The Adipovascular Unit in Lipedema: A Framework for Regional Adipose Tissue Dysregulation

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Abstract

Lipedema is a chronic, predominantly female disorder characterized by disproportionate regional expansion of subcutaneous adipose tissue, pain, tenderness and easy bruising. Although adipocyte hypertrophy, altered progenitor-cell behavior, microvascular dysfunction, extracellular-matrix remodeling, immune-cell alterations and variable lymphatic abnormalities have been reported, their causal and temporal relationships remain unresolved. Here, we propose that these findings may represent interacting manifestations of dysregulation within an adipovascular unit (AVU) rather than independent pathological processes.

We define the AVU as a spatially organized regenerative niche comprising adipose stem and progenitor cells, microvascular endothelial and mural cells, immune populations, extracellular matrix and mature adipocytes, linked through reciprocal cellular, paracrine and extracellular-vesicle-mediated communication. We hypothesize that lipedema may arise when physiological, female hormone-responsive adipose remodeling encounters a regionally susceptible AVU in which regenerative activity is inadequately constrained in space, magnitude or duration. Subsequent cross-compartment remodeling could amplify and stabilize the altered tissue state, potentially linking disproportionate adipose expansion with vascular, interstitial, immune, extracellular-matrix and sensory manifestations.

Current evidence is compatible with this framework but does not establish the AVU as the primary site of disease initiation or demonstrate a self-maintaining regenerative state. We therefore derive falsifiable predictions involving paired affected and spared adipose depots, context-dependent endocrine responses, functional cross-talk between AVU compartments, extracellular-vesicle transfer, spatial biological boundaries and persistence after stimulus withdrawal. Testing these predictions using spatially resolved and multicellular experimental systems should determine whether AVU dysregulation represents a causal organizing principle of lipedema biology or a descriptive consequence of disease.

Keywords: Lipedema; adipovascular unit; adipose stem and progenitor cells; adipose regeneration; estrogen; microvascular niche; regional susceptibility; extracellular vesicles; regenerative lock-in

1. Introduction

Lipedema is a chronic disorder of subcutaneous adipose tissue characterized by a disproportionate and typically symmetrical expansion of the extremities, pain and tenderness, easy bruising, and a striking predominance in women. Despite increasing clinical and scientific recognition, its pathogenesis remains unresolved. Histological and molecular studies have identified adipocyte hypertrophy, altered adipogenic differentiation, microvascular

abnormalities, extracellular-matrix remodeling, immune-cell alterations, and variable impairment of lymphatic function. However, the temporal and causal relationships among these findings remain uncertain. In particular, it remains unclear whether any one of these abnormalities represents the initiating lesion or whether they reflect interacting components of a broader tissue-level disorder. Alterations of adipocyte biology and extracellular-matrix composition are well documented, but available studies cannot establish whether these changes initiate disease or develop secondarily during its progression [1–3].

A central clue to lipedema biology is its close relationship to female reproductive physiology. The disease occurs almost exclusively in women and frequently becomes clinically apparent or worsens during periods of endocrine transition, including puberty, pregnancy, and menopause. Yet this association does not by itself establish a pathological systemic hormonal state. An alternative possibility is that physiological endocrine signals act upon a regionally susceptible adipose-tissue compartment. This distinction may be important because subcutaneous adipose tissue is not a passive lipid reservoir but a dynamic regenerative organ in which adipose stem and progenitor cells, endothelial and mural cells, immune populations, extracellular matrix, and mature adipocytes interact within spatially organized microenvironments [2,4,7,8].

Recent advances in adipose-tissue biology provide a new context in which to reconsider this female and regional specificity. Adipose stem and progenitor cells are heterogeneous, their functional states are spatially related to the microvascular niche, and they are biologically distinct from mural cells. Moreover, female subcutaneous adipose expansion is regulated by sex-dependent and estrogen-sensitive progenitor programs. These observations raise a fundamental question for lipedema: could the disease represent dysregulation of a physiological, hormone-responsive regenerative program rather than the activation of an entirely disease-specific pathway [5,6]?

Disease-associated alterations of the stromal and progenitor compartments have been reported across independent studies, although the direction of altered adipogenic differentiation is not uniform across experimental systems. Priglinger et al. identified an altered stromal vascular fraction phenotype, whereas Bauer et al. reported impaired adipogenic responses of lipedema-derived adipose stem cells; other experimental models have described enhanced or context-dependent adipogenic behavior. Such heterogeneity may reflect differences in anatomical sampling, disease stage, cell isolation, culture conditions or loss of multicellular and spatial context, and cautions against interpreting lipedema as a simple cell-autonomous

hyperadipogenic disorder [9–12]. Stromal vascular fraction-derived extracellular vesicles also carry characteristic miRNA profiles, reflecting altered molecular cargo rather than a simple increase in vesicle abundance [13].

Together, these findings suggest that adipogenesis, vascular function, immune signaling, and extracellular-matrix remodeling may represent interacting components of a dysregulated adipovascular unit (AVU): a spatially organized regenerative niche integrating adipose stem and progenitor cells, microvascular endothelial and mural cells, immune populations, extracellular matrix, mature adipocytes, and their paracrine and extracellular-vesicle-mediated communication.

Lipedema may not require an intrinsically pathological systemic hormonal signal. A physiological endocrine program may instead encounter a regionally susceptible AVU in which the spatial, temporal, or quantitative control of adipose regeneration is altered. Repeated or sustained regenerative activation could promote disproportionate adipose expansion while simultaneously remodeling vascular, stromal, immune, and extracellular-matrix compartments. Reciprocal interactions may ultimately establish a self-reinforcing tissue state and, in susceptible or progressive disease, contribute to impaired interstitial and lymphatic homeostasis.

We therefore hypothesize that lipedema represents a regionally patterned, hormone-sensitive disorder of adipovascular regeneration, arising from loss of coordinated control over an otherwise physiological female subcutaneous adipose remodeling program. In the following sections, we integrate emerging evidence from adipose progenitor biology, microvascular niche organization, lipedema-specific stromal and vascular studies, extracellular-vesicle signaling, immune–stromal interactions, and lymphatic physiology to develop this model and define experimentally testable predictions.

