal structures, such as sweat glands and hair follicles, offers opportunity for careful analysis of dermatological impact of Lipedema, potentially exploitable for screening or diagnosis. Hair loss has been reported in more than half of patients with stage 3 Lipedema (Herbst et al., 2015), and is known to be associated with some primary lymphedemas (Irrthum et al., 2003). The skin's role as a mediator of water and Na⁺/K⁺ homeostasis has been implicated in peripheral vascular resistance and formation of pro-inflammatory environments (Jobin et al., 2021; Rossitto and Delles, 2022). Loss of muscular strength has also been reported in animal models in which the skin's barrier function is impaired (Wild et al., 2021). Notably, observance of dermal tissue sodium accumulation has been reported in Lipedema (Crescenzi et al., 2020) and lymphedema.

Lipedematous alopecia and lipedematous scalp are rare disorders of expanding adipose specifically in the scalp and associated with pain. Like Lipedema, they appear to be sex limited to women. While there is currently no epidemiological or biological mechanism to associate Lipedema and lipedematous scalp, neither has been systematically evaluated for its prevalence in the other condition, though case reports suggest at least occasional comorbidity between the two conditions (El Darouti et al., 2007; Safar and George, 2021).

Hypermobility of joints is frequently associated with Lipedema, along with fallen arches, and may be consistent with patient reports of arthritis, effusion, and of joint pain, especially in the knees (Fetzer and Fetzer, 2014; Harwood et al., 1996; Herbst et al., 2015; Ketterings, 1988; Lipedema Foundation, 2022a; Torre et al., 2018).

Vascular Fragility and Potential Vascular Issues

Capillary fragility is commonly associated with Lipedema as tendency to form hematomas and is expressed as a potential symptom in several diagnostic criteria (Lipedema Foundation, 2022b). Direct measurement of capillary fragility is non-trivial as most assessments require injury to the patient, complicating human welfare in research considerations. Vacuum based angiosterrometry has been employed in a small number of studies supporting the hypothesis that Lipedema capillaries are more fragile than capillaries of obese individuals (Szolnokoy et al., 2017, 2008). An observation that Lipedema affected adipose depots are 'bloodier' than non-affected adipose has also been suggested (Ishaq et al., 2021).

Telangiectasia have been reported in Lipedema patients, but is not presently incorporated into any commonly cited diagnostic criteria (Buck and Herbst, 2016; Herbst et al., 2015; Kruppa and Ghods, 2022; Pavlov-Dolijanovic et al., 2014; Stallworth, 1974).

Skin hypothermia is frequently invoked, though difficult to substantiate in research studies. Recent use of infrared thermography in Lipedema may present opportunities to more carefully document this phenomenon (Sanchez-Jimenez et al., 2023). If present, this phenotype is consistent with vascular and immunological involvement detailed elsewhere (Bilancini et al., 1990; Buck and Herbst, 2016; Crescenzi et al., 2020; Kinmonth, 1982; Meier-Vollrath and Schmeller, 2004).

Circumstantial evidence for a coagulation defect may also be suggested by the implication of Platelet Factor 4 in a cohort of Lipedema and lymphatic conditions (Ma et al., 2020), but examination of people with Lipedema for evidence of such a thrombotic deficiency were inconclusive (Sucker et al., 2021).

Systemic vascular manifestations have been reported. Cerebral blood flow has been reported to be increased in people with Lipedema relative to age and sex matched controls (Petersen et al., 2020). A series of papers have provided evidence for aortic stiffening and dilation (Nemes et al., 2019, 2018, 2018; Nemes and Kormányos, 2022; Szolnoky et al., 2012) that may be phenocopied in Williams syndrome (Waxler et al., 2017). These papers suggest systemic Lipedema specific changes that, if confirmed by other groups, might be leveraged for consideration as a biomarker.

Lipedema Diagnosis – other features

Apart from canonical features, some features described by people with Lipedema have mixed adoption in published clinical criteria. Limb fatigue or a profound sensation of heaviness to the legs is frequently reported as associated with Lipedema, and has been shown to contribute to severity of depression (Dudek et al., 2021). Depression itself, along with anxiety and similar mental health disturbances, are addressed in all guidances, though the degree to which it is related mechanistically to Lipedema, is secondary to Lipedema, or is due to comorbidity has been debated. Attempts to localize onset of mental health concerns are difficult to execute as the possibility of several biases must be controlled. The degree to which determinants of hrQOL are mediated severity of depression has been modelled, and suggests interplay between pain, mobility, and sensations of leg heaviness and their interaction with depression are correlated to hrQOL (Dudek et al., 2021). Anxiety and challenges to emotional regulation have been reported as reduced performance on Difficulties in Emotion Regulation Scale (DERS) along with Anxiety was assessed by the Hamilton Anxiety Scale (HAM-A) (Al-Wardat et al., 2022).

Subjective complaints of attention, memory or fatigue (sometime called ‘brain fog’) are common to inflammatory conditions such as mast cell activation syndrome, fibromyalgia, or lupus (Theoharides, 2013). Though no specific study has been conducted on the prevalence of such complaints in Lipedema, the concept of brain fog is frequently invoked by people with Lipedema.

Frequent citation of increased rates of suicide attempts in Lipedema are thus far limited to unpublished data presented as a conference talk (Stutz, 2015) and should be cited with caution as a research finding. The alarming nature of the topic deserves careful evaluation in an experimental setting as it represents a significant claim on the individual and holds public health implications associable to a Lipedema diagnosis.

Several musculoskeletal issues have been associated with Lipedema. This has been variously reported to include genu valgum (“knock knees”), flat feet, gait disturbances, and arthritis (I. Forner-Cordero et al., 2021; Herbst et al., 2015; Wounds UK, 2017). Sacroiliac joint dysfunction has been suggested in a pooled

lymphedema and Lipedema population (Turhal et al., 2023). Deficiencies in muscle strength have been variously reported. People with Lipedema have shown specific loss of quadriceps strength without functional impairment in the 6 minute walk test compared to obesity controls (van Esch-Smeenge et al., 2017). Muscle weakness has also been observed in more than 50% of stage II-III Lipedema patients (Herbst et al., 2015). A single MRI study has suggested mild atrophy in the proximal thigh (Cellina et al., 2020). Range of motion impairments have been reported (Stutz, 2011), and presented in recent conference papers (Wright, 2022). Improvements in the understanding of the immune and metabolic status of Lipedema-affected tissue may shed light on whether any muscular deficits are primary or secondary consequences of the underlying Lipedema.

Staging and Types of Lipedema

Several efforts have been made to identify subtypes of Lipedema. These divisions can be summarized as efforts to describe Lipedema's progression or severity (stages) or diversity of presentation (types).

