Lipedema as a Female-Specific Adipose Tissue Disease: A Regenerative Imbalance Driven by Estrogen, Microvascular Dysfunction and Stem Cell Activation

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Keywords

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Description, guidelines, and epidemiology

Lipedema is a chronic progressive female-specific adipose tissue disease characterized by disproportionate and symmetrical accumulation of subcutaneous adipose tissue predominantly affecting women. Typically, the legs are affected and less frequently the arms, while the hands and feet are spared. Clinically, the main symptoms include pain, pressure, heaviness, tissue hypersensitivity, and a tendency to spontaneous skin hemorrhage. The current S2k guideline describes lipedema as a distinct disease entity clearly distinguishable from obesity and lymphedema. Hormonal transition phases such

as puberty, pregnancy, and menopause are considered major triggers of disease progression. Recent epidemiological and translational studies further support the concept of lipedema as a predominantly female-specific disease entity. Large clinical cohorts and molecular analyses demonstrate that lipedema overwhelmingly affects women and is closely associated with hormonal transition phases such as puberty, pregnancy, and menopause (38–40). Rare cases described in men are typically associated with endocrine dysfunction, hypogonadism, liver disease, or altered estrogen metabolism, further supporting the central role of estrogen-dependent mechanisms.

Why Lipedema Predominantly Affects Women

Lipedema is widely recognized as a disease that almost exclusively affects women. Epidemiological studies, clinical observations, and recent molecular investigations consistently demonstrate a strong association between disease onset and hormonal transition periods such as puberty, pregnancy, and menopause. Rare cases reported in men are usually associated with endocrine disorders, hypogonadism, liver disease, or altered estrogen metabolism.

These observations suggest that estrogen-dependent mechanisms may play a central role in disease initiation and progression. Estrogens influence adipocyte differentiation, adipose tissue distribution, vascular permeability, and inflammatory signaling. Increased local aromatase activity within adipose tissue may further amplify intracrine estrogen production and thereby promote regional adipose tissue expansion.

Taken together, current evidence supports the concept that lipedema should be regarded as a predominantly female-specific adipose tissue disorder influenced by hormonal, vascular, and regenerative mechanisms. However, the precise interaction between these factors requires further investigation.

The present hypothesis proposes that lipedema may result from an interaction between hormonal predisposition, estrogen-dependent microvascular dysfunction, and

dysregulated adipose tissue regeneration. Experimental and translational studies suggest that increased endothelial permeability ("leaky vessels") may activate mural adipo**se-derived stem cells (ADSCs) located in the perivascular niche. These cells may subsequently promote both angiogenesis and adipogenesis.**

The stromal vascular fraction (SVF) appears to play an important regulatory role in this process. Extracellular vesicles released from SVF cells contain characteristic microRNAs that may contribute to adipocyte differentiation, vascular remodeling, and tissue expansion. Together, these mechanisms could promote adipocyte hyperplasia and hypertrophy, thereby contributing to the characteristic tissue alterations observed in lipedema.

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; and regeneration: replenishment of the cell pool via mural vascular stem cells, ADSCs (adipose-derived stem cells) (5). In patients with lipedema, this physiological process is disrupted in the arms and legs due to genetic and hormonal influences. (3,6)

Finally, about 100 years ago, the anatomists Bauer (7) from Vienna and Günther (8) 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.

Hormonal, Microvascular and Regenerative Mechanisms in Lipedema

The present hypothesis proposes that lipedema may result from an interaction between hormonal predisposition, estrogen-dependent microvascular dysfunction, and dysregulated adipose tissue regeneration (15): Increased vascular permeability activates mural adipose stem cells (ADSCs) located in the periphery of the vessels. These initiate both angiogenesis and adipogenesis (9). 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 (9). This results in large, metabolically inactive adipocytes that fill the entire subcutaneous fat space (hyperplasia and hypertrophy) (10,11).

The body attempts to compensate for this regenerative adipose tissue surplus by activating phagocytic inflammatory cell elements. Specialized mast cells and macrophages are involved in this chronic inflammatory response. Histologically detectable crown-like structures represent the maximum attempt to eliminate excess adipocytes. However, this compensatory mechanism remains insufficient, resulting in persistent regenerative imbalance, chronic inflammation, and disease progression.

