



Review

# Pathogenesis of Lipedema: A Hypothesis-Generating Model of Regenerative Imbalance in Adipose Tissue <sup>†</sup>

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<sup>†</sup> This article is dedicated to the memory of our colleagues and friends Gerhard Sattler and Maurizio Podda.

## Abstract

Lipedema is a chronic adipose tissue disorder characterized by disproportionate and often painful enlargement of the extremities, occurring predominantly in women. Despite increasing clinical recognition, the underlying pathophysiology remains incompletely understood and is likely multifactorial. Existing evidence suggests contributions from vascular alterations, adipose tissue remodeling, inflammatory activation, hormonal influences, and lymphatic dysfunction. This review proposes a hypothesis-generating integrative framework in which lipedema may reflect a regenerative imbalance of subcutaneous adipose tissue. Within this model, genetically and hormonally modulated endothelial permeability could promote activation of perivascular adipose-derived stromal/stem-cell niches and stromal vascular fraction signaling pathways, thereby facilitating coupled angiogenesis and adipogenesis. Progressive adipocyte hyperplasia and hypertrophy may subsequently contribute to inflammatory remodeling, pain generation, and secondary impairment of dermal and subdermal lymphatic drainage. The proposed framework attempts to integrate clinical, histological, imaging, molecular, and endocrine observations into a biologically coherent conceptual model. At the same time, the review emphasizes the current limitations of the available evidence, the heterogeneity of lipedema phenotypes, and the ongoing controversies regarding disease progression, obesity overlap, and the relative role of lymphatic dysfunction. Finally, the potential mechanistic rationale of lymphatic-sparing liposuction is discussed in the context of tissue decompression, restoration of lymphatic transport, and interruption of persistent adipose remodeling. The model presented here should be interpreted as a hypothesis-generating conceptual scaffold requiring prospective validation. Importantly, the present framework should be interpreted as a biologically plausible and hypothesis-generating conceptual model rather than a definitive mechanistic doctrine. Several proposed interactions remain associative and require prospective biological validation.

**Keywords:** angio and adipogenesis; microRNA; mural ADSCs (adipose-derived stem cells); aromatase; dermal/subdermal lymph congestion; hyperplasia; hypertrophy; liposuction; lipedema pain; metabolism; stromal vascular fraction (SVF)



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## 1. Clinical Definition and Epidemiology of Lipedema

Current international guidelines and consensus statements [1] describe lipedema as a distinct clinical phenotype that can overlap with obesity, venous disease, and lymphatic dysfunction while maintaining characteristic distribution patterns and symptom profiles [1,2].

Lipedema is a painful, chronic, progressive disease of the subcutaneous fatty tissue characterized by disproportionate, symmetrical fat accumulation in the extremities. Typically, the legs are affected, and less frequently the arms, while the hands and feet are spared. Clinically, the main symptoms are pressure, heaviness, tension, a tendency for skin bleeding (suffusion) [2–4], pressure pain, and negative skin indentation. The current S2k guideline [4] describes lipedema as a distinct clinical picture that is potentially distinguishable from obesity and lymphedema. Reliable epidemiological data on lipedema remain limited because of heterogeneous diagnostic criteria, underrecognition, referral bias, and the absence of population-based longitudinal studies. Published prevalence estimates therefore vary considerably depending on methodology and study population. Earlier estimates were primarily derived from specialist-clinic cohorts and observational screening studies rather than robust epidemiological investigations [5]. Additional prevalence data have since been reported in occupational cohorts and regional population studies [6,7]. However, despite increasing clinical recognition of lipedema, large-scale standardized epidemiological studies are still lacking.

## 2. Historical Development and Early Concepts

For a long time, fat cells were considered a passive storage site for energy in the form of triglycerides, which grows and shrinks over the course of a lifetime. This simplified view still shapes the layman's understanding today. As early as 1870, Carl Toldt postulated that adipose tissue should be regarded as an independent organ with its own dynamics due to its specific vascular system. Paul Gerson Unna followed up on this by attributing increased fat growth to stagnation of lymphatic or venous tissue. In fact, adipose tissue undergoes an annual turnover of approximately 10% (degeneration: sudden cell death through apoptosis, removal via the lymphatic system and elimination via the liver; regeneration: replenishment of the cell pool via mural vascular stem cells, ADSCs (adipose-derived stem cells)) [8]. In patients with lipedema, this physiological process is disrupted in the arms and legs due to genetic and hormonal influences [2,9].