Lipedema is well known to present differently across different individuals (Table B1). Although Allen and Hines (Allen and Hines, 1940) provides the basis of what we consider to be Lipedema today, a subtype of Lipedema, type rusticanus Moncorps (Jagtman et al., 1984; Jagtman and Kuiper, 1987; Langendoen et al., 2009; Moncorps et al., 1940) was described contemporaneously. This variant was distinguished by cyanotic lower legs, including cinnabar spots, and hyperkeratosis, along with reduced skin elasticity (Jagtman et al., 1984), and of particular note because of an earlier childhood presentation. This "Moncorps type or rusticanus type Lipedema" was later described as being a distinct clinical condition, erythrocyanosis crurum puellarum, which is characterized by acrocyanosis with adipose proliferation in the absence of edema (Langendoen et al., 2009). The advent of biomarkers of Lipedema may offer a more precise means to describe any relationship between these presentations.

Other efforts to categorize Lipedema have included gross body shape, wherein otherwise slender women, with painful adipose accumulation in the upper leg, might be differentiated from women with prominent ankle cuffing, and both differentiated from rusticanus-type Lipedema (Bilancini et al., 1990; Schmitz, 1987). Other efforts have suggested categorization on the basis of overall lower body shape, distinguishing between a columnar leg, and a lobular (funnel-shaped) hip to ankle geometry (Fife et al., 2010; Földi and Földi, 2006; Gregl, 1987; Wounds UK, 2017).

Adipose depot specific descriptions have been used to differentiate types of Lipedema. Such "constitutional figure variations" (Strößenreuther and Baumeister, 2001, p. 42) were invoked to organize prior observations (Brunner, 1982). These efforts suggested that the morphologic diversity with which Lipedema presents might be categorized in five types, reflecting adipose location involvement. These include buttocks, pelvis and hips only (type 1)(Herbst, 2012) buttocks to knees (type 2), buttocks to ankles (type 3), arms only (type 4), lower leg only (type 5) (Meier-Vollrath and Schmeller, 2004). A separate typing system has also been suggested that differentiates upper and lower arm involvement in addition to the preceding types (Herpertz, 2001, 1995, 1993). Whether such Lipedema types correlate to specific symptoms or comorbidities has not been documented.

Such efforts to type Lipedema have some clinical use in recognition of Lipedema, and consideration of appropriate conservative treatments (e.g., compression garment fitting). A biological understanding of the basis for diversity of Lipedema's presentation is not understood. It, however, serves to strongly

reinforce notions that an understanding of individual variation, not limited to race or other genetic contributions, may influence how Lipedema appears in clinical encounters. It also points to a need in literature to consider individual variation when considering mobility or burden of illness, as patient perceptions of such measures may be influenced not only by 'severity' of the condition, but also inter-individual variations in presentation.

Efforts to understand progression or severity of Lipedema have emerged as a clinical staging system. Most contemporary efforts to stage Lipedema are based on size of palpable textures, and visually observable manifestations of these textural changes. An early two stage system (Földi and Földi, 1984) was later adapted to a three clinical stage system with a fourth stage reserved for Lipolymphedema (Strößenreuther and Baumeister, 2001). Comorbid lymphedema has, however, been documentable at any stage, and thus use of stage IV (lipolymphedema) may be uninformative (Fife et al., 2010; Wounds UK, 2017). A possibly prodromal stage characterized by lipohypertrophic changes preceding a Lipedema diagnosis is implied in this staging construct (Brenner, 2005; Cornely, 2005; Foeldi and Foeldi, 2010; Herpertz, 1997; Meier-Vollrath and Schmeller, 2004).

The ideas of progression of Lipedema, or its triggers, are poorly understood, but have been hypothesized to relate to adiposity, or as a consequence of surgery (Földi and Idiazabal, 2000). The conceptualization of Lipedema as a chronic and progressive condition is discounted by some authors as comorbid weight gain, and supported by absence of longitudinal BMI data in prior work, and select case studies (Bertsch and Erbacher, 2018). Other cases have been presented to the contrary (Sandhofer et al., 2020; Wright and Herbst, 2021a). Regression of adipose in the form of weight loss may be considered a parallel concept to progression. Caloric restriction through dietary or bariatric surgical interventions generally support the claim that subsequent mass reduction is preferential to truncal adipose, and less effective at promoting loss of mass in Lipedema-affected tissues (Bast et al., 2016; Cornely et al., 2022; Pouwels et al., 2019; Wright and Herbst, 2021b). Though these studies are generally small and requiring of follow up, difficulty in achieving weight loss in Lipedema affected tissues is widely reported in the patient community (Falck et al., 2022; Fetzer and Fetzer, 2014; Lipedema Foundation, 2022a; Melander et al., 2021).

It should also be noted that many women may never progress from early stages at all. Individual risk of progression by any definition or on any timescale is not currently predictable though aggregate data suggest that decade long transitions between stages is a common presentation (Herpertz, 2004; Lipedema Foundation, 2022a).

Resolution of the issue may not be possible within the current staging system, as the concept of stage challengingly conflates textural changes, with macroscopic observations related to generalized adiposity and BMI. This confounds attempts to experimentally disentangle healthy adiposity, obesity, and Lipedema. Alternatively, Lipedema stage might be considered as limited solely to the concept of textural changes or nodularity. In this construct, the progression through Lipedema stages would be self-evident. The refutation of this construct would require identification of a case in which a woman with high stage Lipedema had never experienced a point in her life in which she had fewer, or smaller sized, nodules!

While texture-based staging may correlate with total nodule count, and anatomical sites at which nodular structures can be found (Herbst et al., 2015), it does not generally correlate to presence or severity of other symptoms and comorbidities, notably pain, mobility, and quality of life (Reich-Schupke et al., 2017). A complementary staging system based on pain has been proposed (Schmeller and Meier-

Vollrath, 2008). Some reports of correlation of texture based staging to numbness, and presence of visible veins on legs have additionally been reported (Herbst et al., 2015).

Though the three stage system was developed to describe Lipedema across the body, some authors have begun using the three stage system to describe Lipedema related changes at specific anatomical sites; thus an affected arm may be of different stage than an affected leg (Hamatschek et al., 2022; Karen L Herbst et al., 2021; Kruppa et al., 2022). A clinical staging system accommodating anatomic region and pain has recently been proposed (Jandali et al., 2022, p. 52).

The future of Lipedema staging is an open question. British guidelines suggest the development of an outcome-based scoring system that would grade patients based on severity of several symptoms and benchmark the numerical score against simple summary terms such as “mild”, “moderate”, and “severe” (Alcolea et al., 2018; Wounds UK, 2017). Such an approach would have the explicit goal of clinical decision support for surgical and non-surgical management of Lipedema and would be analogous to other clinical rating scales (e.g., Prostate Cancer, or non-alcoholic fatty liver disease).

