Review

Genetic Polymorphisms and Vascular Dysfunction in Lipedema: Implications for a Non-Hormonal Pathophysiological Model

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Genetic Polymorphisms and Vascular Dysfunction in Lipedema: Implications for a Non-Hormonal Pathophysiological Model

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Abstract

Lipedema is a chronic, progressive adipose tissue disorder predominantly affecting women and has been widely proposed as an estrogen-dependent condition despite the lack of objective causal evidence. In contrast, increasing data implicate genetic heterogeneity, endothelial dysfunction, and altered vascular permeability as central features of the disease. This review critically reassesses the estrogen-dependence hypothesis in light of emerging genetic and vascular evidence. These findings highlight molecular pathways linking endothelial dysfunction and adipose tissue dysregulation as central features of the disease. Methods: A narrative literature review was conducted using PubMed, Cochrane Library, and Google Scholar databases. Searches combined the terms "lipedema," "lipoedema," "estrogen," "hormonal dependence," "genetic polymorphism," "endothelial dysfunction," "vascular permeability," "microangiopathy," and "adipose tissue,". Original research articles, reviews, consensus statements, and experimental studies were included. Given the narrative design, no formal inclusion criteria, quality assessment, or meta-analytic procedures were applied. Results: Across multiple cohorts, no studies demonstrated that estrogen levels, estrogen receptor expression, aromatase activity, or estrogen-related signaling pathways act as primary causal triggers of lipedema. Conversely, consistent genetic, transcriptomic, and histopathological findings reveal marked genetic heterogeneity, dysregulated adipose tissue proliferation, extracellular matrix remodeling, microangiopathy, and increased endothelial permeability. Variants affecting adipogenesis, connective tissue integrity, vascular function, and lymphatic regulation have been repeatedly identified, alongside early endothelial structural and functional abnormalities. Conclusion: Current evidence does not consistently support classifying lipedema as an estrogen-dependent disease. While estrogen may modulate inflammatory and metabolic processes relevant to disease expression, its role appears secondary rather than causative. Genetic predisposition and vascular dysfunction emerge as more consistent contributors to lipedema pathophysiology, supporting integrative, mechanism-based models to guide future research and clinical approaches.

Keywords: lipedema; endothelial dysfunction; microvascular diseases; adipose tissue; inflammation

1. Literature Search Strategy

A comprehensive literature search was performed to identify studies addressing the pathophysiology of lipedema, with particular emphasis on hormonal mechanisms, genetic polymorphisms, endothelial dysfunction, and vascular permeability. Searches were conducted in PubMed, Cochrane Library, and Google Scholar databases. Search terms included combinations of "lipedema," "lipoedema," "estrogen," "hormonal dependence," "genetic polymorphism," "endothelial dysfunction," "vascular permeability," "microangiopathy," and "adipose tissue," without language restrictions. Studies published up to 2025 were considered. Priority was given to studies addressing molecular, vascular, and endothelial mechanisms.

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Original research articles, narrative and systematic reviews, consensus statements, and relevant experimental studies were considered. Reference lists of selected articles were manually screened to identify additional pertinent publications. Given the narrative nature of the review, no formal inclusion or exclusion criteria, quality scoring, or meta-analytic procedures were applied. The objective was to synthesize and critically appraise the existing body of evidence, highlighting areas of consistency, uncertainty, and conceptual limitation in the estrogen-dependence hypothesis of lipedema. Studies published up to 2025 were considered, with emphasis on those addressing vascular and endothelial mechanisms.

2. Introduction

Lipedema is a chronic and progressive disease characterized by a disproportionate accumulation of fat in the limbs, sparing the extremities and trunk. Although Allan and Hines described lipedema as early as 1940, the condition attracted little attention for many years. The onset of lipedema has been associated by several authors with phases of hormonal fluctuation (puberty, pregnancy, menopause) or with the use of oral contraceptives[1,2,3,4,5], and because it is an almost exclusively female disease, its probable pathophysiology has been strongly linked to the hypothesis of a causal relationship between fluctuations in estrogen levels, alterations in estrogen receptors, and the disease[2].