Finally, about 100 years ago, the anatomists Bauer [10] from Vienna and Günther [11] from Leipzig described the phenomenon of tissue lipophobia: Lipophobic regions are those in which there is no fat under the skin, only bone, cartilage, or ligaments. This affects the ear, the eyelid, the breast, and the shinbone. For us, the accumulation of fat above the shinbone is particularly pathognomonic for lipedema. This phenomenon serves as a diagnostic characteristic (clinical examination, ultrasound, and histological sampling).

The accumulation of fat on the lower leg is also responsible for the fact that lipedema patients can hardly fit into boots or ski boots. This region is often more sensitive to pressure pain than the surrounding tissue. Similarly, patients with upper arm involvement report considerable pain when their blood pressure is measured.

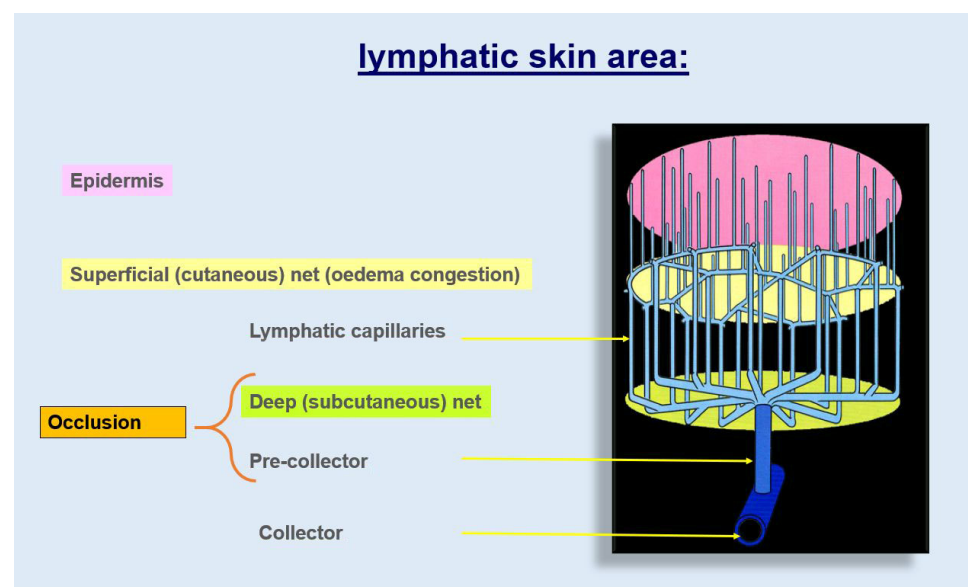
## 3. Anatomical Basics and Pathophysiological Mechanisms (Stem Cell Regeneration and Degeneration)

Lipedema may involve a genetically determined “leaky vessel” situation in the vascular intima caused by estrogen [12]: Increased vascular permeability activates mural adipose stem cells (ADSCs) located in the periphery of the vessels. These initiate both angiogenesis and adipogenesis [13]. The stromal vascular fraction (SVF) plays a key role

in this process: the extracellular vesicles released from it, which contain characteristic microRNAs, ultimately cause angiogenesis and adipogenesis, which are responsible for fat cell formation [13]. This may contribute to large, metabolically inactive adipocytes that fill the entire subcutaneous fat space (hyperplasia and hypertrophy) [14].

The body attempts to compensate for this regenerative cell surplus by activating phagocytic cell elements. Specialized mast cells and macrophages are involved in this painful inflammatory reaction. However, they are unable to efficiently eliminate excess adipocytes in order to restore balance. The histologically proven so-called “crown-like cells” represent the maximum attempt to eliminate excess adipocytes [15]. This may contribute to a regenerative imbalance and the characteristic disease of lipedema.

The hyperplasia of the fatty tissue ultimately may lead to strangulation of the capillaries and precollectors of the draining subcutaneous lymphatic system. This may contribute to dermal and subdermal lymphatic congestion (Figure 1). This congestion was also demonstrated in a clinical MRI study by Crescenzi et al. [12]. Stöberl describes so-called flame-shaped structures [16], Amman-Vesti microlymphatic aneurysms with so-called lymph gaps [17], and Al-Ghadban enlarged lymphological “microvessels” [14].



**Figure 1.** Lymphatic skin area.

In our own investigations, we were able to demonstrate the development of increased stem cell activity [9]. The microRNAs originating from the stromal vascular fraction (SVF) were detected in a further study [13]. Finally, the initial vascular changes (leaky vessels) were presented and a genetic predisposition to increased aromatase expression detected in this fraction was described [12].

Furthermore, the molecular mechanisms described (dermal lymph congestion—stem cell activation) ultimately explain the “perpetuum mobile” of adipocyte hyperplasia and the imbalance between increased regeneration and deficient degeneration.