The degree of utility for evaluation of clinical research studies is, however, questionable. To date, no clinical or patient reported outcome measures have been formally validated in a Lipedema population, with input from that population. Thus, while such a rating scale may have substantial in-clinic value, it may remain more efficient to conduct clinical research using established measures for each domain of interest, validating these individually.

A complementary biomarker-based approach would replace morphological assessment of stage with measures of biological processes known to be disturbed in Lipedema. Such biomarker strategies need not be limited to a diagnostic or monitoring context of use but should be individually explored to support assessments of susceptibility, risk of progression, safety in clinical studies, pharmacodynamic, and individualized likelihood of therapeutic benefit. Such contextualization of biomarkers is increasingly required for regulatory acceptance of future therapeutics (FDA-NIH Biomarker Working Group, 2016).

Until then, emphasis should be placed on collecting substantial knowledge of demographics and comorbidities.

Frequent Comorbidities

A list of commonly cited comorbidities derived from published accounts is presented in Table B1. Where presented, frequencies of individual comorbidities differ significantly between published studies, though some conditions such as comorbid metabolic syndrome or diabetes are represented at lower rates than would be expected. A protective effect of Lipedema has been postulated, but requires additional study to confirm (Torre et al., 2018).

Lipedema, has been hypothesized to be a disorder of loose connective tissue (Herbst, 2020). Thus, several conditions associated with tissue and joint laxity are frequently reported as comorbid to Lipedema. Few systematic approaches to the prevalence of comorbid conditions have been published. A recent study of electronic medical records, suggests that the presence of Lipedema and lymphatic conditions likely dispose individuals to a characteristic spectrum of potential comorbid conditions linked through as yet unknown lymphatic-related mechanism (Rockson et al., 2022).

Additional clusters of comorbidities, including immune mediated conditions such as allergies and sensitivities consistent with mast cell activation syndrome, as well as more standard rheumatic complaints, are especially prominent in both the published literature and by patient report.

Notably, Lipedema, in its early stages, may be associated with reduced incidence of metabolic syndrome, and diabetes (Ghods et al., 2020; Schmitz, 1980; Torre et al., 2018), despite increased adiposity. The reproducibility of the observation warrants significant attention to an understanding of the metabolic status of Lipedema affected adipose.

Epidemiology of Lipedema

Lipedema is often described as rarely diagnosed, but not rare. Available epidemiological data is scarce, and of limited quality. Prevalence of Lipedema has been estimated by its prevalence in lymphedema clinics, where it has variably been estimated as 5-17% of women treated for lymphedema (Dean et al., 2020; Forner-Cordero et al., 2012; Herpertz, 1997; Marshall and Schwahn-Schreiber, 2011; Meier-Vollrath et al., 2005). Pediatric referrals for lymphedema have been reported as misdiagnosed Lipedema cases in 6.5% of a single US childrens' hospital (Schook et al., 2011). Extrapolation of similar numbers to an overall prevalence, has resulted in the suggestion that Lipedema may affect 1.1:10 (11%) of women unpublished data (Foeldi and Foeldi, 2002). More recent authors have questioned this (Child et al., 2010; Fife et al., 2010; Ghods, 2021), and ventured a restatement of the 11% number as approximately .5-2:1000 (.05-0.24%) of German women (unpublished data in (Herpertz, 2021, 2004)). A second estimate based on 67 cases seen in 15 years in a British dermatology department allowed a minimum estimate of 1:72,000, reported as likely to be a significant underestimate (unpublished data in (Child et al., 2010)).

Some efforts have been made to consider the prevalence of Lipedema via community screening. In the first case 4.8-9.7% women were estimated to have moderate to pronounced Lipedema, based on a screening of 62 women in German professional practices (Marshall and Schwahn-Schreiber, 2011). Preliminary data suggesting 5% prevalence of Lipedema cases in a screen of 813 women in a German general practice has been reported (Rapprich et al., 2015). A survey-based Lipedema screening tool (Amato et al., 2020) was used to screen 253 responding women in a Brazilian population. Using an assumption of 0.9 specificity, the authors reported a $12.3 \pm 4\%$ predicted prevalence in 18-69 year old Brazilian women (Amato et al., 2022).

With the exception of one study (Amato et al., 2022), prior Lipedema prevalence estimates do not report demographics of the study participants. Thus, it must be assumed that current population estimates do not adequately consider issues such as age, race, or other demographic factors that would be required to formally estimate population prevalence of Lipedema. In the absence of minimally necessary data such as age, Lipedema has, nevertheless, been described in one prominent European epidemiology database, with the declarative statement that Lipedema is "Not rare in Europe." (Orphanet, 2022). This decision was reached following "discussion with several experts on the subject" (personal communication, GSE). Until better diagnosis and epidemiological data become available, the range of reported prevalence data would suggest that a statement about the frequency or rarity of Lipedema data is not possible.

Well-designed prevalence estimates, once available, will also allow development of cost of care and similar health economics estimates that currently represent a gap in public health understanding. Such estimates would ideally include direct health care costs in addition to indirect costs attributable to patient out of pocket expenses and workforce impact. In addition to morbidity estimation, mortality estimates for a Lipedema population are currently limited to speculation. Rigorous estimations of epidemiological data in both treated and untreated populations are necessary to consider Lipedema as a serious public health concern.

Future epidemiology data are likely to come less from community screening or single center approaches than from risk assessments in large public health databases. Predictive markers of risk as might be developed from imaging or genetics based approaches may be useful in such queries as demonstrated recently in GWAS replication studies where 93 diagnosed Lipedema patients were identified within the Cardiovascular Genomics England Clinical Interpretation Partnership program of the UK 100,000 genomes project (Grigoriadis et al., 2022; Klimentidis et al., 2022).

Racial Diversity in Lipedema Research

Race is inconsistently reported in Lipedema literature. Studies that do report racial background lead to the conclusion that available literature is dominated by Caucasian ancestries. Despite this, considerable evidence has accumulated to suggest that genetic background may affect adipose metabolism and depot utilization (Sun et al., 2021), and that women of specific ancestries may differentially metabolize and store energy in a manner that could pose a challenge to recognizing Lipedema based on current clinical diagnostic criteria.

The prevailing theory in Western clinical communities has historically been that the condition is 'practically absent among women of Asian origin' (Damstra et al., 2014). Publication of a recent Mandarin language review (Long, 2021), and submission of Pakistani and Indian proposals to the Lipedema Foundation investigator initiated research funding program (GSE, unpublished) are consistent with an increased interest in Lipedema in these regions. Specific case studies from Japan (Koyama et al., 2017), Korea (Shin et al., 2011), Pakistan (Suga et al., 2009), and Malaysia (Ruh and Hasan, 2017) suggest that Lipedema may either truly be rare, or simply underrecognized, in these communities.