2. The Adipovascular Unit as a Regenerative Niche

Adipose tissue is a highly dynamic organ capable of substantial structural remodeling throughout adult life. Expansion occurs through adipocyte hypertrophy as well as hyperplasia, the latter requiring recruitment and differentiation of resident adipose stem and progenitor cells (ASPCs). Importantly, these progenitor populations do not function in isolation. Their identity

and differentiation state are shaped by anatomical location, sex, and the local microenvironment, including their spatial relationship to the microvasculature. [4,5]

Recent single-cell and spatial analyses have substantially refined the traditional view of adipose progenitor biology. Uhrbom et al. demonstrated that adipose stem cells constitute heterogeneous fibroblast-like populations with a dual functional identity: they act as adipocyte precursors while also contributing to the organization of the extracellular matrix. Their transcriptional states show sexual dimorphism, including differences in genes associated with estrogen signaling, and their degree of adipogenic commitment is linked to their anatomical position within the microvascular niche. These findings establish a direct conceptual connection between adipogenic potential, extracellular-matrix regulation, sex, and microvascular organization. [5]

A particularly important consequence is the distinction between ASPCs and vascular mural cells. Earlier models of adipose expansion frequently emphasized vascular-associated or mural progenitor populations, and our previous model of lipedema likewise referred to “mural adipose-derived stem cells.” However, current single-cell evidence indicates that adipose stem cells and mural cells represent distinguishable cellular populations, despite their close spatial relationship within the vascular niche. This distinction is mechanistically important: proximity to the vasculature should not be interpreted as cellular identity with the vascular wall [5]. The microvasculature itself is more than a passive supply network for expanding adipose tissue. Endothelial cells, mural cells, progenitor populations, fibroblast-like stromal cells, immune cells, and extracellular matrix coexist within a spatially organized environment in which reciprocal signaling can coordinate tissue expansion and remodeling. The close association between adipogenesis and vascular organization is therefore compatible with a model in which adipose expansion requires coordinated adaptation of both the adipogenic and vascular compartments rather than independent activation of either system.

This concept is particularly relevant to lipedema because the disease preferentially affects specific subcutaneous adipose depots while sparing others. Regional adipose depots are biologically distinct: differences have been described in progenitor proliferation, adipogenic differentiation, lipid handling, secretory profiles, and developmental gene expression. Importantly, even upper- and lower-body subcutaneous depots should not necessarily be considered biologically equivalent. Such depot specificity provides a plausible biological

substrate for a disease characterized by striking regional distribution despite exposure of all adipose tissues to the same systemic endocrine environment [5,7,8].

2.1. Defining the adipovascular unit

On this basis, we propose the term adipovascular unit (AVU) as a functional and spatial framework describing the regenerative microenvironment in which adipose progenitor biology and microvascular adaptation are coordinated.

- adipose stem and progenitor cells (ASPCs), which provide adipogenic progenitors and participate in extracellular-matrix regulation;
- microvascular endothelial cells, which regulate barrier function, nutrient and oxygen exchange, angiogenic adaptation, and paracrine signaling;
- vascular mural cells, including pericytes and vascular smooth-muscle cells, which support microvascular stability and function but should be distinguished from ASPCs;
- extracellular matrix, which provides structural organization while also influencing cellular phenotype and mechanotransduction;
- resident and recruited immune cells, capable of modifying progenitor, endothelial, and matrix behavior;
- and mature adipocytes, whose expansion and metabolic activity alter the requirements imposed upon the surrounding vascular and stromal compartments.

These components should not be interpreted as a newly discovered anatomical organ. Rather, the AVU is proposed here as a systems-level construct describing a spatially coupled regenerative niche. The term ‘adipovascular’ emphasizes the spatial and functional coupling of adipogenic and microvascular compartments, while immune and extracellular-matrix components are incorporated as integral regulators of this regenerative niche.

This distinction separates the proposed functional niche from a newly defined anatomical structure. Reciprocity is central to the proposed AVU. Adipose expansion requires vascular adaptation, while vascular and stromal signals can influence progenitor-cell state. ASPCs themselves can contribute to extracellular-matrix organization, and matrix remodeling can in turn alter the mechanical and biochemical environment experienced by vascular and progenitor

cells. Immune populations can modify adipogenesis and vascular behavior, while expanding adipocytes alter local metabolic and interstitial conditions.

Accordingly, the AVU is better conceptualized as a reciprocal network in which microvascular, progenitor, extracellular-matrix, immune, and adipocyte compartments continuously influence one another, rather than as a linear sequence of vascular activation, progenitor recruitment, and adipocyte formation.

Applied to lipedema, this reciprocal architecture revises our earlier regenerative-imbalance model, which proposed a predominantly sequential pathway involving endothelial dysfunction, activation of vascular-associated adipose progenitors, adipogenesis, lymphatic compression, and inflammation. The present framework replaces that largely linear sequence with a spatially organized, multicellular feedback system [14].

2.2. Physiological adipose regeneration and regional susceptibility

A hormone-responsive adipose regenerative program is not inherently pathological. Experimental models demonstrate sex-dependent differences in subcutaneous adipose hyperplastic capacity, with estrogen contributing to the preservation and recruitment of female adipose progenitor populations [6]. Although these observations derive from a murine model and cannot be directly extrapolated to human lipedema, they establish a physiological principle by which estrogen can regulate subcutaneous adipose progenitor availability and hyperplastic capacity.

The relevant distinction is therefore between physiological regenerative capacity and loss of its regional control. Estrogen-driven adipogenesis alone does not constitute lipedema. Physiological endocrine signals normally operate through a tightly regulated adipovascular

regenerative system in which progenitor recruitment, adipocyte formation, vascular adaptation, matrix remodeling, and immune regulation remain coordinated.

The pathological transition could therefore occur not because the regenerative program exists, but because its regional control is altered. In a susceptible adipose depot, this could involve altered progenitor availability, differentiation thresholds, receptor responsiveness, stromal signaling, extracellular-matrix constraints, microvascular responses, or combinations of these factors. The critical abnormality may not be activation of adipose regeneration, but failure to appropriately terminate, spatially restrict, or quantitatively constrain it. Failure to terminate, spatially restrict, or quantitatively constrain regeneration is therefore a central proposition of the model. Three features of lipedema particularly support testing this framework.

First, the disease is regional. Affected and spared adipose depots coexist within the same systemic endocrine and metabolic environment. This argues against a purely systemic explanation and suggests that tissue-intrinsic or niche-specific properties contribute to disease expression.

Second, the disease is strongly sex-associated and hormone-sensitive. Normal adipose progenitor biology itself is sexually dimorphic and influenced by estrogen signaling. Uhrbom demonstrated sex-related transcriptional differences in adipose stem cells involving estrogen-signaling genes, while Scheidl experimentally demonstrated estrogen-dependent regulation of female subcutaneous APC recruitment and hyperplastic capacity [5,6].

Third, lipedema abnormalities span multiple cellular compartments. Adipogenic alterations, microvascular abnormalities, immune-cell changes, extracellular-matrix remodeling, altered stromal signaling, extracellular-vesicle signatures, and variable lymphatic abnormalities have all been reported. A model assigning disease causality exclusively to one compartment may therefore be insufficient.

Together, these observations support an alternative interpretation: these abnormalities may represent different manifestations of dysregulation within the same regenerative tissue system.