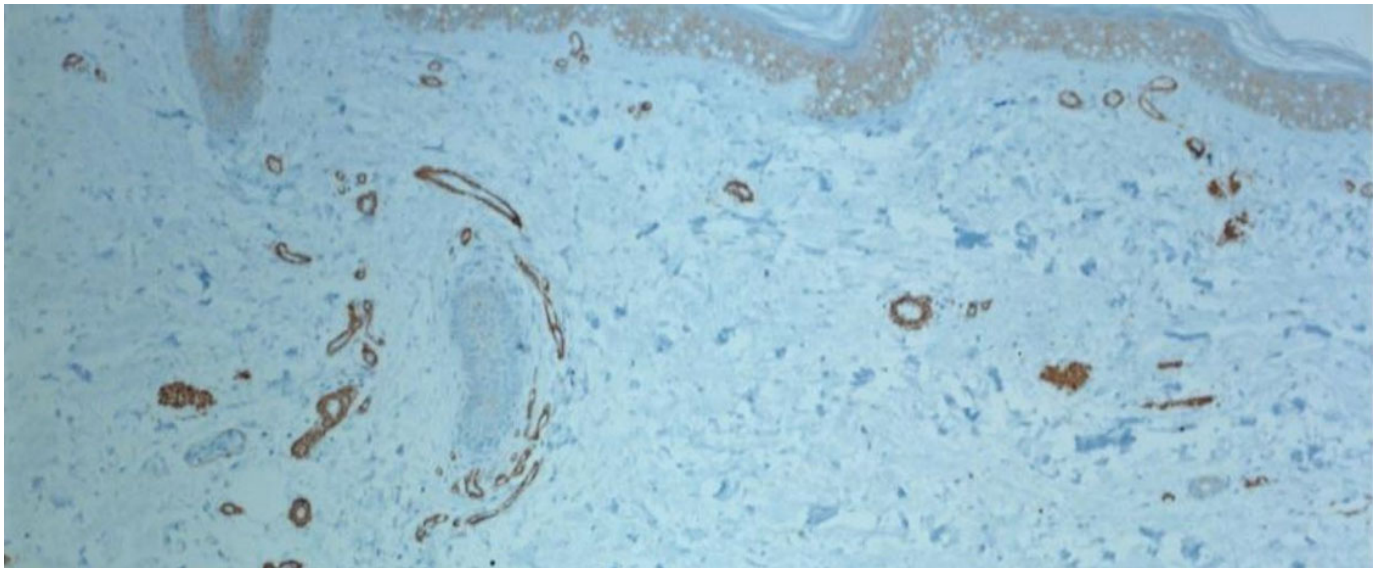
This also may help explain the clinical picture of the progressive development of lipedema:

1. Spontaneous skin bleeding and bleeding tendency (suffusions) due to fragile neocapillaries in the context of increased angiogenesis and adipogenesis (own histo-system staining) (Figure 2).
2. Negative pitting in dermal–subdermal oedema [18].

3. Pain/pressure/tension and heaviness caused by inflammatory activation) of phagocytic cell elements (macrophages, mast cells) [14] (Figure 3).
4. Negative influence on basal metabolic rate in the majority of cases: activation of storage function or metabolism with secondary fat accumulation (hypertrophy) in the abdominal area (100%) and additional metabolic accumulation in areas of mixed fat (buttocks, thighs, and upper arms) [16]. Interestingly, this metabolic storage function associated with lipedema does not lead to metabolic diseases such as type 2 diabetes mellitus [16,19]. This correlation was already described around 100 years ago by internists experienced in clinical observation as “healthy fat people.”
5. Triggerable pressure pain due to fascial congestion. This results on the one hand from the subcutaneous lipedema compartment (adipofascial congestion) and on the other hand from a mostly visceroadominal lymphatic drainage disorder in the context of metabolic fat accumulation (myofascial congestion) [20,21].
6. The genetically determined increase in aromatase activity also plays a significant clinical role in lipedema flare-ups during menopause [12].



**Figure 2.** Successful liposuction of a lipedema in 2 sessions with disappearance of all symptoms of the disease and metabolic belly fat.



**Figure 3.** Dermal–subdermal angiogenesis in lipedema (SMA staining).

Aromatase (CYP19A1) is a key enzyme in estrogen synthesis that converts androgens into estrogens and thus determines the local availability of active estrogens in adipose tissue [20,22,23]. These estrogens promote adipogenesis, i.e., the differentiation of preadipocytes into mature adipocytes, and influence lipogenesis, inflammatory processes, and regional fat distribution [24,25]. Accordingly, studies show that aromatase is up-regulated in adipose and inflamed adipose tissue, thereby driving paracrine estrogen production [22,23].