Understanding the prevalence of Lipedema in East Asian populations may be complicated by reports that women of Asian ancestry may possess higher truncal adipose and higher Waist to Hip ratios than Caucasian populations (Karastergiou et al., 2012; Lim et al., 2011; Morimoto et al., 2012). As the clinical diagnosis of Lipedema is based significantly on a clinical observation of disproportionate accumulation of mass in the lower extremities, such baseline differences may pose a challenge to recognizing Lipedema in East Asian populations. Conversely, a higher ratio of small to large adipocytes in subcutaneous adipose, and low prevalence of the CAV1 rs4236601 variant in South Asian populations has been proposed to modulate tissue swelling relative to Caucasian backgrounds via influence on tissue fibrosis (Kruglikov et al., 2020). Influence of diet and basal differences in circulating sex steroids have also been suggested as factors that might reduce prevalence of Lipedema in Asian population (Ehrlich et al., 2017).

Women of African descent with Lipedema are included in some research reports, albeit at low levels in papers reviewed here (collectively n=13 patients) (Beltran and Herbst, 2017; Crescenzi et al., 2019; Ma et al., 2020; Rasmussen et al., 2022; Rockson et al., 2022; Wold et al., 1951). Only a single case report of an African American woman with Lipedema presents a focused examination of Lipedema in this context (Greer, 1974). As in Asian populations, depot utilization and triglyceride synthesis may differ between women of Caucasian and African backgrounds (White et al., 2018).

Similarly, future diagnostics strategies should be designed and tested with consideration for variation in skin tone if the platform is reliant on dermal reflectivity or absorbencies (e.g., photoplethysmography).

Available studies from diverse populations (e.g., (Amato et al., 2021; Atan and Bahar-Özdemir, 2021)) do not clearly demonstrate notably divergent presentations of Lipedema. However, the absence of a thorough examination of Lipedema in the context of race represents a significant gap in the research. Such studies should not only examine standard morphometry, and prevalence of symptoms, but should also acknowledge that health care experiences and health-related quality of life may be significantly influenced directly or indirectly by demographic parameters including, but not limited to race.

Health related Quality of Life (hrQOL) and Patient Reported Outcome Measures

The effects of Lipedema on patient health and quality of life have routinely been expressed in relevant literature as patient histories interpreted by health care professionals. In recent years attempts to both quantify subjective expressions and reduce interpreter bias have resulted in efforts to develop Lipedema specific surveys and introduce standard Patient Reported Outcome Measures (PROM) and health related Quality of Life (hrQOL) measures. The use of this data supports both epidemiological approaches to understanding the burden of disease and provides a basis for establishing quantified patient report data as outcome measures in clinical studies. Discussion of specific patient reported outcomes measures related to common features of Lipedema is distributed throughout this document, notably in the sections of this text related to mental health, fatigue, and pain.

The hrQOL of women with Lipedema is consistently reported to be lower than reference populations in all cultures and languages studied. Qualitative research on hrQOL is limited. Narrative interview approaches were used in Swedish populations to assess the impact of late-stage Lipedema on daily lives. This approach codifies the deliberate attention required to move an 'unreliable' body and the interplay between Lipedema related exhaustion and lack of support in healthcare and social encounters (Melander et al., 2021). Such concerns echoed similar focus group based approaches, that bring detail to specific mobility and emotional challenges and experiences with available therapeutic options (Fetzer, 2020).

Studies with a specific quantitative approach to hrQOL are typically survey based, relying on patients to self-administer the instrument outside of a clinical setting. Reporting of the administration environment is not provided in all studies, though may be suspected from other fields to have an influence on study demographics (Weldring and Smith, 2013).

Like other symptoms, the effect of Lipedema on hrQOL is diverse, and has been reported to vary by age at onset, stage, and duration of symptoms as a function of pain and mobility (Clarke et al., 2022; Falck et al., 2022; Hamatschek et al., 2022). Concomitant increases in the number and severity of comorbidities is likely to influence measurements of hrQOL (Falck et al., 2022; Ghods et al., 2020; Romeijn et al., 2018), and should be considered in study design. Detriments to emotional well-being may also be negatively affected by socio-economic status (Falck et al., 2022). In one study, depression severity mediated the relationship between symptom severity quality of life, suggesting a correlation between Lipedema specific symptoms and depression (Dudek et al., 2021). Existing patient cohorts and registries such as those studies cited here and including large patient groups (e.g., Lipedema Foundation Registry, Lipoedema UK, Lipoedema Australia) represent convenient populations against which to continue to pilot-test novel hypotheses regarding patient reported outcomes.

As in other PROMs, there is a lack of formal validation for hrQOL measures in Lipedema populations, though some work is progressing in this area. Two studies have reported validation of Patient Benefit Index (PBI) and a Turkish version of the PBI-Lymphedema (PBI-L), in a mixed Lipedema and lymphedema cohort (Blome et al., 2014; Duygu et al., 2020; Duygu Yildiz et al., 2022). Retrospective and prospective interventional studies have also variously used PROMs evaluated hrQOL, and provide guidance for understanding responsiveness of individual instruments in future validation studies (Amato et al., 2020; Atan and Bahar-Özdemir, 2021; Di Renzo et al., 2021; Donahue et al., 2022; Herbst et al., 2017; Karen L. Herbst et al., 2021; Ibarra et al., 2018; Kruppa et al., 2022; Paling and Macintyre, 2020; Schneider, 2020).

The degree to which Lipedema compares to other chronic conditions with respect to important measurement domains has received appreciable attention. Cross instrument construct validity has been tested in lymphedema and Lipedema and suggests that both generic (SF-36) and disease specific (FLQA-LS) hrQOL instruments may elicit differential responses from lymphedema and Lipedema populations principally based on pain and physical function. Subsequent factor analysis revealed differences in loading between the two conditions, suggesting that physical functioning had less contribution to Lipedema mental health scores than to lymphedema (Angst et al., 2020b). In a study comparing SF-36 across six chronic pain conditions, the same team demonstrated correlation between pain and depression in Lipedema similar to five of six other chronic pain conditions (Angst et al., 2020a).

Future Lipedema interventional studies are likely to incorporate Lipedema into larger studies such as obesity or chronic pain trials. There remains, therefore, a substantial need for a Lipedema specific validation effort with respect to established PROMs. It is, however, unclear to what degree the Lipedema field would benefit from the establishment of novel disease-specific hrQOL instruments that would sacrifice comparability to other disease conditions or reference populations. In either case, the utility of PROMs in clinical research will be dependent on their ability to provide informative data relative to the trial. As such, there is a priority on PROMs for which a Lipedema-specific and well-defined minimally clinically important difference (MCID) can be used as a target in studies. To do this may be non-trivial and require large studies that can be representative of the diversity of ages, stage, comorbidities, and present in Lipedema populations. As the prevalence of Lipedema in men is especially rare, special attention must be paid to gender-matching of Lipedema and control populations in any study analyzing uninterpreted data from patients, the definition of a patient reported outcome

measurement. Likewise, the nature of direct collection of patient report opens opportunity for introduction of avoidable biases (including recall, ascertainment, and social acceptability biases) that should be appropriately controlled for in study design.