Although some researchers suggest that changes in estrogen receptors or signaling pathways may be responsible for triggering the disease, no line of investigation to date has been able to demonstrate that estrogen itself, its serum or tissue levels, imbalances in its receptors, or its signaling pathways constitute the causal triggers of lipedema. The role of estrogen level fluctuations therefore remains speculative, theoretically grounded in the participation of this hormone in inflammation and lipid metabolism, while the pathophysiological mechanisms of lipedema remain incompletely understood [1,2,4]. Emerging evidence suggests that lipedema may be fundamentally characterized by early microvascular dysfunction, positioning it within the spectrum of vascular and microcirculatory disorders.

A narrative literature review was conducted in search of objective data that could support the concept of lipedema as an estrogen-dependent disease, using PubMed, Google Scholar, LILACS, and SciELO databases, focusing on studies addressing the pathophysiology of lipedema.

As this is a narrative review, the present work does not aim to perform a systematic or meta-analytic evaluation of the available literature, nor to formally rank levels of evidence of the included studies. The interpretations presented should therefore be understood as an integrative critical analysis of current evidence, subject to the inherent limitations of this methodological approach. Although this is a narrative review, studies were preferentially selected based on relevance to vascular, genetic, and endothelial mechanisms, prioritizing original research and translational studies. This review aims not only to reassess the estrogen-dependence hypothesis, but also to propose a mechanistic framework integrating genetic, endothelial, and inflammatory pathways in lipedema.

3. Role of Estrogen in Adipose Tissue Metabolism and Inflammation

Estrogens and estrogen receptors (ERs) regulate metabolism and the distribution of female body fat. Estrogen receptor alpha (ER-α), estrogen receptor beta (ER-β), and G protein–coupled estrogen receptors (GPER) are differentially expressed in upper- and lower-body fat in premenopausal women with overweight and obesity, indicating that estrogen influences subcutaneous adipose tissue (SAT) distribution through ER-mediated signaling. ER-α signaling regulates adipose-derived cells in their development and function, whereas ER-β exerts direct anti-adipogenic effects in adipocytes by inhibiting the transcriptional activity of peroxisome proliferator–activated receptor gamma (PPARγ).

Estrogen also regulates the expression of leptin and lipoprotein lipase (LPL) genes and increases angiogenesis and vascular endothelial growth factor (VEGF) expression, a phenomenon observed in the SAT of patients with lipedema. GPER has been implicated in the regulation of body weight, metabolism, inflammation, and pain. In adipose tissue, LPL is synthesized by adipocytes but remains inactive until it is translocated to the luminal side of endothelial cells lining blood vessels. This

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enzyme allows free fatty acids to enter adipocytes for the synthesis of triacylglycerol (TAG) molecules. Regulation of LPL synthesis in adipose depots occurs via estrogen signaling[1].

PPARγ is an important regulator of glucose and lipid metabolism in multiple tissues, particularly skeletal muscle and adipose tissue. Signaling through PPARγ stimulates TAG synthesis and storage in adipocytes, contributing to increased adipocyte size, while also activating adipogenesis and differentiation of preadipocytes into mature adipocytes[1].

Although some researchers postulate that fluctuations in estrogen levels, alterations in estrogen receptors, and changes in signaling pathways are responsible for triggering lipedema, no objective, quantitatively measured data to date demonstrate that estrogen alone, its serum or tissue levels, or receptor alterations constitute primary causal triggers of the disease[1,2,3,4,5,7].

4. Genetic Polymorphisms

The inheritance pattern of lipedema appears to be X-linked, autosomal dominant with sex limitation, and/or oligogenic [8]. Lipedema has been established as a genetic condition through classical family studies (Online Mendelian Inheritance in Man – OMIM 614103); however, the specific genetic factors and underlying mechanisms responsible for fat deposition in lipedema remain poorly understood [9].