2.3. From physiological to dysregulated AVU

A useful conceptual distinction can therefore be drawn between physiological and dysregulated AVU states.

In the physiological state:

endocrine/metabolic signals → controlled ASPC recruitment → coordinated microvascular adaptation → appropriate ECM remodeling → limited adipocyte formation → restoration of tissue homeostasis.

In the proposed lipedema state:

physiological endocrine signal ↓ → regionally susceptible AVU ↓ → altered ASPC recruitment/differentiation ↕ microvascular + stromal + ECM + immune remodeling ↓→ disproportionate adipose expansion ↺ progressive reinforcement of the altered niche.

The second sequence is not an experimentally established pathway; it represents the hypothesis generated by integrating normal adipose regenerative biology with disease-specific observations. Scientific value requires the AVU concept to generate predictions beyond a descriptive grouping of lipedema abnormalities. If regional AVU susceptibility exists, then affected and spared adipose depots within the same individual should retain measurable differences in progenitor state, cellular composition, spatial organization, or response to standardized endocrine stimulation. If multicellular cross-talk contributes to disease propagation, perturbation of one AVU compartment should alter the phenotype of another. And if the pathological state becomes self-reinforcing, disease-associated cellular behavior should persist at least partly after removal from the original systemic environment.

These predictions distinguish the AVU hypothesis from a purely descriptive grouping of known abnormalities.

3. Female Reproductive Physiology and Regional AVU Susceptibility

The striking female predominance of lipedema and its frequently reported association with puberty, pregnancy, and menopause strongly suggest that reproductive physiology is relevant

to disease expression. However, the observation that lipedema manifests during hormonally dynamic periods should not be interpreted as evidence that circulating estrogen concentrations are intrinsically pathological or that lipedema results from a simple state of systemic estrogen excess. A more biologically plausible question is whether physiological reproductive signals are processed differently by susceptible adipose-tissue regions. Female subcutaneous adipose tissue is physiologically specialized for substantial remodeling across the reproductive lifespan. Sex hormones influence adipose distribution, progenitor-cell behavior, adipogenesis, vascular function, extracellular-matrix organization, and metabolic phenotype. In lipedema, the biological problem may therefore lie not in the existence of these female-specific regenerative programs, but in their regional regulation.

3.1. Sexual dimorphism and hormone-responsive adipose regeneration

Sexual dimorphism in adipose-tissue distribution is one of the most evident biological differences between women and men. Women preferentially accumulate subcutaneous adipose tissue in gluteofemoral and other peripheral depots, whereas men show a greater tendency toward visceral fat accumulation. Importantly, these differences reflect more than variations in mature adipocyte size. Human adipogenesis itself exhibits sex- and depot-dependent characteristics, indicating that regional progenitor behavior contributes to sexually dimorphic adipose distribution [7,8].

Recent experimental evidence substantially strengthens this concept. In a murine model, Scheidl et al. demonstrated marked sex differences in adipose progenitor responses, with female subcutaneous depots showing enhanced preservation and recruitment of committed progenitor populations during adipogenic stimulation [6]. Female tissue contained a greater number of committed preadipocytes, and this difference was dependent on ovarian hormonal status. Ovariectomy reduced this female progenitor phenotype, whereas 17β-estradiol replacement restored it [6]. These findings establish an important premise for lipedema pathogenesis: estrogen-responsive hyperplastic expansion of subcutaneous adipose tissue is part of normal female adipose physiology rather than an inherently pathological process.

Consequently, the central mechanistic question cannot simply be why adipogenesis occurs in women with lipedema. Rather, it is why a physiological capacity for female subcutaneous

hyperplasia might become excessive, regionally restricted, persistent, or insufficiently terminated in susceptible individuals. The work of Uhrbom et al. provides a second important layer of evidence. Adipose stem cells were shown to display sexual dimorphism in transcriptional programs involving estrogen signaling, homeobox transcription factors, and the renin–angiotensin–aldosterone system. These differences may reflect hormonal influences, developmental origin, or a combination of both [5].

Equally important, adipose stem-cell identity was influenced by anatomical location and the microvascular neighborhood, and the degree of commitment toward adipogenic differentiation was related to spatial position within the microvascular niche. Female adipose biology is therefore not merely a systemic hormonal phenomenon. It is also spatially encoded at the tissue and progenitor-cell level. These spatial differences provide a potential mechanistic bridge between two defining features of lipedema that are often considered separately: its almost exclusive occurrence in women and its characteristic anatomical distribution.

If adipose progenitor populations differ according to sex and anatomical location, systemic reproductive signals could plausibly generate quantitatively different regenerative responses among regional adipose depots without requiring major differences in circulating hormone concentrations.

3.2. Reproductive transitions and altered estrogen responsiveness in lipedema

Clinical descriptions repeatedly associate lipedema onset or progression with major reproductive transitions, particularly puberty, pregnancy, and menopause. These reproductive transitions differ profoundly in their endocrine physiology and should therefore not be treated as equivalent states of “high estrogen” [2,15].

Puberty establishes the adult female reproductive endocrine environment and is accompanied by major changes in body composition and regional adipose distribution. Pregnancy represents an extreme but physiological state of endocrine, metabolic, vascular, and adipose-tissue adaptation. Menopause, in contrast, is characterized by declining ovarian estrogen production and substantial changes in adipose distribution and metabolic risk. The occurrence or progression of the same clinical disorder across such different endocrine states argues against a simplistic model in which absolute circulating estrogen concentration alone determines

disease activity. These transitions therefore share not a uniform estrogen concentration, but the requirement for substantial adaptation to a changing reproductive endocrine environment. Within the AVU framework, reproductive transitions can therefore be considered periods in which regional regenerative systems are challenged to adapt to changing endocrine and metabolic demands. This interpretation shifts the mechanistic focus from hormone concentration toward tissue response.

The Scheidl study is particularly informative in this context because it provides experimental evidence that estrogen can regulate the progenitor compartment itself. Removal of ovarian hormonal influence altered committed subcutaneous adipose progenitor abundance, whereas 17β-estradiol replacement restored the female phenotype. Furthermore, estrogen supported hyperplastic subcutaneous expansion and preservation of adipose progenitor availability [6]. These preclinical findings suggest that estrogenic signaling can participate in regulation of the regenerative capacity of female adipose tissue. Such a function is physiologically coherent. During periods requiring adipose expansion, generation of additional adipocytes through progenitor recruitment may permit storage capacity to increase without relying exclusively on excessive hypertrophy of existing adipocytes. Accordingly, estrogen-responsive adipogenesis should not be conceptualized simply as a disease-promoting pathway. It may represent a normal adaptive regenerative mechanism that becomes pathological only if its spatial control, amplitude, duration, or termination is disturbed.