Statement on Medical Reimbursement

Women with Lipedema often face significant barriers to medical coverage for effective treatments. The motivations for this may be explicitly fiscal incentives but may also be more influenced by well-documented biases that present barriers to care on the basis of parameters such as gender or weight. Despite gaps in research knowledge, safe and effective treatments are available. As made clear in this document, Lipedema is a distinct medical condition. It is accompanied by adverse outcomes, as established by measures of health-related Quality of Life. The same measures have shown improvement following contemporary surgical and physiotherapeutic interventions. No statement made in this document detracts from the authors' professional opinion that sufficient data is available to justify reimbursement for Lipedema diagnosis and standard therapeutic interventions.

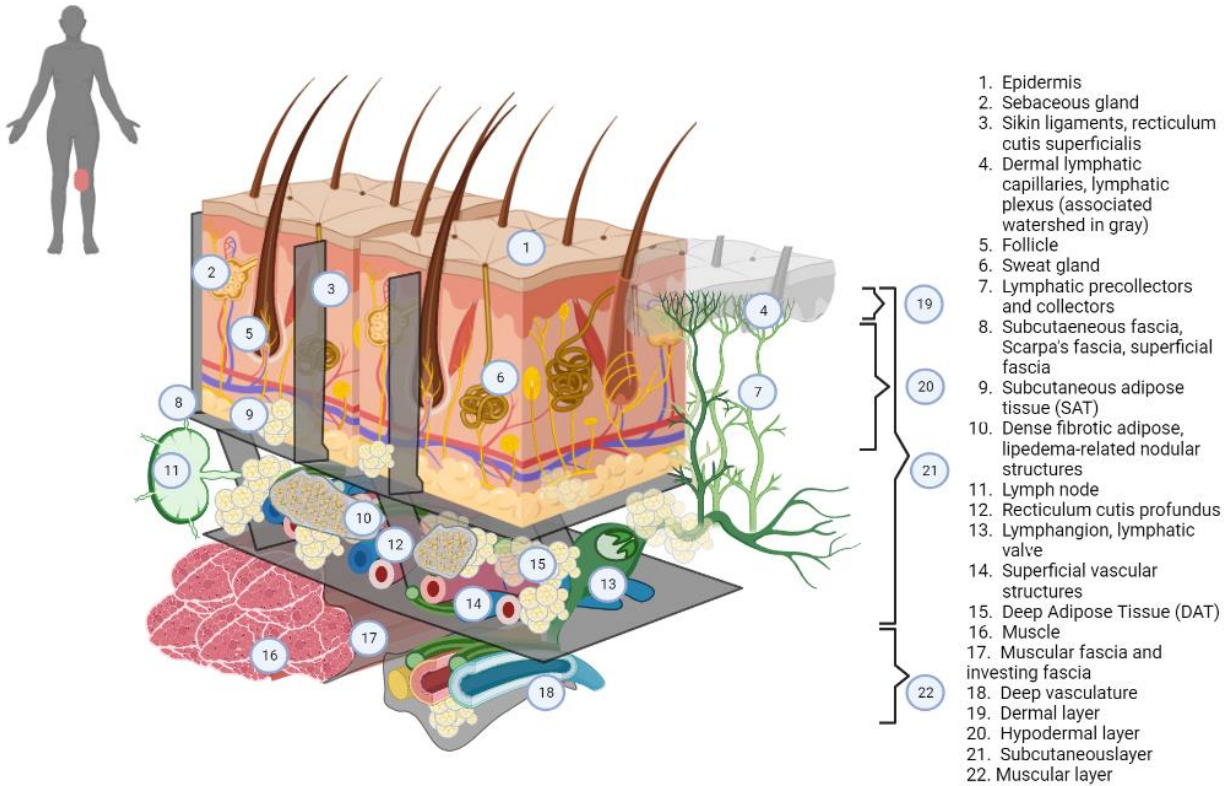
Conclusions

This review serves as look back on the history of Lipedema, spanning many decades and languages to arrive at a relatively simple conclusion. Lipedema represents a long-known condition, for which many initial insights remain to be challenged with modern research tools. This document covers data related to pathogenesis and natural history. It does not cover current understanding of clinical diagnosis and therapeutic outcomes. A companion "Lipedema Research Roadmap" document provides forward looking recommendations oriented towards maximizing the impact of Lipedema research effort on behalf of patients. These are intended as living documents, capable of being edited semi-regularly. As such, they are curated on the Lipedema Foundation website, under the concept that future versions can be collectively influenced and written by the larger research community.

Appendices

Appendix A: Figures

Figure A1. Histology Illustration Outlining Tissue Architecture.



Caption: Schematic rendering of adipose and fascial anatomy in the thigh. Adapted from Jobst poster (Asmussen, 2018). Created with Biorender.com

Appendix B: Tables

Table B1. Lipedema Signs and Symptoms, Comorbidities, and Demographics in Primary Data Papers

Table B1. Lipedema signs and symptoms, comorbidities, and demographics reported in primary data papers.

	Number of Studies Reporting	Range of Values Reported	Citations
Demographic Parameters Reported			
n	17	10-522	a-q
Female n(%)	15	10-209 (98-100%)	a,c-l,n-q
Race/Ethnicity			
White n(%)	6	9-141 (51-100%)	a,d,h-i,l,n
Black n(%)	4	1-6 (1-10%)	d,h,l,n
Hispanic n(%)	2	5 (2-9%)	d,h,n
Asian n(%)	2	1 (0.7-2%)	d,h
Other/Unknown n(%)	1	(37%)	d
		*d only study to utilize "other"	
Age mean or median yrs (range)	16	35.6-57 (15-82)	a-l,n-q
		*f,j, k reported median rather than mean	
BMI mean or median (range)	15	27.5-39 (18.7-58.8)	a-i,k-p
		*c reported median; g reported median and IQR	
BMI Classification			
Normal (18-24.9) n(%)	6	4-32 (4-23.2%)	a-b,f-g,o-p
Overweight (25-29.9) n(%)	6	7-48 (11-42%)	a-b,f-g,o-p
Obese Class 1 (30-34.9) n(%)	6	18-52 (8-76.1%)	a-b,f-g,o-p
		*g and o indicated obesity class 1 or more	
Obese Class 2 (35-39.9) n(%)	4	11-42 (8-27%)	a-b,f,p

Table B1. Lipedema signs and symptoms, comorbidities, and demographics reported in primary data papers.