Genetic inheritance remains a factor requiring further clarification, as patient reports indicate a positive family history in approximately 60–80% of cases. Several genes have been implicated in isolated patients or families with lipedema, including *POU1F1A*, *NSD1*, and *AKR1C*. [10]

Ishaq et al., through global gene expression analysis and pathway enrichment analysis, demonstrated significant alterations in the molecular signature of lipedema tissue. The identified gene expression profile involved *ZIC1*, *UGT1A7*, *GREM1*, *TRIM67*, *BUB1*, and *HOTAIR*, genes related to cell cycle regulation and cellular proliferation, thereby favoring adipose hyperproliferation, fibrosis, and inflammation—features consistent with the key clinical characteristics of lipedema. *BUB1* mRNA expression was significantly increased both in lipedema tissue and in adipose-derived stem cells. Overexpression of *BUB1* is associated with hyperproliferation and dysregulation of key cellular processes in various cancers, as *BUB1* is a mitotic checkpoint protein whose hyperactivation leads to increased cellular proliferation and chromosomal instability via histone H2A hyperactivation. The finding that *BUB1* mRNA is overexpressed in adipose-derived stem cells from lipedema suggests that *BUB1* may play a similar role in lipedema as it does in cancer, namely driving excessive cellular proliferation. The authors reported a 77% reduction in adipose-derived stem cell proliferation after three days of treatment with the molecule 2OH-BNPP1 in lipedema patients, whereas proliferation inhibition in non-lipedema controls was more modest (approximately 40%). This suggests that the hyperproliferative state of lipedema-derived stem cells renders them more sensitive to cell-cycle inhibitory agents, supporting *BUB1* modulation as a potential therapeutic target. [11]

Harvey et al., in a study of an adult-onset obesity and lymphatic vascular disease model in mice with functional inactivation of a single allele of the homeobox gene *PROX1*, reported hyperpermeable lymphatics and consequent obesity. Another possible candidate gene involved in lipedema pathogenesis is *PIT-1*. A *PIT-1* mutation was identified in a 23-year-old man and his mother, with short stature and leg swelling affecting women across four generations in the family. This finding is consistent with observations by Földi et al., who reported a higher incidence of lipedema following surgery for pituitary adenomas. Bone morphogenetic protein 2 (BMP-2), which is estrogen-regulated, can induce inflammatory reactions with edema, stimulates adipogenesis, and has been reported as a cause of acute lipedema. The *NSD1* mutation, known to be associated with Sotos syndrome, may also be responsible for estrogen-mediated lipedema formation. These studies may represent a possible link between genetic background and the role of estrogen in lipedema development. [12]

Morgan et al. described the first reported case of monozygotic twins affected by lipedema within a studied patient cohort. In a genetic ontology analysis of identified variants, mutations were found in 469 genes, with no single gene mutated across all families, indicating that no unique exomic factor is responsible for lipedema in all cases. This finding reinforces the multifactorial and heterogeneous nature of lipedema, suggesting that different genetic and environmental combinations may converge

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toward similar clinical phenotypes. The authors also observed an overrepresentation of variants related to vasopressin receptor activity and microfibril binding. This connection is particularly relevant, as microfibrils play a crucial role in connective tissue function, and lipedema is a connective tissue disorder. Variants were identified in several extracellular matrix (ECM)–related genes, including *STAB1*, which encodes a scavenger receptor involved in clearing collagen-binding proteins from the ECM and has been associated with waist-to-hip ratio in humans, and *TNXB*, which encodes the ECM glycoprotein tenascin-X. Tenascin-X deficiency causes abnormal elastin fiber morphology and reduced dermal collagen levels. *TNXB* haploinsufficiency causes the hypermobile type of Ehlers–Danlos syndrome, which is more prevalent in women and is characterized by joint hypermobility and spontaneous bruising—both features of lipedema. This study was the first exome-wide analysis to identify rare ECM-related genetic variants in families with lipedema, supporting a genetic background in which multiple variants, combined with environmental factors, confer susceptibility to the disease. [10]