Hormonal factors play a central role in lipedema, a chronic progressive fat distribution disorder that almost exclusively affects women [26–29]. Clinically, the disease often occurs during hormonal transition phases such as puberty, pregnancy, or menopause [26,27].

Recent pathophysiological models describe that, despite a systemic drop in estrogen during menopause, local estrogen production in subcutaneous adipose tissue is increased by upregulation of aromatase and steroidogenic enzymes such as 17 $\beta$ -HSD1 [29].

This may lead to an intracrine estrogen effect with persistent adipogenesis, inflammatory changes, and fibrosis in the subcutaneous adipose tissue [29].

These mechanisms could contribute to symptom persistence and tissue remodeling during hormonal transition phases. These observations raise the possibility that local endocrine and stromal mechanisms may contribute to symptom modulation; however, prospective evidence remains limited.

Hormonal and pharmacological influences such as estrogen-containing contraceptives, especially depot preparations such as the “three-month injection,” pregnancy, glucocorticoids, antidepressants (primarily tricyclic), and hormonal stimulation substances used in IVF, can also promote the progression of lipedema [16].

It is also striking that lipedema often only occurs in patients after their second pregnancy. Between the first and second pregnancy, there are indeed differences in the mother’s hormonal environment, resulting from the body’s experience, immunological adaptations, and, in some cases, altered tissue and receptor responses.

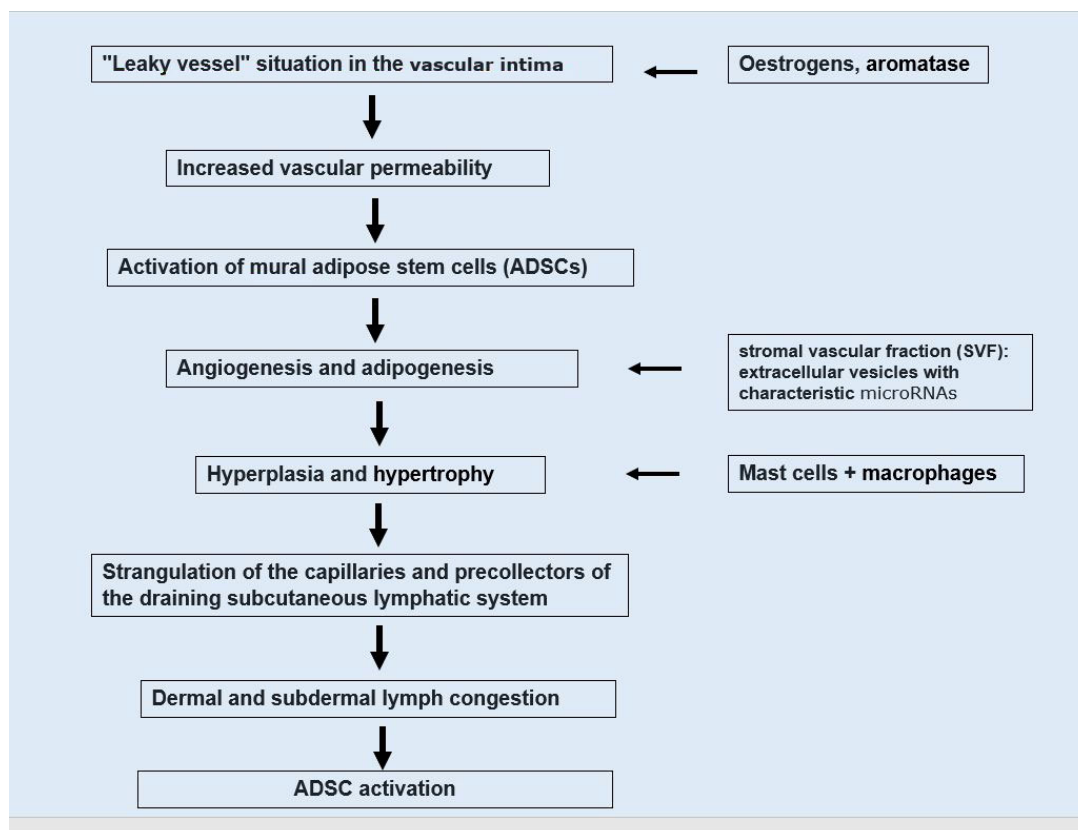
During the second pregnancy, the body is already “familiar” with this hormonal state. This means that receptors in the uterus, mammary glands, and immune system respond more efficiently in some cases. The hormone levels themselves (progesterone, estrogens, hCG) are very similar, but the tissue response and immunological regulation are more efficient in the second pregnancy [30].