	Number of Studies Reporting	Range of Values Reported	Citations
Obese Class 3 (>40) n(%)	3	33 (17.2-50%)	a-b,p
WHR Mean (range)	3	0.71-0.76 (0.40-0.93)	a,e-f
WHR Mean (range)	1	0.6 ± 0.1 (0.32-0.88)	e
Stage			
Stage 0 n(%)	1	(42.4%)	b
Stage 1 n(%)	10	4-52 (4.1-40%) (11.8-45.5%) (arms)	b-c,f-i,k-l,n-o
Stage 2 n(%)	10	3-79 (25.3-64.7%) (36-55.7%) (arms)	a-b,f-i,k-l,n-o
Stage 3 n(%)	10	0-55 (0.0-37.2%) (9.9-76.5%) (arms)	a-b,f-i,k-l,n-o
Stage 4 or Lipolymphedema n(%)	7	5-16 (1.4-30%)	e-f,h,k-l,n-o
Type			
Type I n(%)	5	0-2 (0.0-6.7%)	f-g,i,k-l
Type II n(%)	5	1-19 (10-33.3%)	f-g,i,k-l
Type III n(%)	5	9-98 (49-90%)	f-g,i,k-l
Type IV n(%)	4	6-16 (10.8-60%)	f-g,k-l
Type V n(%)	3	1-3 (1.2-2.2%)	f-g,k
Disease Duration yrs (range)	2	23.4-29.2 (1-62)	a,f
Age of Onset yrs (range)	8	15.9-26.7 (10-54)	a-b,e,g,j-l,o
		*k reported median	

Table B1. Lipedema signs and symptoms, comorbidities, and demographics reported in primary data papers.

	Number of Studies Reporting	Range of Values Reported	Citations
Onset trigger			
Puberty n(%)	5	3-79 (15.7-67.3%)	b-c,e-f,k
Pregnancy n(%)	5	12-22 (9.5-63.1%)	b-c,e-f,k
Menopause n(%)	5	2-8 (1.9-21%)	b-c,e-f,k
Contraceptives n(%)	3	1-4 (1.2-3.8%)	c,f,k
Not Indicated n(%)	1	28 (20.3%)	f
Other n(%)	2	6-18 (5.7-21.7%)	c,k
Canonical Symptoms			
Symmetrical involvement n(%)	5	15-200 (100%)	a,f,i,k,q
Upper arm involvement n(%)	4	15-65 (15.2-100%)	c,f,h-i
Spared Feet n(%)	3	74 -200 (89.2-100%)	a,f,k
Fat pads around the knees n(%)	3	22 (53.3-85%)	h-i,p
Negative Stemmer's Sign n(%)	5	15-119 (80.7-100%)	f,i,k,n,q
Pain and/or tender to touch n(%)	10	27-127 (62-100%)	a-c,f-i,k,p-q
		*b,c,j reported utilizing VAS scales	
Bruising n(%)	11	31-139 (28.1-93.3%)	a-c,f-i,k,n,p-q
		*b,c reported utilizing VAS scales	
Swelling or edema n(%)	7	14-117 (14.5-79%)	a-b,f,h-i,k,n
		*b reported utilizing VAS scale	
Heaviness n(%)	2	31 (69%)	b,g
		*b reported utilizing VAS scale	
Fatigue n(%)	3	7 (15-66.7%)	g,i,n
Hypermobility n(%)	4	33 (17.8-58%)	a,h-i,n
Fibrosis n(%)	4	8-86 (6.5-58%)	f,h,k,n
Cold skin n(%)	5	33-59 (41.3-94%)	b,f,i,k,q
		*b reported utilizing VAS scale	
Pes plantus or flat feet n(%)	3	21-40 (15.2-96%)	a,f,q
Spider veins n(%)	4	15-124 (23.9-89.9%)	a,k,m,p

Table B1. Lipedema signs and symptoms, comorbidities, and demographics reported in primary data papers.

	Number of Studies Reporting	Range of Values Reported	Citations
Altered gait n(%)	2	(60-81%)	h-i
Family History n(%)	5	10-116 (14.9-89.2%)	
Comorbidities			
Obesity n(%)	3	74-186 (37.6-79.6%)	c-d,m
T1D n(%)	2	3 (0.0-1.4%)	c,j
T2D n(%)	7	2-6 (0.7-6.5%)	b-d,j,m-o
Hypertension n(%)	6	17-28 (5.5-31%)	c-d,j,m-o
High Cholesterol/ Dyslipidemia/ Hypercholesterolemia/ Hyperlipidemia n(%)	5	4-19 (1-38%)	c,d,j,m,o
Allergies n(%)	2	72 (34.4-36.8%)	c,j
Hypothyroidism n(%)	4	23-75 (24.7-35.9%)	c-d,j,n
PCOS n(%)	3	4 -12 (2.8-5.7%)	c-d,j
Migraine n(%)	4	15-47 (7-22.6%)	c-d,j,n
Hypertonia n(%)	1	(10.2%)	b
Skin Problems/ Disorders n(%)	2	(19.2-25.5%)	b-c
Joint Pain n(%)	2	(31.3-57%)	b,o
Asthma n(%)	3	17-27 (12.9-19.2%)	c-d,j
GI Disorders n(%)	2	27 (10.4-12.9%)	c,j
GERD n(%)	1	22 (23.7%)	d
Rheumatism n(%)	3	(8.5-38%)	c,n-o
Osteoarthritis n(%)	2	23-37 (24.7-58.7%)	d,f
Fibromyalgia n(%)	3	6 (6.5-44%)	d,n,q
Anemia n(%)	1	8 (8.6%)	d
Venous problems n(%)	1	25 (13.2%)	a
Chronic Venous Insufficiency (CVI) n(%)	2	14-43 (16.1-31.2%)	d,f
Cellulitis n(%)	2	7-24 (7.5-68%)	d,q
Venous telangiectasia	1	20 (52.6%)	p
Lymphedema n(%)	2	5-25 (13.2-26.3%)	a,e
Sleep Disorders/ Insomnia n(%)	3	7-45 (7.5-25.5%)	c-d,j
Depressive Disorders n(%)	4	19-48 (10.1-25.5%)	c-d,j,m

Table B1. Lipedema signs and symptoms, comorbidities, and demographics reported in primary data papers.

	Number of Studies Reporting	Range of Values Reported	Citations
Generalized Anxiety Disorder n(%)	1	14 (15.1%)	d

Citations: a) (Grigoriadis et al., 2022) b) (Hamatschek et al., 2022) c) (Ghods et al., 2020; Kruppa et al., 2022) d) (Rockson et al., 2022) e) (Ünlü et al., 2022) f) (I. Forner-Cordero et al., 2021) g) (Buso et al., 2021) h) (Karen L. Herbst et al., 2021) i) (Crescenzi et al., 2020) j) (Bauer et al., 2019) k) (Forner-Cordero et al., 2018) l) (Crescenzi et al., 2018) m) (Sandhofer et al., 2017) n) (Beltran and Herbst, 2017) o) (Herbst et al., 2015) p) (Child et al., 2010) q) (Bilancini et al., 1990)

Table B2. Histology Characterization in Lipedema Samples

Table B2. Histology characterization in Lipedema samples.