In a recently published study, Wang et al., using whole-genome sequencing, identified mutations in the *PROC* gene as the only common candidate among patients affected by lipedema. They examined the role of protein C (PC) zymogen in adipocyte progenitors, revealing a PC–PROCR–HIF-1α signaling axis involved in adipogenesis. PC is primarily expressed by hepatic cells and secreted into the circulation to bind its receptor (PROCR) in other tissues. Although *PROC* expression was not detectable in the examined cell groups, PROCR was abundantly expressed in early adipocyte progenitors marked by CD55 and DPP4 expression. These findings indicate that PROCR is expressed in adipocyte progenitors and that an intact PC–PROCR axis is essential for suppressing adipocyte progenitor differentiation. PC likely targets PROCR-expressing adipocyte progenitors to promote HIF-1α accumulation, thereby inhibiting adipocyte differentiation. Traditionally recognized for its anticoagulant role, PC was shown in this study to have a novel function in inhibiting adipose progenitor cell differentiation, offering new insights into lipedema pathogenesis. [9]

Recent studies have further demonstrated that the *PROCR* gene is strongly associated with body fat distribution and identified a population of PROCR-high mesenchymal progenitors in the adventitial layer of human blood vessels, capable of osteogenesis and adipogenesis in vitro[13,14]. These findings suggest that *PROC* gene variants may contribute to lipedema susceptibility, possibly in interaction with vascular, inflammatory, and environmental factors[9,13,14].

Whole-genome sequencing of 162 italian and american patients with lipedema identified 21 heterozygous deleterious variants according to three of five predictive tools, including variants in *PLIN1*, *LIPE*, *ALDH18A1*, *PPARγ*, *GHR*, *INSR*, *RYR1*, *NPC1*, *POMC*, *NR0B2*, *GCKR*, and *PPAR-α* in 17 patients. Variants in most of these genes (except *GHR* and *ALDH18A1*) have been linked to fat disorders. Variants in *ALDH18A1* have been associated with connective tissue disorders such as cutis laxa, characterized by reduced elastic tissue formation and skin folds, resembling the joint hypermobility observed in lipedema[15]. These findings suggest that lipedema may involve dysregulation of key molecular pathways related to hypoxia signaling, extracellular matrix remodeling, and endothelial barrier integrity. The main genetic variants and their potential functional implications in lipedema are summarized in Table 1

Table 1. Genetic variants associated with lipedema.

Gene	Biological Function	Evidence Type	Potential Role in Lipedema	Vascular/ECM Relevance
PROCR	Endothelial protein C receptor signaling	Whole-genome sequencing	Regulates adipocyte progenitor differentiation via HIF-1α	Endothelial signaling
BUB1	Mitotic checkpoint regulator	Gene expression analysis	Promotes adipose hyperproliferation	Tissue expansion
TNXB	Extracellular matrix glycoprotein	Exome sequencing	Connective tissue fragility	ECM elasticity

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STAB1	Scavenger receptor	Variant analysis	ECM remodeling	Vascular structure
PPARγ	Adipogenesis regulator	Genetic studies	Adipocyte differentiation	Indirect vascular
PLIN1	Lipid droplet regulation	WGS	Lipid metabolism alteration	Adipose expansion
LIPE	Lipolysis enzyme	WGS	Fat metabolism dysregulation	Indirect vascular
ALDH18A1	Connective tissue metabolism	Association	Connective tissue disorder	ECM support
GHR	Growth hormone receptor	Genetic studies	Adipose metabolism	Indirect vascular

Table 1. Summary of genetic variants associated with lipedema, including their biological functions, type of supporting evidence, and potential contributions to disease pathophysiology. The table highlights the genetic heterogeneity of lipedema and emphasizes the involvement of pathways related to adipogenesis, extracellular matrix organization, and vascular regulation.

5. Endothelium and Vascular Permeability

Microangiopathy is one of the earliest histological features of lipedema pathogenesis, resulting from a primary defect in endothelial barrier function[12].

Multiple studies have postulated correlations between lipedema onset and progression and microangiopathy, lymphangiopathy, adipocyte hyperplasia and hypertrophy, tissue hypoxia, fibrosis, and macrophage infiltration, without identifying causal triggers or clarifying the pathophysiological role of hormones. Early microangiopathy associated with adipose tissue growth may lead to endothelial barrier disruption and increased capillary permeability, allowing protein-rich vascular fluid to extravasate into the interstitium. Macroangiopathy may also develop, primarily affecting the venous system and increasing hydrostatic pressure, thereby contributing to edema formation. Chronic tissue exposure to protein-rich fluid may induce secondary inflammatory reactions and promote fibrosis[16].