#### 4. Confirmation of Pathophysiological Processes After Therapeutic Liposuction

Lymphatic-sparing liposuction has emerged as a potentially effective therapeutic option in selected patients with lipedema, particularly regarding symptom relief, mobility, and quality of life. Within the present framework, the beneficial effects of liposuction may extend beyond simple volume reduction and could involve tissue decompression, reduction in interstitial pressure, improvement of lymphatic transport, and partial interruption of persistent adipose remodeling. However, the extent to which liposuction modifies the underlying biology of lipedema rather than primarily reducing tissue burden remains incompletely understood.

The use of vessel-destroying energy such as lasers, radio frequency, plasma, or ultrasound is obsolete [31,32].

Postoperatively, there is an immediate cessation of pressure and pain symptoms, as well as the tendency to bleed from the skin. This is followed by a rapid recovery of psychological well-being and quality of life [16,32,33]. The ability to move without pain allows most patients to engage in more physical activity, thereby reducing metabolic fat deposits (Figure 2). Our pathophysiological approach is depicted in (Figure 4).



**Figure 4.** Flow chart of the proposed pathogenesis of lipedema.

#### 5. Discussion

The concept presented in this review interprets lipedema as a disorder of adipose tissue homeostasis in which regeneration persistently exceeds degeneration. Rather than explaining the disease by a single isolated abnormality, the model integrates several observations that have often been discussed separately: increased endothelial permeability, activation of perivascular progenitor niches, expansion of the stromal vascular fraction, angiogenesis, adipocyte hyperplasia and hypertrophy, inflammatory remodel-

ing, pain generation, and secondary lymphatic dysfunction [9,12–14,18]. In this sense, lipedema can be viewed as a self-reinforcing tissue program, consistent with recent integrative reviews emphasizing complex adipose-tissue remodeling and vascular-stromal interaction [12,26,34]. Once started in a predisposed anatomical region, repeated vascular leakage and local estrogenic signaling may continuously stimulate mural adipose-derived stem cells and thereby promote the formation of new adipocytes and microvessels. The resulting tissue enlargement increases interstitial pressure and mechanical stress, which may further compromise venous–lymphatic transport and perpetuate edema and inflammation.

A major strength of this integrative view is that it links the clinical hallmarks of lipedema with a plausible biological sequence. Patients typically report heaviness, tenderness, spontaneous bruising, and worsening during puberty, pregnancy, or menopause and substantial impairment in quality of life and mobility. These features are difficult to reconcile with simple obesity alone, but they fit well with a scenario characterized by microvascular fragility, neuro-inflammatory activation, and hormonally modulated adipose remodeling [2–4,19,26–29,35]. The sparing of the hands and feet as well as the pathognomonic fat deposition in lipophobic zones further suggest that regional anatomic and stromal characteristics influence where the process can be initiated and maintained. A disease model that incorporates local stem-cell niches, stromal signaling, and regional lymphatic vulnerability therefore offers an attractive explanation for the striking distribution pattern of lipedema.

Another important implication of the regenerative-imbalance hypothesis is that lipedema should not be understood as a static storage disorder. Adipose tissue is a dynamic organ with continuous turnover, vascular cross-talk, immune surveillance, and endocrine activity [8]. In lipedema, this physiological turnover appears to become uncoupled. Regenerative input is amplified, whereas degenerative clearance of excess adipocytes remains incomplete. Histological descriptions of adipocyte death, macrophage accumulation, and crown-like structures support the idea that the tissue attempts to remove surplus cells but does not fully restore equilibrium [14,15]. This incomplete resolution is likely relevant to symptom persistence. Even if gross tissue enlargement develops gradually over years, inflammatory and mechanical pain may fluctuate because the underlying remodeling process remains biologically active.

The role of the stromal vascular fraction is especially noteworthy because it provides a mechanistic bridge between vascular biology and adipose expansion. SVF-derived extracellular vesicles and microRNAs may influence endothelial behavior, progenitor activation, adipogenic differentiation, and immune-cell recruitment in a coordinated manner [9,13]. This means that lipedema is not merely a disease of enlarged mature adipocytes; rather, it may be a disease of the adipose microenvironment. If the stromal compartment is reprogrammed toward persistent pro-adipogenic and pro-angiogenic signaling, then progressive enlargement of the affected limbs becomes biologically understandable. Such an interpretation also aligns with recent multi-omics efforts, suggesting that lipedema has a specific molecular signature that may eventually support disease prediction and biologically informed classification [26].