Citation	Anatomic location	Sample Depth	Lipedema Stage	Findings
(Rank and Wong, 1966) ‡	Nr	Nr	Nr	Thickening of adipose tissue, fibrosis
(Greer, 1974) ‡	Right thigh	Nr	Nr	No dilation of lymphatics Epidermis, dermis, and fat were normal
(Stallworth, 1974) ‡	Nr	Nr	Nr	Unremarkable by Hematoxylin & Eosin stain
(Rudkin and Miller, 1994)	Nr	Nr	Low BMI	Absence of fibrosis and dermal thickening relative to lymphedema
(Strößenreuther and Baumeister, 2001) ‡	Nr	Nr	III*	Increased vascularity CD68+ macrophage, fibroblast, and mast cell infiltration Slightly hypertrophic and necrotic adipose Increased fibrosis
(Stutz and Krahl, 2009)	Proximal lower leg and distal thigh	IHC of lipoaspirate, presumed interfascial SAT layer	II-III	Low levels of lymphatic vessels in lipoaspirate
(Suga et al., 2009) ‡	Medial patellar fat pad and unaffected inguinal subcutaneous	Nr	III*	Edematous and necrotic adipose Macrophage infiltration Hypertrophic adipocytes No vascular changes Proliferating CD34+ adipose stem/progenitor Cells
(Koyama et al., 2017) ‡	Right hip	Skin punch biopsy	II/III*	Large adipocyte size Adipocyte lysis Plasma cell or lymphocyte infiltration
(Al-Ghadban et al., 2019)	anterolateral thigh	5 mm punch biopsy	I-III	Increase in macrophage count No mast cell differences Increased dermal blood vessels in non-obese Lipedema Lymphatic dilation but not vessel number difference in obese Lipedema Increased angiogenesis in skin
(Allen et al., 2020)	Thigh and abdomen	5 mm punch biopsy	I-III	Altered vascular structure inversely correlated with BMI

Table B2. Histology characterization in Lipedema samples.

Citation	Anatomic location	Sample Depth	Lipedema Stage	Findings
(Felmerer et al., 2020a)	Nr†	Nr†	I-III	Immune infiltration and enlarged perivascular spaces Adipocyte hypertrophy Increase in CD45+/Cd68+ macrophages
(Felmerer et al., 2020b)	Nr†	Nr†	I-III	Increase in M2 polarized macrophages No structural changes to vasculature
(Ishaq et al., 2021)	Nr	Nr	II-III	Increased numbers of CD29+/CD34+ ADSCs in nodules Increased adipogenic differentiation and proliferation in ADSCs
(Wolf et al., 2021)	Nr†	Nr†	I-III	Adipocyte hypertrophy
(Chakraborty et al., 2022)	Abdomen and anterolateral thigh	5 mm punch biopsy	I-III	Reduced dermal neuron density in abdomen, not in thighs Stage dependent expression pattern of neuropeptides in thigh and abdomen
(Strohmeier et al., 2022)	Lateral thigh	dermal biopsy	I-II	Increased macrophages near endothelial structures, but not other areas of tissue No fibrosis or epidermal thickness changes
(Von Atzigen et al., 2023)	Ventral aspect of lower extremities	At the level superficial to the Scarpa fascia	II-III	Increased adipocyte size Increased number of hypertrophic adipocytes No adipose tissue fibrosis Increased epidermal thickness No skin fibrosis Increased numbers of CD45+ hematopoietic cells and CD68+ and CD163+ macrophages
Studies reported by citation, but unavailable for review				
** (Curri, 1984)			Nr	
** (Curri and Merlen, 1986)				

Nr: not reported

* stage estimated from figures in original paper

† SAT residing between the deep and superficial fascial layers, collected by scalpel from thighs, personal communication Epa Gousopoulos)

‡ Data expressed as single subject observation, or without reference to number of subjects studied

Table B2. Histology characterization in Lipedema samples.

Citation	Anatomic location	Sample Depth	Lipedema Stage	Findings
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** If your manuscript is referenced here, please consider using “personal communication” to supplement any information that may not have been reported in the published version. If we inadvertently omitted any items that were published, we kindly request that you bring those to our attention and accept our apologies for the oversight.

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
Functional Change in presence of Structural Change				
(Stöberl et al., 1986)	Subepidermal injection of contrast at malleolar adipose depot	+++ Cavitation of prelymphatic spaces	+++ No evidence of outflow to lymphatic collectors	Indirect lymphangiography N=11 "severe" Lipedema
(Ketterings, 1988)	Phlebography - Nr Radiolabeled colloid, injected intracutaneously 6 hr observation	+++ Incompetent venous valve system, post thrombotic changes	+++ Increased lymph transport (65%) Reduction in lymphatic vessels, "foamy" lymph nodes	Photoplethysmography lymphoscintigraphy Lymphangiography N=45 Lipedema
(Bilancini et al., 1995)	Radiolabeled colloid. Depth not reported 1 hr observation	+++ Asymmetric appearance of lymph node signal + collateral pathways	++ Slower lymphatic flow	Lymphoscintigraphy N=12 Lipedema
(Lohrmann et al., 2009)	Intracutaneous injection of gadolinium contrast to foot Upper and lower leg ~55 min observation	+ enlarged lymphatic vessels (20-40%) ++ venous enhancement (100%)	+ slowing of lymph transport	T2 weighted MRI N=5 Lipedema, N=8 lipolymphedema
(Cellina et al., 2020)	Upper and lower leg 5 min scan time	+ Lymphatic and venous dilatation at later stages	+ Vascular stasis	Non contrast MRI lymphangiography N=11 Stages I-III

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
Functional Change in presence of Structural Change				
(Gould et al., 2020)	Radiolabeled colloid, injected subcutaneously Up to 3 hr observation	++ 34% Collateral pathways	+++ Reduction in transport correlated to severity ++ 20% Dermal backflow	Lymphoscintigraphy N=19 Lipedema Stages I-IV
(Rasmussen et al., 2022)	Intradermal ICG injection at several locations 2 hr observation	+ Dilatation of lymphatic vessels + tortuosity	+++ Increased lymphatic pumping rate +++ no dermal backflow	NIRFLI imaging N=20 stage I/II Lipedema
(Zaleska et al., 2022)	Subcutaneous ICG or radiolabeled colloid injection to toe webbing Up to 1 hr observation	+++ Abnormal appearance and number of lymphatic vessels at all sites and stages	+++ Reduced lymph flow + High skin water concentration	ICG lymphography N=50 Lipedema, stage I-III
Functional Change Only				
(Weissleder et al., 1995)	Radiolabeled colloid, "subepidermal" injection to "fatty tissue of ankle region" 3 hr observation	+ Narrow lymphatic lumen +tortuous lymph collectors	+ 25% with longer transport times	Lymphoscintigraphy N=17 Lipedema
(Harwood et al., 1996)	Photoplethysmography at calf Lymphoscintigraphy Radiolabeled colloid injection depth not reported.	Nr	+ Minor venous dysfunction (20%), sub clinical lymphatic impairment (80%)	Photoplethysmography lymphoscintigraphy N=10