The concept of increased vascular permeability in inflammation dates back to 1873, when Julius Cohnheim observed that the inflammatory tumor was better explained by an increase in the permeability of the vascular wall. In 1961, thanks to electron microscopy and the availability of chemically pure inflammatory mediators, it became clear that histamine, serotonin, and bradykinin induced gaps in the endothelium of venules, while capillaries were almost completely spared. Studies based on the principle of vascular labeling then showed that local injury (mechanical, thermal, or toxic) caused indiscriminate leakage (as expected) from all segments of the microcirculation: arterioles, capillaries, and venules; this was defined as “leakage by direct injury” [6].

Although the endothelium was initially considered merely a functional barrier, it is now recognized as a dynamic unit regulating numerous critical physiological processes, including those of adipose tissue, such as lipid storage volume and distribution. To maintain a healthy adipose tissue microenvironment, adipocytes are surrounded by interstitial fluid and supported by an extracellular matrix protein network that provides structural integrity[15].

High sodium intake has increasingly been recognized as a risk factor for inflammatory pathologies and autoimmune diseases. The endothelial glycocalyx, an electronegatively charged mesh of glycoproteins, proteoglycans, glycosaminoglycans, and associated plasma proteins, functions as a sodium-sensitive vasculoprotective barrier. Sodium-induced collapse of the glycocalyx disrupts its barrier function, alters nanomechanical properties, increases monocyte–endothelium adhesion, and is associated with pro-inflammatory cytokine release and vascular inflammation[17].

Elevated free fatty acid levels may also lead to endothelial dysfunction and altered transendothelial transport. Under hypoxic conditions, HIF-1α–induced fibrosis may develop, compromising compensatory lymphatic drainage. Leptin further modulates angiogenesis under hypoxia, directly affecting the endothelium and increasing VEGF production. In addition to hypoxia, adipose hyperplasia and local capillary hypertension may contribute to microangiopathy and hyperpermeability. Increased aortic stiffness and peripheral vascular resistance with arteriolar remodeling may also occur[12].

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One proposed pathogenic mechanism involves inadequate extracellular matrix remodeling, in which uncoupling of the MMP-14–caveolin-1 axis in adipocytes leads to abnormal matrix processing and hypertrophic expansion of subcutaneous adipose tissue. Early studies identified slightly reduced expression of MMP-2, MMP-9, and MMP-11 in lipedema compared with controls, without significant differences in fibronectin or collagen expression. Alterations in extracellular matrix composition or connective tissue compliance warrant further investigation, particularly in relation to joint hypermobility and reduced skin and aortic elasticity observed in some lipedema patients[18].

Insufficient interstitial fluid drainage is a hallmark of lipedema, leading to excessive fluid accumulation in the interstitium. Excess interstitial fluid is directly associated with adipocyte hypertrophy and hyperplasia, resulting in hypoxia, microangiopathy, and increased endothelial capillary permeability. Persistent exposure of tissues to interstitial fluid that is not adequately drained by lymphatic vessels nourishes surrounding cells, perpetuating endothelial dysfunction, excessive fat growth, and pathological adipose tissue remodeling in a cyclical manner. Similar to obesity, this remodeling contributes to hypoxic conditions within lipedema adipose tissue, leading to necrosis, inflammation, and fibrosis[15].

Advanced lipedema cases may progress to lymphatic abnormalities, potentially secondary to lipedema-induced microangiopathy, plasma protein extravasation, pericellular fluid accumulation, and dilation of pre-lymphatic drainage systems. Fluorescence microlymphography studies have confirmed pathological lymphatic changes, including microlymphatic aneurysm formation, in affected skin areas. Lymphoscintigraphy studies have demonstrated abnormal lymphatic profiles and reduced lymphatic flow in lipedema patients, and a recent prospective study involving 83 women diagnosed with lipedema demonstrated the presence of abnormal lymphoscintigraphic findings in 47% of the patient population[19].