The lymphatic component of the proposed model deserves particular attention. Historically, there has been controversy regarding whether lymphatic dysfunction is primary or secondary in lipedema. The present framework does not require advanced lymphatic failure to be the initiating event. Instead, it proposes that progressive fat-tissue hyperplasia and hypertrophy, together with interstitial fluid accumulation, gradually impair dermal and subdermal lymphatic drainage [17,18,28,36]. This distinction is clinically relevant. It may help explain why many patients show oedema-like symptoms and imaging abnormalities without meeting the criteria of classical lymphedema. It also may help explain why pain,

pressure, and tension may improve substantially when tissue volume and compartment pressure are reduced. In other words, lymphatic congestion may be both a consequence of adipose expansion and an amplifier of disease progression.

Inflammation in lipedema is also likely to be qualitatively different from the low-grade inflammation described in common obesity. The available literature and histological observations suggest a localized, mechanically and hormonally modulated inflammatory process involving macrophages, mast cells, endothelial activation, and altered tissue innervation [4,14,15]. This may help explain why patients can experience marked tenderness even when systemic metabolic markers are not severely disturbed. The notion of a metabolically less active but clinically highly symptomatic adipose compartment is consistent with the long-standing observation that many patients with lipedema do not fit the classical profile of insulin-resistant visceral obesity, despite substantial fat accumulation in affected regions [16,19]. However, this should not lead to the mistaken assumption that lipedema is metabolically irrelevant. Rather, it indicates that regional adipose biology may differ substantially between subcutaneous lipedema fat and centrally accumulated metabolic fat.

The endocrine dimension further strengthens the proposed model. Lipedema almost exclusively affects women and often manifests or worsens during periods of hormonal transition, which strongly argues against a purely mechanical explanation [2,26–29]. Increased local aromatase activity and altered steroidogenic enzyme expression could create an intracrine environment that favors persistent adipogenesis, inflammatory remodeling, and altered extracellular matrix organization in affected tissues [12,20,22,23,29]. Such local estrogenic amplification may be particularly relevant in menopause, where systemic estrogen levels decline but tissue-specific estrogen formation may remain elevated. This concept could explain the apparent paradox that some women report worsening of lipedema symptoms precisely when ovarian estrogen production is falling. It may also help explain why exogenous hormones or hormonally active medications can modulate the clinical course.

Taken together, the model presented here does not compete with established clinical definitions of lipedema; rather, it attempts to provide a biologically coherent scaffold beneath them. It accommodates the current guideline-based distinction from obesity and lymphedema while also acknowledging the frequent overlap with both conditions in daily practice [2]. Obesity may aggravate tissue load and metabolic strain, whereas lymphatic impairment may intensify fluid retention and symptoms. Yet dysregulated regenerative behavior of subcutaneous adipose tissue in genetically and hormonally susceptible regions may represent one important contributing mechanism in lipedema, potentially supported by emerging genome-wide association studies identifying candidate susceptibility loci [26,37]. This perspective has the advantage of explaining why some patients deteriorate despite weight-loss efforts and why symptom severity does not always correlate linearly with body mass index alone.

Several conceptual frameworks have been proposed to explain the pathophysiology of lipedema, including obesity-centered, lymphatic-centered, hormonal, and integrative stromal-regenerative models. These concepts are not necessarily mutually exclusive and may reflect overlapping biological processes. A comparative overview is summarized in Table 1.

**Table 1.** Comparison of Conceptual Models of Lipedema.

| Conceptual Model       | Primary Focus                                | Strengths                                          | Limitations                                                     |
|------------------------|----------------------------------------------|----------------------------------------------------|-----------------------------------------------------------------|
| Obesity-centered model | Adipocyte hypertrophy and metabolic overload | Explains overlap with obesity and tissue expansion | Does not fully explain pain, bruising, or regional distribution |

Table 1. Cont.

| Conceptual Model             | Primary Focus                                          | Strengths                                                                | Limitations                                    |
|------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------|
| Lymphatic-centered model     | Lymphatic dysfunction and edema                        | Explains fluid accumulation and imaging abnormalities                    | May not fully explain early adipose remodeling |
| Hormonal model               | Estrogenic and endocrine signaling                     | Explains female predominance and hormonal triggers                       | Mechanistically incomplete                     |
| Regenerative imbalance model | Stromal–endothelial dysregulation and adipose turnover | Integrates vascular, inflammatory, endocrine, and lymphatic observations | Requires prospective biological validation     |

## 6. Clinical Implications

From a clinical standpoint, the regenerative-imbalance model encourages a more differentiated therapeutic strategy. If lipedema is driven by a combination of vascular leakiness, stromal signaling, inflammatory activation, and secondary lymphatic compromise, then treatment should not be reduced to weight counseling alone. Weight management remains relevant, particularly to reduce concomitant metabolic adiposity and overall tissue load, but it is unlikely to normalize the local disease process in all patients. Conservative measures such as compression, exercise, manual techniques, and patient education can still play an important symptomatic role by supporting fluid transport, mobility, and self-efficacy. Their benefit may be greatest when they are integrated early, before severe compartmental enlargement and advanced fascial congestion have developed.