Although physiological estrogen responsiveness is therefore expected in female adipose tissue, emerging lipedema-specific experimental findings suggest that the response of disease-derived cells may differ from that of healthy adipose tissue. Three-dimensional lipedema models are particularly informative. Lipedema-derived ASC spheroids demonstrate adipogenic differentiation accompanied by disease-associated alterations in inflammatory and extracellular-matrix-related gene expression [11,12].

More importantly, exposure to 17β-estradiol produces responses that depend strongly on cellular context and dimensionality. In two-dimensional cultures, estrogen affects proliferation and mesenchymal markers, whereas three-dimensional lipedema spheroids display distinct estrogen-receptor behavior. ERβ expression is higher in lipedema-derived ASCs and spheroids, while estrogen-treated lipedema spheroids show changes in Erα and GPER expression. In differentiated lipedema systems, estrogen additionally influences adipogenic signaling, including PPAR-γ [12]. Beyond individual receptor changes, these findings indicate that the

biological response to estrogen depends on the tissue context in which responding cells are organized.

The fact that responses differ between monolayer and three-dimensional systems supports the broader proposition that cell–cell, cell–matrix, and spatial niche interactions influence hormonal responsiveness. This observation is highly compatible with an AVU-level model. Circulating hormone concentrations represent only one component of estrogenic signaling within adipose tissue [16–18].

The stromal vascular fraction contains multiple cell populations capable of modifying the local tissue environment, including adipose progenitors, endothelial cells, pericytes, fibroblasts, and immune cells. Lipedema-specific analyses have identified alterations within this compartment. Priglinger et al. reported increased cell yield from lipedema-derived SVF and enrichment of CD90-positive mesenchymal and CD146-positive perivascular populations. Subsequent cell-specific analysis by Strohmeier et al. separated endothelial cells, pericytes, ASCs, SVF, and whole adipose tissue and identified molecular alterations across several compartments [9,19].

Of particular relevance, CYP19A1 expression was increased in affected thigh adipose tissue and differed regionally within lipedema patients, while ZNF423, an early regulator of adipogenic commitment, was increased in endothelial- and pericyte-associated compartments [19]. This is compatible with altered adipogenic signaling within the vascular niche without implying identity between ASPCs and endothelial or mural cells.

These findings raise the possibility that regional adipose tissue may not simply respond to circulating estrogen but may also modify its local estrogenic microenvironment. Increased CYP19A1 expression is compatible with altered local estrogen metabolism, but it does not demonstrate increased aromatase activity, increased local estradiol concentrations, or an initiating role for aromatase in lipedema. Rather, the finding supports the testable hypothesis that local steroid metabolism may modify regional AVU responsiveness independently of systemic hormone levels.

3.3. The regionality paradox and regional AVU susceptibility

The most important limitation of any purely endocrine explanation of lipedema is anatomical.

Puberty, pregnancy, and menopause alter the hormonal environment of the entire organism. Yet lipedema does not affect all adipose tissue equally. Characteristic extremity depots undergo disproportionate expansion, while other adipose regions remain relatively spared. Even within an affected individual, diseased and clinically unaffected adipose tissue therefore coexist under essentially the same systemic endocrine conditions.

This creates a regionality paradox:

If the hormonal signal is systemic, why is the pathological adipose response regional?

We therefore propose regional AVU susceptibility as a central component of the model. Under this hypothesis, systemic reproductive signals act upon adipovascular units whose cellular composition, developmental identity, progenitor state, microvascular organization, extracellular matrix, local steroid metabolism, and immune environment differ according to anatomical location. A susceptible AVU may consequently have a lower threshold for regenerative activation or may generate a quantitatively or temporally different response to an otherwise physiological stimulus. Importantly, susceptibility does not require that every AVU component be abnormal before disease begins. A relatively subtle alteration in one component could modify the behavior of others because the AVU is reciprocal.

At present, the available evidence does not allow one of these mechanisms to be assigned as the universal initiating event. The AVU hypothesis therefore deliberately avoids imposing a single mandatory trigger. Instead, it predicts that different initiating perturbations may converge on a common regional regenerative phenotype.

3.4. From physiological adaptation to pathological persistence

This framework defines a critical transition from physiological adaptation to pathological persistence. A physiological reproductive stimulus should generate an adaptive tissue response that is proportional to demand and terminates when homeostasis has been restored.

We hypothesize that in a susceptible adipovascular unit this response may instead become excessive in magnitude, prolonged in duration, regionally misallocated, or incompletely

terminated. Initially, the cellular processes involved may remain physiologically recognizable: progenitor proliferation, adipogenesis, vascular adaptation, matrix remodeling, and immune participation are all components of normal tissue remodeling. Pathology may emerge not because an entirely foreign biological pathway appears, but because the coordination and termination of a normal regenerative program fail.

We therefore propose a threshold model rather than a deterministic hormonal model. In a physiologically resilient AVU, reproductive and metabolic signals remain below the threshold for persistent remodeling. Transient adipogenesis, vascular adaptation, and matrix turnover occur and subsequently return toward homeostasis. In a susceptible AVU, the same systemic signal may cross a regional regenerative threshold. Once this threshold is exceeded, reciprocal interactions among progenitor, vascular, adipocyte, immune, and extracellular-matrix compartments may amplify the original response.

A key prediction follows: abnormal circulating hormone concentrations are not required. Disease-associated abnormalities may instead reside in regional tissue responsiveness, making paired affected and unaffected adipose depots from the same patient an especially informative experimental comparison. Regional susceptibility alone, however, does not explain why lipedema can persist long after the reproductive transition associated with its onset or progression has passed. Persistence after a transient hormonal event could reflect durable structural consequences, continuing tissue-level maintenance, or both. The resulting mechanistic question is how an initially adaptive or hormonally triggered regenerative response becomes self-sustaining.

We propose that once sufficient AVU dysregulation has developed, reciprocal signaling among progenitor, vascular, adipocyte, extracellular-matrix, immune, interstitial, and ultimately lymphatic compartments may progressively reduce dependence on the original endocrine trigger. At this stage, the disease may transition from susceptibility and initiation toward self-reinforcing tissue remodeling. That transition forms the basis of Section 4.

4. From Regional Susceptibility to Regenerative Imbalance and Multicellular Amplification

Regional AVU susceptibility provides a potential explanation for where lipedema may develop, but susceptibility alone does not explain how a localized regenerative response becomes a persistent tissue disorder. The next mechanistic question is therefore how an initially physiological or adaptive response could lose homeostatic control and become progressively self-reinforcing.

Our previous regenerative-imbalance hypothesis proposed a predominantly sequential mechanism linking microvascular permeability, activation of perivascular adipose-derived stem cells, adipogenesis, tissue expansion, lymphatic impairment, and inflammation. The central contribution of that model was to conceptualize lipedema as a dynamic disturbance of adipose-tissue turnover rather than as passive fat accumulation. However, its linear architecture and broad attribution of adipose progenitor identity to mural/perivascular cells require refinement in light of current spatial and functional evidence [14].