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a multistep process involving vasodilation, matrix degradation, endothelial activation, migration, and lumen formation. Angiogenesis has been repeatedly identified in lipedema across multiple studies. Increased dermal vessel density, capillary dilation, macrophage infiltration, and extension of dermal vessels toward the epidermis—previously reported mainly in inflammatory dermatoses—have been documented in lipedema. These findings highlight the role of macrophages in inflammation and angiogenesis and suggest that increased dermal vascularization may serve as a marker of underlying adipose angiogenesis[20].

Increased capillary permeability resulting from connective tissue elasticity loss, endothelial barrier dysfunction, and subsequent extravasation of protein-rich fluid into the extracellular space has been proposed as a key pathophysiological mechanism in lipedema. [16,18,20-25]

Morphological differences in endothelial junctions between lipedema patients and controls have been demonstrated using immunoassays for ZO-1 and CD31, corresponding to tight and adherens junctions, respectively. Furthermore, supernatants from stromal vascular fraction cultures of lipedema patients were sufficient to alter endothelial cells from healthy individuals[16].

Ultrastructural electron microscopy analyses made by Michelin et al have revealed endothelial abnormalities that may underlie adipocyte hypertrophy, disrupted calcium metabolism, and macrophage infiltration[26]. These findings suggest that endothelial dysfunction—characterized by increased endothelial proliferation and pericyte density—contributes to pathological adipose tissue remodeling in lipedema. Continuous immune cell accumulation and sustained cytokine release may perpetuate localized inflammatory cycles, contributing to tissue damage and disease progression [24].

The concept that ASCs are endothelial cells is supported by several published findings: 1) isolated mature human adipocytes can differentiate into endothelial-like cells, and endothelial cells can be converted into mesenchymal stem cells capable of differentiating into adipocytes; 2) capillary networks and single-cell suspensions from microvessels of human fat explants give rise to well-characterized adipocyte progenitors that can independently develop into mature adipocytes; 3) perilipin, adiponectin, and preadipocytes have been found emerging in inguinal white adipose tissue and proliferate to form clusters that strongly interact with the growing adipose vasculature, and specific depletion of VEGRF-2 in the endothelium led to vascular disruption and impaired adipogenesis in vivo; 4) an endothelial origin would imply endothelial-mesenchymal transition,

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which is linked to bone morphogenetic protein/transforming growth factor β signaling, and the absence of myocardin-related transcription factor-A appears to induce progenitor commitment impairment along the adipogenic lineage; and 5) capillary endothelial cells from adipose tissue express the adipogenic commitment factor ZFP423. Therefore, the endothelial and pericyte hyperplasia found here, mainly in adipose tissue from affected areas in patients with lipedema, aligns with the idea that these cells, by developing into adipocyte precursors, give rise to the development of abnormal hyperplastic adipose tissue, which is a clear pathogenic event and a clinical hallmark of lipedema [25].

Although multiple studies point to early endothelial changes in lipedema, it is not yet fully established whether such alterations represent a primary event or an adaptive response to adipose expansion and local inflammation. It is plausible that lipedema develops from a bidirectional model, in which endothelial dysfunction, abnormal adipogenesis, and inflammation perpetuate each other cyclically [15-18, 20-25]. The principal endothelial and vascular alterations described in lipedema, along with their clinical implications, are summarized in Table 2. A proposed pathophysiological cycle integrating endothelial dysfunction, adipose tissue expansion, and inflammation is presented in Table 3.

Table 2. Vascular and endothelial alterations in lipedema.

Mechanism	Description	Evidence in Lipedema	Clinical Implication
Capillary hyperpermeability	Endothelial barrier disruption	ZO-1/CD31 alterations	Edema
Microangiopathy	Microvascular structural damage	Histopathology	Hypoxia
Endothelial dysfunction	Impaired vascular regulation	Functional/ultrastructural evidence	Inflammation
Glycocalyx disruption	Loss of vascular barrier	Inflammation/sodium effects	Leakage
Angiogenesis	Increased vessel formation	Dermal vascular density	Remodeling
Lymphatic dysfunction	Impaired drainage	Lymphoscintigraphy	Persistent edema
Hypoxia	Reduced oxygen	Secondary effect	Fibrosis

Table 2. Overview of endothelial and vascular alterations described in lipedema, including underlying mechanisms, supporting evidence, and clinical implications. These findings support the role of microangiopathy, increased capillary permeability, and endothelial dysfunction as central features in disease development and progression.