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
	3 hr observation.			
Functional Change Only				
(Brauer and Brauer, 2005; Brauer, 2000)	Radiolabeled colloid, injected subcutaneously to interdigital webbing 60 min Observation time	None	Increased lymph transport in young patients, that reduces below controls in later ages	Lymphoscintigraphy N=39 Lipedema legs
(Boursier et al., 2004)	Radiolabeled colloid, injected intradermally	None	Lymphatic insufficiency	Lymphoscintigraphy N=15 Lipedema
(Forner-Cordero et al., 2018)	Radiolabeled colloid, injected subcutaneously 3hr observation	Nr	++ slower lymphatic flow in 47%, independent of age, stage, or BMI	Lymphoscintigraphy N=83 Lipedema Stages 1-IV
(van de Pas et al., 2020)	Subcutaneous radiotracer injection 2 hr observation	Nd	+++ Lymph transport deficit in 79-87% of legs, with no significant change 6 mo. after surgical intervention	Lymphoscintigraphy N=117 Lipedema patients
(Buso et al., 2021)	Subcutaneous ICG injection 25 min observation	None	+++ reduced transport velocity, negatively correlated to BMI +++ no dermal backflow	ICG Lymphography N=45 Lipedema stages I-III

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
Structural Change Only				
(Stallworth, 1974)	Nr	+ varicosity + leakage	Nr	Phlebogram Lymphangiogram N=14 Lipedema
(Kinmonth, 1982)		++ Tortuous lymphatic vessels		Lymphangiography N=1
(Partsch et al., 1988)		+normal lymph collectors +perturbed prelymphatic structures	Nr	N=10 Lipedema
(Tartaglione et al., 2020)	Intradermal Radiotracer injection 1 hr observation	+++ 75% of patient had tortuous vessels +++ 49% collateral lymphatic vessels	+ lymphatic transport deficits in 15% of patients considered unremarkable	Radiotracer injections N=54 consecutive Lipedema pts injected intradermally
(Dean et al., 2020)	2d turbo spin echo sequencing	+Dilated vessels without reflux, contrasted to lipolymphedema, where obstructions and reflux were evident	Nr	MRI N=22 Lipedema N=30 lipolymphedema
(Amann-Vesti et al., 2001)	Subepidermal injection of fluorophore at dorsum of foot, medial ankle, ventral thigh 15 min observation	+++ no differences in capillary diameter, or breadth of network +++ microaneurysms in thigh and feet	Nd	Fluorescence microlymphography N=12 Lipedema, no clinical lymphedema

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
Structural Change Only				
(Chachaj et al., 2023)	Radiolabeled colloid, injected simultaneously in both feet between the second and third interdigital space of the foot.	+++ 76.5% collateral lymphatic vessels	+++ no dermal backflow (5.9% lipedema patients with dermal backflow)	Lymphoscintigraphy N=51 Lipedema. Stage I-III
No Change in Either Function or Structure				
(Hadjis et al., 1985)	4 sections of lower leg, scanned at 5 sec	Nr	Nr	Computed Tomography N=3 Lipedema
(Tiedjen and Schulz-Ehrenburg, 1985)	“foot webbing” radiotracer injection	None, some asymmetric changes attributed to comorbidities	None	N=12 mixture of Lipedema and erythrocyanosis cruris puellarum
(Vaqueiro et al., 1986)	Subcutaneous radiotracer injection (foot)	None	None	n=2 Lipedema patients
(Duewell et al., 1992)	DOTA (extracellular contrast) injected through catheter at unreported site. 8 min observation of calves	Marked adipose swelling only	Nd	T1/T2 weighted MRI N=5 Lipedema
(Werner and Rodiek, 1993)	Upper and lower leg	Subcutaneous thickening Absence of Lymphangiectatic formations	Nd	Non contrast T1/T2 weighted MRI N=15 Lipedema

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
No Change in Either Function or Structure				
(Bräutigam et al., 1998)	Subcutaneous and Intramuscular/subfascial radiotracer injection (foot)	None, some changes attributed to comorbidities	None	n=9 Lipedema patients
(Monnin-Delhom et al., 2002)		Nr	Nr	Computed Tomography N=20 Lipedema (excluded patients with lymphoscintigraphic or doppler findings)
(van Geest et al., 2003)	Epifascial lymphoscintigraphy, injection of radiolabelled colloid to subcutaneous fat (1-2 cm deep) at 15 cm above malleolus Subcutaneous lymphoscintigraphy, Subcutaneous injection to toe webbing 2 hr observation	Nr	Subcutaneous lymphatic transport difference between Lipedema subtypes, but not controls	Lymphoscintigraphy n=22 Lipedema n=6 Moncorps Lipedema
(Felmerer et al., 2020b)	Biopsy of thigh	+++No structural deficit to lymphatics	Nd	Histological approach N=11 Lipedema
(Mackie et al., 2023)	Subcutaneous ICG injection (foot) Observations made after dye had	+++No structural deficits to lymphatics (85% of participants)	+++no dermal backflow (85% of participants)	ICG Lymphography N=40 Lipedema stages I-IV

Table B3. Assessments of Lymphatic Structure and Function in Lipedema

Citation	Anatomic location of observation or administration of tracer, duration of observation	Lymphatic Structural Change Reported	Lymphatic Functional Change Reported	Method and sample
	stabilized, between 30-45 minutes			
No Change in Either Function or Structure				
(Von Atzigen et al., 2023)	Ventral aspect of lower extremities, level superficial to Scarpa fascia	+++No structural deficit to lymphatics	Nd	Histological approach N=10 Lipedema
Studies Reported by Citation, but Unavailable for Review				
(Tiedjen et al., 1992)			Stage dependent transport deficit tracer accelerates in stage 1 and decelerates in stage II,III with occurrence of lymphedema.	
(Infante et al., 2012)		** reprint requested – unlikely to be Lipedema		
(Åström et al., 2001)				
(Monnin-Delhom et al., 2002)				

+ indicative of level of support expressed by authors

Nd: not determined/ not studied. Nr: studied but not reported. None: studied with unremarkable findings

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Version 1

Acknowledgements

History of Contributions

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