The AVU framework retains the concept of regenerative imbalance but changes its architecture. Rather than imposing a single obligatory sequence, dysregulation may arise within an interconnected system in which progenitor, vascular, immune, adipocyte, extracellular-matrix, and interstitial compartments modify one another. The critical transition may be loss of coordinated regenerative control followed by progressive multicellular amplification.

4.1. Regenerative imbalance and altered progenitor control

Physiological adipose remodeling requires several processes to occur in concert. Progenitor recruitment must be matched to adipogenic demand; expanding adipose tissue requires appropriate vascular adaptation; extracellular matrix must permit remodeling without excessive fibrosis; immune cells must support tissue adaptation and repair; and interstitial fluid generated by microvascular exchange must remain compatible with tissue clearance.

Regenerative imbalance therefore denotes more than excessive adipogenesis: it describes mismatch in the magnitude, timing, spatial restriction, or termination of normally coordinated regenerative processes. Current evidence does not establish which abnormality occurs first. The available data are more compatible with an evolving tissue state than with a single fixed lesion.

Adipose expansion ultimately requires enlargement of existing adipocytes, generation of new adipocytes, or both. Disease-associated alterations of stromal and progenitor biology have been reported across independent experimental systems, but their direction is not uniform. Studies describe differences in SVF composition, proliferation, differentiation and adipogenic behavior, whereas other models show comparable or context-dependent adipogenic capacity [9–12,20]. These discrepancies argue against a simple constitutive cell-autonomous hyperadipogenic defect and provide a rationale for testing whether progenitor behavior is dynamically shaped by the surrounding niche. Histological evidence of adipocyte death with concurrent regeneration further supports active tissue remodeling rather than passive fat accumulation [21].

Cell-specific analyses indicate that some disease-associated progenitor behavior may depend on cellular context or the surrounding niche rather than representing a completely stable cell-autonomous defect. A susceptible progenitor population may contribute to disease, but its behavior may be continuously shaped by vascular, immune, matrix, endocrine, and paracrine signals within the AVU.

4.2. Multicellular communication within the dysregulated AVU

Functional evidence already indicates that disease-associated signals can cross cellular boundaries within lipedema tissue. Strohmeier et al. showed that lipedema-associated stromal signals alter endothelial junctional organization, increase endothelial permeability, and reduce CDH5 expression [19], demonstrating that endothelial phenotype can be modified by factors originating in the surrounding stromal vascular compartment. This finding argues against an exclusively endothelial-cell-autonomous interpretation of vascular dysfunction, although reciprocal endothelial-to-stromal signaling remains untested. Changes in interstitial fluid composition, local mechanics, and clearance demand are plausible downstream consequences of impaired barrier integrity, but these links remain mechanistic inferences that require direct testing.

A complementary functional connection is provided by immune–stromal signaling. Lipedema tissue contains increased CD163-positive macrophages, and conditioned medium from lipedema SVF enhances lipid accumulation during adipose-derived stem-cell differentiation [22]. Experimental modification of the macrophage-associated phenotype reduced CD163

expression and normalized this enhanced adipogenic effect toward control levels, providing proof of principle that altering one disease-associated cellular compartment can modify the behavior of another through soluble signaling [22]. This does not establish macrophages as disease initiators; rather, it supports a role for specific immune–stromal interactions within a broader regenerative network.

This network interpretation is reinforced by complementary molecular evidence. Multi-omics analyses identify coordinated disease-associated changes across metabolic, adipokine, and immune-regulatory programs rather than a single invariant inflammatory signature [23]. In parallel, extracellular vesicles derived from the lipedema stromal vascular fraction carry characteristic miRNA profiles [13], providing a plausible additional route for intercellular communication. Neither observation establishes causal hierarchy or disease propagation: functional transfer experiments are still required to determine whether lipedema-derived EVs can modify endothelial barrier function, progenitor commitment, adipogenesis, macrophage state, or extracellular-matrix remodeling in recipient cells.

4.3. Adipocyte expansion, extracellular-matrix remodeling, and interstitial homeostasis

As regenerative imbalance progresses, changes in mature adipose tissue may themselves alter the AVU environment. Lipedema tissue demonstrates adipocyte hypertrophy, with stage-dependent differences reported particularly in affected thigh tissue [24,25].

Expansion of the adipocyte compartment changes local metabolic demand, diffusion distances, tissue mechanics, vascular requirements, and the physical relationship between cellular and extracellular compartments. Once adipose expansion is established, the altered tissue geometry itself may become part of the environment that sustains further remodeling.

Extracellular-matrix remodeling is particularly important for understanding disease persistence. Histological analyses demonstrate increased interstitial collagen in lipedema tissue, with stage-associated increases in interstitial fibrosis reported in affected thigh tissue [25]. The ECM is not merely a passive structural consequence of tissue remodeling. Changes in matrix composition and stiffness can alter cellular organization, mechanotransduction, diffusion, vascular behavior, and progenitor-cell state. Within our model, ECM remodeling represents a potential mechanism through which a predominantly dynamic signaling abnormality becomes progressively embedded in tissue structure [26].

Vascular permeability, adipose expansion, and matrix remodeling intersect with interstitial fluid homeostasis. Histological, interstitial-fluid, microlymphatic, lymphographic, and imaging studies report heterogeneous abnormalities across patients and disease stages [27–34].

The AVU model therefore does not assume that lymphatic impairment is necessarily a late and purely secondary event. Altered microvascular filtration may increase interstitial load; adipose and ECM expansion may alter tissue mechanics and clearance pathways; and lymphatic dysfunction, if present, may further increase interstitial stress. Whether lymphatic dysfunction precedes, follows, or develops in parallel with other AVU abnormalities remains an experimental question.

4.4. Multicellular amplification and regenerative lock-in

Taken together, disease-associated evidence supports several functional relationships: stromal signals can induce endothelial barrier dysfunction; macrophage-associated SVF states can alter ASC adipogenesis; EV-miRNA alterations are demonstrated while functional transfer remains unresolved; and adipocyte hypertrophy and fibrosis are established tissue features whose causal position remains uncertain.

Once several AVU compartments become altered, reciprocal signaling may allow the tissue state to become increasingly self-reinforcing. The resulting system is no longer adequately represented by a single directional chain. It becomes a network state. This is what we mean by multicellular amplification. We term this hypothetical transition regenerative lock-in: a state in which reciprocal cellular signaling and structural tissue remodeling become sufficiently self-

sustaining that the altered tissue phenotype no longer depends entirely on the candidate initiating or amplifying signal.