Table 3. Proposed pathophysiological cycle in lipedema.

Step	Pathophysiological Event	Consequence
1	Endothelial dysfunction	Increased permeability
2	Fluid extravasation	Interstitial edema
3	Lymphatic impairment	Fluid accumulation
4	Adipocyte hypertrophy/hyperplasia	Tissue expansion
5	Hypoxia	HIF-1α activation
6	Inflammation	Cytokine release
7	Fibrosis	Tissue remodeling
8	Microangiopathy progression	Cycle perpetuation

Table 3. Proposed pathophysiological cycle of lipedema, illustrating the dynamic interplay between endothelial dysfunction, interstitial fluid accumulation, adipose tissue expansion, hypoxia, inflammation, and fibrosis. This model highlights the self-perpetuating nature of disease progression.

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6. Discussion

Hormonal pathways proposed as common between lipedema and estrogen-predominant gynecological diseases currently lack direct pathophysiological evidence. Their coexistence in some lipedema patients likely reflects general epidemiological distribution rather than shared causal mechanisms, potentially amplified by the frequent coexistence of obesity, without a common pathophysiological link [5,7,26-30].

The fact that most cases of lipedema begin during female reproductive milestones may merely reflect a greater statistical probability, as most of a woman's life is indeed marked by periods of hormonal fluctuation. However, cases that begin in childhood—when these hormonal changes have not yet occurred—are not explained by these theories. Furthermore, during menopause, there is often a paradoxical clinical improvement in estrogen-dependent diseases, which further challenges the alleged relationship between lipedema and these conditions. Several studies have shown that a decrease in estrogen levels results in increased expression of pro-inflammatory cytokines, including interleukins (IL)-6, IL1-β, and Tumor Necrosis Factor-alpha (TNF-α), as observed in women undergoing menopause or who have had oophorectomy. This could explain the onset of the disease during the menopausal period.[31]

In their study, Strohmeier et al. demonstrated that no significant difference was observed in estrogen receptor alpha and beta (ER-α, ER-β) between healthy fat and lipedema fat or their cells, and that although ER-α mRNA expression showed a trend toward upregulation in lipedema compared to the stromal vascular fraction (SVF) of healthy thigh tissue, this regulation was not significant. Likewise, no significant increase was found in aromatase expression in isolated SVF from thighs with lipedema, due to high donor variability.[16]

Bauer et al. showed in their work that aromatase (CYP19A1) expression was significantly reduced in adipocytes with lipedema compared to control cells. They also highlighted that, since leptin increases aromatase activity and transcription in stromal vascular cells, its interaction in adipose tissue with lipedema should be considered and evaluated.[32]

Even the claims that most lipedema cases begin at puberty have been contested in a European consensus, raising further doubts about the role of estrogen level fluctuations in triggering the disease.[33] Together, these findings support a systems-level model in which genetic susceptibility, endothelial dysfunction, and adipose tissue remodeling interact dynamically. These insights may contribute to the development of targeted therapeutic strategies focusing on vascular and inflammatory pathways.

7. Conclusions

In contrast to the absence of objective evidence supporting estrogen, its serum or tissue levels, receptor imbalance, or signaling pathways as causal triggers of lipedema, genetic polymorphisms and vascular alterations have been consistently demonstrated across investigated cases [8-16,18,20-25]. A comparison between the traditional estrogen-dependence hypothesis and current evidence is summarized in Table 4.

Table 4. Estrogen hypothesis versus current evidence.

Aspect	Estrogen Hypothesis	Current Evidence
Disease trigger	Estrogen fluctuations initiate disease	No consistent causal evidence
Receptor expression	Altered ER drives pathology	No significant differences
Aromatase activity	Increased local estrogen	Variable/reduced expression
Clinical correlation	Linked to hormonal phases	Occurs outside hormonal changes
Mechanistic role	Primary causal factor	Secondary/modulatory

Table 4. Comparison between the traditional estrogen-dependence hypothesis and current evidence in lipedema. The table summarizes key discrepancies between proposed hormonal mechanisms and available data, supporting the view that estrogen may act as a modulatory rather than a primary causal factor.