The model also helps explain why carefully performed lymphatic-sparing liposuction can produce benefits that exceed simple volume reduction. By removing a substantial proportion of pathologically expanded subcutaneous fat while preserving the superficial subdermal layer, the intervention may reduce interstitial pressure, improve tissue compliance, decompress lymphatic capillaries and precollectors, and interrupt continuous stimulation of the local regenerative loop [32,33,38]. This interpretation is compatible with the reported rapid improvement in pain, tenderness, mobility, quality of life, and susceptibility to bruising after surgery [16,32,36]. The surgical outcome should therefore not be judged only by aesthetic contour change; mechanistically, it may represent a tissue-resetting procedure in selected patients.

At the same time, the present pathophysiological concept supports a cautious and technique-sensitive approach to surgery. If the aim is to restore tissue drainage and reduce pathological fat burden without additional vascular or lymphatic injury, then atraumatic methods are essential. This is one reason why tumescence-based, lymphatic-sparing approaches using vibrating cannulas have gained strong support, whereas energy-based destructive modalities appear difficult to justify within this framework [31,32,38]. For the same reason, perioperative management should not focus solely on aspirated volume. Functional endpoints such as pain relief, restoration of mobility, reduction in edema, improved tolerance to compression, and sustained stabilization of limb disproportion are equally important.

The proposed model may also help improve diagnostic reasoning. In practice, lipedema is often underdiagnosed, overdiagnosed, or diagnosed late because symptoms overlap with obesity, venous disease, lymphedema, and generalized pain syndromes. A mechanistic understanding emphasizes that diagnosis should integrate distribution pattern, tenderness, bruising tendency, pitting behavior, hormonal history, and the distinction between localized limb adiposity and central metabolic adiposity. Imaging and tissue studies may not yet define routine diagnostic criteria, but they can increasingly be understood in relation to microvascular permeability, lymphatic congestion, and adipose remodeling rather than as isolated findings. This may ultimately support a more biologically grounded staging system than one based on surface appearance alone.

Finally, the current model has implications for patient communication. Many affected women have experienced repeated dismissal of their symptoms as merely lifestyle-related. Explaining lipedema as a disorder of regional adipose regulation, rather than a failure of personal discipline, can be clinically meaningful in itself. It validates the reality of pain and tenderness while still allowing room for active treatment strategies such as movement, strength training, metabolic optimization, compression, and surgery when indicated. Such communication may reduce stigma and improve adherence because it frames treatment as modulation of a chronic tissue disorder rather than punishment for body shape.

The relationship between lipedema and obesity also remains debated, with some investigators emphasizing overlap with obesity-associated adipose remodeling while others support a more distinct disease entity [19,34,35,37,39].

## 7. Limitations of the Proposed Model

Despite its integrative appeal, the present concept remains a hypothesis-driven synthesis and must be interpreted with appropriate caution. Lipedema research is still limited by small cohorts, heterogeneous diagnostic criteria, variable staging systems, and incomplete separation of pure lipedema from lipedema with obesity, venous disease, or secondary lymphatic dysfunction. Many published studies are cross-sectional and therefore cannot definitively establish temporal causality. Although many patients clinically report worsening symptoms over time, robust prospective longitudinal studies documenting universal progression are still lacking, and the progressive nature of lipedema therefore remains debated [40]. Increased endothelial permeability, inflammatory-cell accumulation, and lymphatic abnormalities are all compatible with the proposed sequence, but their exact order and relative contribution may vary among patients and disease stages.

A further limitation is that the molecular data currently available are still insufficient to define a single unifying pathway. SVF-derived extracellular vesicles, microRNAs, endothelial alterations, aromatase upregulation, and inflammatory remodeling are highly plausible elements, but they likely represent interacting modules rather than one linear cascade [12,13,26,29]. It is equally possible that lipedema comprises several biological subtypes that converge on a similar phenotype. Some patients may show stronger vascular predominance, others stronger hormonal or lymphatic components, and others a mixed phenotype shaped by obesity and mechanical load. The regenerative-imbalance model is therefore best understood as a framework for integration, not as a finished molecular doctrine.