This state has not been demonstrated in lipedema and represents a central, experimentally testable prediction of the AVU model. It is introduced to address an important clinical and mechanistic problem: if puberty, pregnancy, or another reproductive transition contributes to disease manifestation, why does the affected tissue persist after that transition has ended?

The critical prediction is that established lipedema tissue should retain at least part of its disease-associated phenotype after withdrawal of a candidate initiating or amplifying stimulus. Conversely, if disease-associated cellular behavior disappears completely after removal from the native environment or after withdrawal of the experimental stimulus, the concept of stable regenerative lock-in would be weakened.

The term “lock-in” should not be interpreted as synonymous with irreversible disease. A self-maintaining biological system can remain reversible if one or more critical feedback mechanisms are interrupted.

The Wolf experiments provide a proof of principle for the modifiability of one disease-associated intercellular interaction: modifying the macrophage-associated SVF state substantially normalized the enhanced adipogenic effect of lipedema-conditioned medium [22]. They do not demonstrate reversal of lipedema or regenerative lock-in, but they demonstrate that a disease-associated multicellular interaction can be experimentally modified.

4.5. From dynamic dysregulation to a self-reinforcing adipovascular system

Lipedema progression may therefore be conceptualized not simply as increasing adipose volume, but as transitions among biological states: regional susceptibility, trigger-dependent regenerative dysregulation, multicellular amplification, structural remodeling, and regenerative lock-in.

This sequence represents a conceptual progression, not a proven universal temporal order. Individual AVU components may become abnormal at different times in different patients. The central conceptual shift is from a linear pathogenetic cascade to a self-reinforcing regional tissue system. The key question is whether dysregulation arising in one component of a regionally

susceptible adipovascular niche can propagate across other compartments until the regenerative system itself becomes disease-maintaining.

Existing lipedema studies provide direct experimental evidence for selected interactions within this proposed network. What remains unknown is whether these interactions occur in a defined temporal hierarchy, whether they are sufficient to generate disease, and whether their combination produces a stable self-maintaining state. Those uncertainties define the experimental tests of the hypothesis.

5. From AVU Dysregulation to the Clinical Lipedema Phenotype

A mechanistic model of lipedema is only meaningful if it can account for the characteristic clinical phenotype of the disease. Lipedema is defined by a distinctive combination of regional adipose-tissue expansion and symptoms rather than by excess adipose mass alone. Common diagnostic features include pain or pressure sensitivity, bilateral and symmetrical disproportionate enlargement of the extremities, easy bruising, a negative Stemmer sign, and characteristic sparing of the feet [1–3,35].

These clinical manifestations need not arise from independent pathological mechanisms. Instead, they may represent different expressions of a common disturbance of regional adipose-tissue homeostasis involving adipogenic, vascular, stromal, matrix, immune, interstitial, and neural compartments.

5.1. Regional adipose expansion and structural remodeling

The most visually distinctive feature of lipedema is the regional distribution of adipose tissue. Affected limbs typically demonstrate bilateral and symmetrical disproportionate enlargement, while the feet are frequently spared [1–3].

Regional susceptibility provides a potential explanation: if adipose depots differ in progenitor composition, developmental identity, microvascular organization, local steroid metabolism, extracellular matrix, and regenerative threshold, identical systemic signals need not generate identical tissue responses. The model predicts that tissue sampled across an affected-to-spared anatomical transition should show corresponding changes in AVU composition or state.

Histological studies identify adipocyte enlargement in established lipedema tissue, while experimental studies indicate altered adipogenic differentiation potential in lipedema-derived cells. The AVU model therefore considers established adipocyte hypertrophy together with the possibility of increased hyperplastic recruitment as complementary contributors to tissue expansion [9–12,24,25]. The clinically visible increase in limb volume may reflect different combinations of hyperplastic and hypertrophic expansion at different disease stages or in different patients.

The changing texture of lipedema tissue provides a visible and palpable correlate of structural remodeling. Histologically, affected thigh tissue shows increased interstitial collagen accumulation, with stage-associated increases in interstitial fibrosis in affected thigh tissue [25]. Progressive matrix remodeling may thus transform a predominantly dynamic cellular abnormality into an increasingly structural tissue state.

5.2. Microvascular and interstitial manifestations

Easy bruising is a characteristic clinical feature of lipedema. Clinical and experimental literature describes capillary fragility, vascular dilation, increased permeability, and altered endothelial behavior [1,19,24]. Endothelial permeability and bruising are not synonymous. Bruising also depends on vessel-wall integrity, mechanical trauma, perivascular support, coagulation, and potentially other local factors. Easy bruising may therefore be compatible with altered microvascular and perivascular tissue stability within the affected AVU, although its precise structural basis remains unresolved.

Many patients report heaviness, swelling, or worsening symptoms with heat or prolonged dependency. However, lipedema should not be equated with primary lymphedema [27–34]. Available imaging studies reveal heterogeneous lymphatic findings, ranging from largely preserved transport to subclinical flow abnormalities in subsets of patients [27–34]. The AVU model is compatible with clinically relevant disturbances of interstitial homeostasis occurring before or without severe lymphatic failure.

Thus, heaviness and swelling may reflect an emerging load–clearance mismatch rather than an obligatory primary lymphatic defect.

5.3. Pain and the dissociation between symptoms and morphology

Pain and pressure sensitivity are defining characteristics of lipedema. Clinical and experimental work supports peripheral pain, dermal hypersensitivity and neurogenic inflammatory signaling, while quantitative sensory testing demonstrates regionally altered sensory thresholds, including pressure-pain and vibration measures in affected tissue [36–38]. Potential contributors include altered interstitial mechanics, fibrosis, vascular dysfunction, inflammatory mediators, tissue pressure and peripheral sensory dysfunction. The precise causal hierarchy remains unknown. Pain may therefore be conceptualized as an emergent neurovascular–stromal phenotype of the altered tissue environment rather than placed at the end of a simplistic linear pathway. Morphological stage and symptom severity are not necessarily equivalent. Different tissue abnormalities emerge at different stages, and clinically important pain biology may not simply reflect total adipose volume [25,38]. Two patients with similar external morphology may therefore have substantially different underlying biological states.

5.4. Persistence and progression as loss of tissue homeostasis

If reproductive transitions contribute to disease manifestation, persistence of the tissue phenotype after the transition resolves implies either durable structural consequences or a continuing tissue-level maintenance mechanism. The latter possibility is captured by the regenerative lock-in hypothesis.

The initiating trigger and the maintaining mechanism need not be identical. Clinical persistence alone does not prove regenerative lock-in, but it offers a testable explanation for the separation between disease initiation and disease maintenance. Conventional lipedema staging is based largely on external morphology and palpation. Biologically, disease progression may represent a transition from altered cellular signaling and regenerative responsiveness toward adipose expansion, multicellular amplification, fibrosis, altered interstitial mechanics, and potentially lymphatic impairment [25].