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Current data do not support classifying lipedema as an estrogen-dependent disease. The role of estrogen remains speculative and theoretically based on its participation in inflammation and lipid metabolism, particularly in postmenopausal women with associated obesity [1,2,4].

Likewise, although genetic and vascular findings are promising, they do not yet allow the definition of a single causal model, reinforcing the need for integrative approaches to further elucidate the pathophysiology of lipedema [8-18,20-25]. It is plausible that lipedema results from a bidirectional interaction between endothelial dysfunction and adipose tissue expansion. From a vascular perspective, lipedema may be better understood as a disorder of microvascular regulation and interstitial fluid dynamics, rather than a primarily endocrine disease as illustrated in Figure 1. These mechanisms may directly explain hallmark clinical features such as pain, easy bruising, and disproportionate limb enlargement.

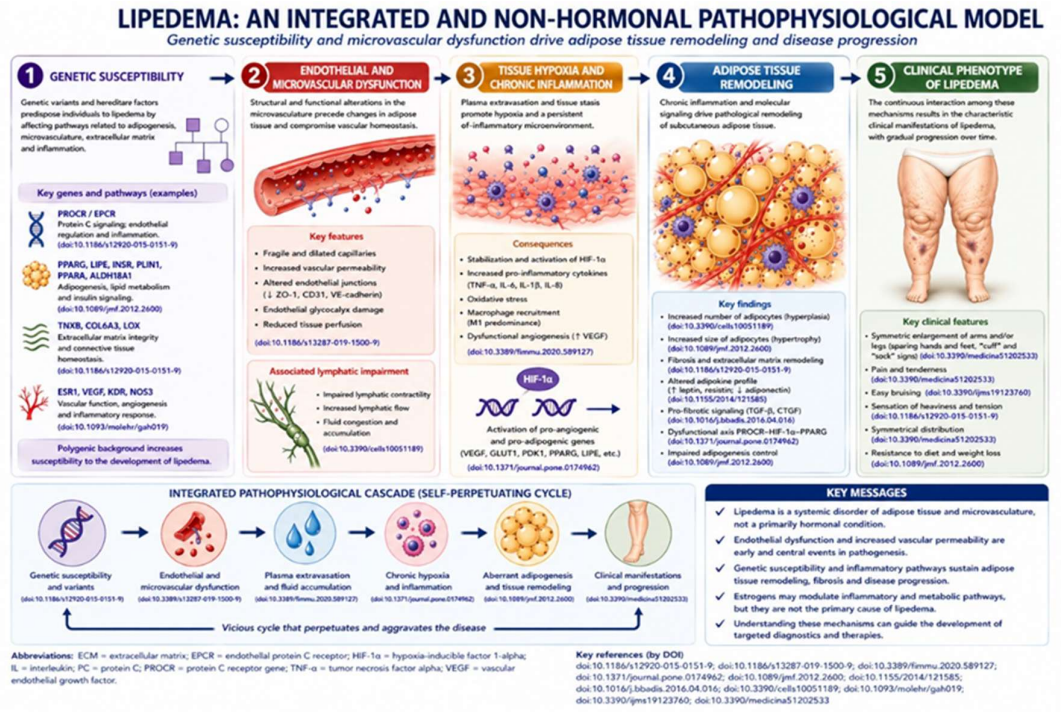

Figure 1. Integrated and non-hormonal pathophysiological model of lipedema. Genetic susceptibility interacts with endothelial and microvascular dysfunction, leading to increased vascular permeability and interstitial fluid accumulation. These alterations promote tissue hypoxia and chronic inflammation, resulting in dysregulated adipogenesis and pathological remodeling of adipose tissue. The interplay between these mechanisms establishes a self-perpetuating cycle that drives disease progression and clinical manifestations. Although estrogen-related pathways may modulate inflammatory and metabolic processes, current evidence does not support a primary causal role in lipedema pathogenesis.

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