The hyperplasia of the fatty tissue ultimately leads to strangulation of the capillaries and precollectors of the draining subcutaneous lymphatic system. This results in dermal and subdermal lymphatic congestion (Figures 1). This congestion was demonstrated in an MRI study by Crescenzi et al. (13). Stöberl describes so-called flame-shaped structures (34), Amman-Vesti microlymphatic aneurysms with so-called lymph gaps (14), and Al-Ghadban enlarged lymphological "microvessels" (10).

In our own investigations, we were able to demonstrate the development of increased stem cell activity. (6) The microRNAs originating from the stromal vascular fraction (SVF) were detected in a further study (9). Finally, the initial vascular changes (leaky vessels) were presented and a genetic predisposition to increased aromatase expression detected in this fraction was described (15).

Mast Cell Activation and Neurovascular Inflammation in Lipedema

Emerging histopathological evidence suggests that mast cells may represent a central immunoregulatory component in lipedema-associated adipose tissue remodeling. In our mast-cell staining, increased perivascular and interstitial mast-cell accumulation was observed within the affected subcutaneous tissue (Figure 2). Mast cells are potent effector cells capable of releasing vasoactive, proinflammatory, and profibrotic mediators including histamine, tryptase, interleukins, TNF-αand vascular endothelial growth factors.

This inflammatory signaling may contribute directly to endothelial hyperpermeability ("leaky vessel phenotype"), **dermal/subdermal edema formation, lymphatic dysfunction, neurogenic inflammation, and pain sensitization. Furthermore, mast-cell-derived mediators may interact with adipose-derived stem cells (ADSCs), macrophages, and stromal vascular fraction (SVF)-associated signaling pathways, thereby promoting angiogenesis, adipogenesis, extracellular matrix remodeling, and chronic inflammatory persistence.**

Together, these findings support the hypothesis that lipedema represents a hormonally modulated neurovascular-inflammatory adipose tissue disease characterized by progressive regenerative imbalance and chronic lymphatic congestion.

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 explains 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).**
2. **Negative pitting in dermal-subdermal edema (13).**
3. **Pain/pressure/tension and heaviness caused by inflammatory activation of phagocytic cell elements (macrophages, mast cells) - (10). (Figure 2)**
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) (32,35). Interestingly, this metabolic storage function associated with lipedema does not lead to metabolic diseases such as type 2 diabetes mellitus (16,35). 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 visceroabdominal lymphatic drainage disorder in the context of metabolic fat accumulation. (17,37). (myofascial congestion)**
6. **The genetically determined increase in aromatase activity also plays a significant clinical role in lipedema flare-ups during menopause. (15).**

The 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 (18,19,20). These estrogens promote adipogenesis, i.e., the differentiation of preadipocytes into mature adipocytes, and influence lipogenesis, inflammatory processes, and regional fat distribution (21,22). Accordingly, studies show that aromatase is upregulated in adipose and inflamed adipose tissue, thereby driving paracrine estrogen production (19,20).

Hormonal factors play a central role in lipedema, a chronic progressive fat distribution disorder that almost exclusively affects women (23,24,25,26). Clinically, the disease often occurs during hormonal transition phases such as puberty, pregnancy, or menopause (23,24).

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 17β-**HSD1 (26,27).**

This leads to an intracrine estrogen effect with persistent adipogenesis, inflammatory changes, and fibrosis in the subcutaneous adipose tissue (26,27).

These mechanisms could contribute significantly to the persistence and progression of lipedema, especially during periods of hormonal change. This mechanism may partially explain why severe climacteric symptoms and lipedema flare-ups may occur after testosterone-activating athletic activities. 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. (35)

Clinical oservations suggest that some patients report disease onset or progression after repeated pregnanacies. The biological mechansims underlying this observation remain poorly understood. 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. (36)

Therapeutic Implications of Liposuction in Women with Lipedema

Subtotal liposuction of the subcutaneous hyperplastic fat while preserving the superficial fat layer (subdermis) leads to restoration of the patency of the entire subcutaneous lymphatic system and drainage of the dermal/subdermal edema. This also eliminates the perpetual activation of stem cells. (ADSC) This is only technically and surgically possible through maximum application of TLA (full tumescence) and suction techniques with vibrating liposuction cannulas (28,29,33).