This sequence remains hypothetical and should not replace established clinical staging. Its value lies in predicting that the dominant biological mechanism may change during disease progression.

5.5. A convergent phenotype and its experimental implications

Regional fat expansion points toward depot-specific regenerative biology; bruising toward microvascular/perivascular instability; heaviness and swelling toward disturbed interstitial homeostasis; fibrotic texture and nodularity toward matrix remodeling; and pain toward interacting mechanical, vascular, inflammatory, stromal, and neural mechanisms.

These features may represent different macroscopic manifestations of the same regional failure of tissue homeostasis. At the clinical level, a regionally susceptible adipose tissue niche develops an abnormal regenerative response, altering adipose volume, vascular and interstitial behavior, extracellular-matrix architecture, and potentially sensory function.

The characteristic lipedema phenotype may therefore represent the clinical expression of a regional failure of adipose-tissue regenerative homeostasis rather than the sum of several independent diseases occurring in the same tissue. If the regional distribution truly reflects AVU susceptibility, affected and spared depots from the same woman should be biologically distinguishable. If bruising reflects local microvascular instability, vascular abnormalities should correlate with regional tissue phenotype. If heaviness and swelling reflect load–clearance imbalance, measurements of vascular filtration, interstitial fluid, and lymphatic transport should reveal stage- or phenotype-dependent relationships.

These predictions move the model from clinical plausibility toward experimental validation.

6. Testable Predictions and Experimental Validation of the AVU Hypothesis

The value of the adipovascular unit (AVU) hypothesis depends not on its ability to accommodate existing observations, but on whether it generates predictions that distinguish it from alternative explanations of lipedema. The model proposes that lipedema arises from a regionally susceptible adipose-tissue niche in which normally coordinated interactions among vascular, stromal, adipogenic, immune, extracellular-matrix, and interstitial compartments become

persistently dysregulated. A central implication is that the characteristic clinical phenotype should therefore be accompanied by reproducible biological differences between affected and spared adipose depots, ideally detectable within the same individual.

The following predictions define experiments capable of supporting, refining, or falsifying the model.

6.1. Regional and context-dependent predictions

Existing paired-depot, progenitor and hormonal-response studies establish regional and context-dependent differences but have not determined whether these differences define the anatomical susceptibility of lipedema [6,12,19,25].

Prediction 1 — Regional AVU dysregulation. If lipedema reflects systemic hormonal or metabolic exposure acting on a regionally susceptible AVU, affected adipose tissue should differ biologically from anatomically spared adipose tissue within the same patient.

The strongest experimental design would compare paired biopsies from affected thigh or lower-leg tissue, clinically spared adipose tissue from the same patient, and anatomically matched tissue from women without lipedema. If carefully matched studies repeatedly demonstrate that affected and spared adipose depots within the same patient are biologically indistinguishable at the level of AVU composition, cellular state, spatial organization, and intercellular signaling, the concept of regional AVU susceptibility would be substantially weakened.

Prediction 2 — Hormonal context dependence. The AVU model predicts an interaction between hormonal signaling and regional tissue susceptibility. Physiologically relevant estrogenic or other reproductive endocrine signals should produce different biological responses in affected and spared AVUs from the same patient. If affected and spared AVUs repeatedly demonstrate identical responses across physiologically relevant hormonal conditions, the hypothesis that differential regional endocrine responsiveness contributes substantially to AVU susceptibility would be weakened.

Prediction 3 — Biological boundary. If tissue susceptibility is regionally encoded, the clinical transition from affected to spared tissue should correspond to a measurable change in tissue biology. Spatially resolved sampling across clinically defined transition zones should determine

whether the anatomical boundary corresponds to a molecular, cellular, structural, or functional AVU transition. If no biological gradient or boundary can be identified despite precise spatial sampling across clinically affected and spared regions, the hypothesis that the anatomical phenotype reflects regionally encoded AVU susceptibility would require substantial revision.

6.2. Multicellular communication and causal reconstruction

Functional studies already demonstrate selected cross-compartment effects, but the necessity, directionality and sufficiency of these interactions remain unresolved [13,19,22].

Prediction 4 — Multicellular dependence. The AVU model predicts that isolated adipocytes or progenitor cells studied under conventional monoculture conditions may reproduce only part of the disease phenotype, whereas increasingly physiological systems incorporating endothelial cells, mural cells, adipose stromal/progenitor cells, extracellular matrix, immune cells, and adipocytes should reproduce a broader and more physiologically relevant spectrum of disease-associated behavior. If key disease-associated cellular phenotypes can be reproduced consistently by isolated adipocytes or progenitor cells independently of endothelial, immune, stromal, or matrix interactions, the necessity of multicellular AVU dysfunction as the principal pathological mechanism would be reduced.

Prediction 5 — Endothelial–stromal cross-talk. The model predicts bidirectional interaction between the microvasculature and the surrounding regenerative compartment. Reciprocal co-culture experiments combining endothelial cells and adipose stromal/progenitor cells derived from affected tissue, spared tissue, and controls could determine whether either compartment carries a dominant transferable abnormality or whether the strongest phenotype emerges only through their interaction. If manipulating endothelial state has no reproducible effect on stromal/progenitor behavior and manipulating the stromal compartment has no effect on endothelial phenotype, a central prediction of the adipovascular interaction model would not be supported.

Prediction 6 — Extracellular-vesicle transfer. Evs isolated from affected lipedema tissue or disease-associated AVU cell populations should transfer measurable disease-associated cellular phenotypes to recipient cells if they contribute functionally to disease propagation. Transfer experiments followed by inhibition or depletion are required to demonstrate function. If

purified Evs from affected tissue consistently fail to transfer any relevant phenotype under physiologically appropriate conditions, the importance assigned to EV-mediated amplification would need to be reduced.

Prediction 7 — Network perturbation. If AVU compartments are functionally coupled, selective perturbation or normalization of one pathological component should produce measurable secondary effects elsewhere in the network. If each abnormal AVU compartment behaves independently and correction of one produces no reproducible change in any other, the proposed network architecture would require reconsideration.

6.3. AVU states, clinical phenotype, and regenerative lock-in

Stage-dependent tissue remodeling and disease-associated molecular signatures raise the possibility that lipedema comprises distinct biological states, but this has not been tested longitudinally [23,25].

Prediction 8 — Changing AVU states. The model predicts reproducible patterns or trajectories of AVU state characterized by different combinations of adipogenic activity, vascular dysfunction, immune-cell composition, matrix remodeling, interstitial disturbance, and potentially neural involvement [25]. These states may not correspond perfectly to conventional morphological staging. If molecular, cellular, and functional abnormalities simply increase uniformly with tissue volume or BMI and provide no information beyond conventional stage or adiposity, the proposed concept of biologically informative AVU-state patterns or trajectories would have limited explanatory value.