The historical and clinical observations cited in this review are valuable because they capture enduring morphological patterns that modern medicine continues to recognize. Nevertheless, older descriptive literature has methodological limitations when interpreted through the lens of contemporary pathobiology. Terms such as lymphatic stagnation, lipophobia, and healthy obesity are conceptually useful but do not substitute for standardized imaging, molecular profiling, or prospective interventional studies. Where this manuscript extrapolates from such observations, the intention is heuristic: to connect older anatomic insight with newer vascular, stromal, and endocrine findings.

Another unresolved issue concerns pain generation. The model presented here links pain to inflammatory activation, oedema, and fascial congestion, which is clinically plausible and supported by emerging literature [3,4,14,41]. However, the relative importance of neurogenic inflammation, peripheral sensitization, altered mechanotransduction, and central pain amplification remains incompletely defined. Likewise, the absence of overt metabolic syndrome in many patients does not exclude important endocrine and immunologic consequences of chronic regional adipose dysfunction. These uncertainties should encourage further research rather than oversimplification.

## 8. Conclusions and Future Directions

In conclusion, currently available vascular, stromal, inflammatory, endocrine, imaging, and adipose-tissue observations can be integrated into a biologically plausible framework in which lipedema may reflect a dysregulated regenerative state of regional adipose tissue. The proposed model attempts to connect endothelial permeability, adipose-derived stromal-cell activation, adipose remodeling, inflammatory signaling, and secondary lymphatic alterations into a coherent hypothesis-generating concept. At the same time, substantial uncertainties remain regarding disease heterogeneity, progression dynamics, obesity overlap, and the relative contribution of individual mechanisms, including the unresolved question of whether lipedema is universally progressive [42]. The present framework should therefore be interpreted not as a definitive molecular doctrine, but rather as an integrative conceptual model intended to stimulate further translational and clinical investigation.

Future longitudinal, molecular, imaging, and multi-omics studies will be necessary to determine whether biologically distinct lipedema subtypes exist and to clarify the relative contribution of vascular, endocrine, inflammatory, and lymphatic mechanisms [26,42,43].

Future research should test this model prospectively and at multiple biological levels. First, longitudinal studies in early-stage disease are needed to clarify whether endothelial permeability changes and SVF signaling abnormalities precede detectable lymphatic congestion and adipocyte hypertrophy. Second, standardized tissue sampling combined with transcriptomics, proteomics, extracellular-vesicle analysis, and spatial histology may identify robust biomarkers for diagnosis, staging, and treatment response. Third, improved imaging protocols should examine how dermal and subdermal lymphatic transport changes across disease stages and after conservative or surgical therapy. Fourth, endocrine studies are needed to define the contribution of local estrogen synthesis, aromatase expression, and hormone receptor signaling in different life phases, especially puberty, pregnancy, and menopause.

Equally important is the need to translate mechanistic insight into clinically meaningful endpoints. Future trials should not focus solely on limb circumference or aspirate volume, but also include validated measures of pain, tenderness, bruising, mobility, quality of life, physical activity, and tissue texture. Such multidimensional outcomes would better capture the lived burden of lipedema and would help distinguish therapeutic benefit from simple cosmetic change. Comparative studies of conservative management, metabolic co-interventions, and different surgical techniques are also warranted. In particular, the extent to which liposuction modifies the underlying biology rather than merely debulks tissue should be investigated through pre- and post-interventional tissue, imaging, and symptom analyses.

Finally, the field would benefit from a more precise nosology. If lipedema is indeed a disorder of regional adipose regeneration, future classifications may move beyond purely descriptive staging and toward biologically informed phenotyping. Such a shift could improve patient selection, timing of intervention, and development of non-surgical therapies aimed at vascular permeability, stromal signaling, inflammation, or hormone-dependent adipogenesis. Until such tools are available, the present model may serve as a practical conceptual map: it acknowledges the complexity of lipedema, respects the clinical reality of patient suffering, and offers a rationale for integrated management strategies that combine conservative care, metabolic support, and, where indicated, technically appropriate lymphatic-sparing liposuction.

A further priority for the field is the development of practical translational tools for daily care. Prospective registries with harmonized diagnostic criteria could clarify the natural history of untreated and treated disease, identify predictors of progression, and distinguish responders from non-responders to conservative and surgical interventions.

In parallel, biobanking of adipose tissue, blood, and extracellular vesicles from well-characterized patients could accelerate the discovery of biomarkers that are suitable not only for research but also for routine monitoring. Such efforts would be especially valuable if they are linked to standardized phenotyping, including symptom burden, hormonal status, ultrasound or MRI findings, and long-term functional outcome. Ultimately, a future evidence-based lipedema pathway should enable earlier diagnosis, more rational timing of surgery, and the emergence of adjunctive targeted therapies that modify disease biology before irreversible tissue remodeling occurs.

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