The use of vessel-destroying energy such as lasers, radio frequency, plasma, or ultrasound is obsolete (30,33).

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 (31,33,35). The ability to move without pain allows most patients to engage in more physical activity, thereby reducing metabolic fat deposits (Figure 3).

Conclusion

The present review proposes a hypothesis-generating model in which lipedema represents a chronic hormone-sensitive female-specific adipose tissue disorder characterized by an imbalance between adipogenesis and adipocyte degeneration.

Current evidence suggests that estrogen-dependent microvascular dysfunction, activation of adipose-derived stem cells, stromal vascular fraction-derived extracellular vesicles, microRNA signaling, and secondary lymphatic alterations may collectively contribute to disease progression. Rather than representing isolated mechanisms, these processes may interact within a self-reinforcing regenerative cycle that promotes adipose tissue expansion and chronic inflammation.

Although several components of this model are supported by experimental and translational studies, the causal relationships remain incompletely understood. Prospective clinical, molecular, and mechanistic investigations are therefore required to validate the proposed concept.

Nevertheless, this integrative model provides a biologically plausible framework for future research and may contribute to improved diagnostic and therapeutic strategies in women's **health.**

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Figure Legends

Figure 1. Dermal and subdermal lymphatic congestion in lipedema.
Schematic illustration of the proposed lymphatic pathophysiology in lipedema demonstrating compression and functional obstruction of superficial lymphatic precollectors within the dermal and subdermal adipose compartment. Progressive adipocyte hyperplasia and hypertrophy may impair lymphatic drainage, resulting in dermal/subdermal fluid congestion, microvascular dysfunction, tissue remodeling, and chronic inflammatory activation.

Figure 2. Increased mast-cell accumulation in lipedema tissue.
Histological mast-cell staining of subcutaneous adipose tissue in lipedema demonstrating increased perivascular and interstitial mast-cell infiltration within the dermal/subdermal adipose compartment. Mast-cell activation may contribute to chronic inflammatory remodeling, increased vascular permeability, nociceptive sensitization, lymphatic dysfunction, and progressive adipose tissue expansion. These findings support the

concept of lipedema as a chronic low-grade inflammatory adipose tissue disease with neurovascular and lymphatic involvement.

Figure 3. Clinical presentation of advanced lipedema.

Representative clinical appearance of lipedema demonstrating symmetrical disproportionate enlargement of the lower extremities with characteristic sparing of the feet. Typical clinical findings include abnormal subcutaneous adipose tissue accumulation, tissue tenderness, pressure sensitivity, heaviness, and altered body contour associated with progressive adipose tissue remodeling. Liposuction was successfully performed in two sessions, resulting in marked clinical improvement with resolution of pain, pressure symptoms, and reduction of associated metabolic abdominal adiposity.

Figure 4. Proposed central pathophysical model of lipedema.

Conceptual translational model illustrating the proposed sequence of events in lipedema pathogenesis. Estrogen-dependent endothelial dysfunction and increased vascular permeability may activate mural adipose-derived stem cells (ADSCs) and stromal vascular fraction (SVF)-associated signaling pathways. Subsequent angiogenesis, adipogenesis, adipocyte hyperplasia, lymphatic precollector compression, chronic inflammatory activation, and neurovascular sensitization may contribute to progressive disease development and regenerative imbalance.

Figure 5. Why Lipedema Predominantly Affects Women

Figure 6. Proposed hormone-driven mechanistic model of lipedema development.

The model integrates current evidence regarding hormonal transitions, estrogen signaling, microvascular dysfunction, adipose-derived stem cell activation, extracellular vesicle signaling, adipose tissue remodeling, lymphatic impairment and inflammation in lipedema. Proposed mechanistic links are intended as a conceptual framework and require further experimental validation.