Prediction 9 — Regenerative persistence. Patient-derived multicellular systems could first be exposed to a candidate initiating or amplifying stimulus and subsequently studied after withdrawal of the experimental stimulus. If regenerative lock-in exists, disease-associated features should persist for a measurable period after withdrawal of the candidate initiating or amplifying stimulus. If the abnormal phenotype disappears rapidly and completely after withdrawal of the candidate stimulus, a self-maintaining AVU state would not be supported.

Prediction 10 — Clinical correlation. Future studies should integrate tissue biology with standardized clinical characterization rather than grouping patients exclusively according to conventional stage. If reproducible AVU abnormalities can be identified but show no relationship

to anatomical distribution, symptoms, progression, or any other clinically meaningful phenotype, their relevance to lipedema pathogenesis would be uncertain.

6.4. Experimental roadmap and falsification

A staged experimental program could progressively challenge the central assumptions of the model: Phase I, spatial definition using paired affected and spared tissue; Phase II, functional reconstruction in controlled multicellular systems; Phase III, causal perturbation of candidate pathways; and Phase IV, clinical translation against anatomical distribution, symptoms, progression, and therapeutic response. This sequence moves progressively from association to reconstruction to causality to clinical relevance. The AVU hypothesis would be substantially weakened if affected and spared tissue within the same patient are biologically equivalent; disease-associated abnormalities are entirely cell-autonomous; endothelial and stromal compartments do not functionally influence one another; regional tissue responses do not differ under identical hormonal conditions; no biological transition corresponds to the characteristic anatomical distribution; regional cross-compartment interactions are not reproducible; or AVU abnormalities have no reproducible relationship to the clinical phenotype.

Conversely, strong support for the model would arise from experimental demonstration that regional reciprocal interactions among AVU compartments are required to reproduce key disease-associated phenotypes and that targeted disruption of these interactions attenuates or reverses them.

7. Clinical and Therapeutic Implications of the AVU Model

The AVU hypothesis is a pathogenetic framework rather than a proposal for immediate changes in clinical management. Current treatment of lipedema remains directed predominantly toward symptom reduction, preservation of mobility and function, management of associated obesity and metabolic comorbidity, and, in selected patients, reduction of pathological adipose-tissue

burden. Its potential clinical contribution is not to replace existing treatment principles, but to distinguish phenotype-directed treatment from future mechanism-directed intervention.

7.1. Current phenotype-directed treatment within the AVU framework

Compression, physical activity, weight management, rehabilitation, and other conservative strategies can reduce symptoms or improve function through changes in mechanical load, interstitial fluid handling, mobility, or associated metabolic factors [2,3]. These interventions may modify the clinical phenotype but do not remove the affected adipose-tissue compartment itself; their symptomatic efficacy therefore neither proves nor disproves a specific initiating mechanism.

7.2. Reduction surgery and the affected tissue niche

Among currently available interventions, lipedema reduction surgery occupies a distinct position because it physically removes substantial amounts of the affected subcutaneous adipose-tissue compartment rather than primarily modifying downstream manifestations [39–41]. Reduction surgery also raises a biological question because liposuction removes a substantial portion of affected tissue containing adipocytes together with stromal, vascular, immune, extracellular-matrix, and interstitial elements.

Within the AVU framework, reduction surgery may not only reduce pathological tissue mass and mechanical burden but also disrupt part of the multicellular and extracellular environment capable of sustaining the pathological tissue state. Whether this constitutes true disease modification, or whether residual susceptible tissue retains the capacity to reconstruct the pathological AVU state, remains unknown. Patients undergoing lipedema reduction surgery could be characterized before and after treatment using systemic and tissue-associated markers identified in Section 6. If removal of affected tissue produces biological changes extending beyond the mechanically removed tissue volume, this would support the possibility that the removed niche had contributed actively to maintenance of the pathological state. Tissue-

preserving surgical principles are conceptually compatible with reducing affected tissue burden while minimizing unnecessary injury to vascular, lymphatic, neural, and connective-tissue structures [26,42–44].

The hypothesis does not establish superiority of one surgical technology over another. It instead provides a biological rationale for the broader principle of reducing pathological tissue burden while preserving the architecture required for tissue homeostasis.

7.3. From phenotype-directed to mechanism-directed intervention

If future experiments identify causal interactions that maintain AVU dysregulation, candidate intervention points could include progenitor-cell activation, stromal–endothelial signaling, immune–stromal communication, EV-mediated signal transfer, maladaptive ECM remodeling, or local endocrine signal processing. Before any such pathway is considered a credible disease-modifying target, it should ideally satisfy a causal sequence of association, functional transfer, perturbation, and phenotypic normalization. This distinction is important because female subcutaneous progenitor recruitment and hyperplastic expansion are physiological processes; indiscriminate suppression of adipogenesis would therefore not represent a rational therapeutic objective [5,6].

A mechanism-directed strategy would instead aim to restore physiological control of adipose regeneration. The AVU model proposes that reproductive signals may reveal or amplify regional susceptibility, not that systemic estrogen excess is the universal cause of lipedema; it therefore provides no rationale for systemic anti-estrogen therapy or hormonal suppression. The Wolf experiments nevertheless offer proof of principle that a disease-associated intercellular interaction can be experimentally modified and that doing so can alter adipogenic behavior [22]. Whether such an approach can modify disease in vivo remains unknown.

This distinction separates treatment of initiating susceptibility from disruption of mechanisms that maintain established disease. If a self-reinforcing AVU state exists, targeting a causal network node may ultimately prove more relevant than attempting to normalize every abnormal compartment simultaneously.

7.4. AVU states, biological signatures, and therapeutic reversibility

If regenerative lock-in occurs, disease stage may influence therapeutic responsiveness at the biological level. Earlier or more dynamically dysregulated AVU-state patterns may depend more strongly on reversible signaling abnormalities, whereas structural remodeling may progressively stabilize the pathological state. The model therefore predicts that biological reversibility may decrease as dynamic signaling abnormalities become structurally embedded in the tissue. Rather than searching for a single diagnostic lipedema biomarker, it may be more informative to identify combinations of markers that define dominant biological patterns or trajectories in the affected tissue. Such signatures might eventually distinguish regenerative-active, vascular/interstitial, immune-amplified, or structurally remodeled AVU-state patterns. These patterns are currently hypothetical and should not be introduced as a new clinical classification.

7.5. Restoring tissue homeostasis: translational perspective

Successful disease modification would be expected to restore coordinated tissue behavior. At present, established clinical treatments should continue to guide patient care; mechanism-directed interventions remain research questions. The immediate translational value of the AVU hypothesis is therefore not a new treatment algorithm, but a framework for biological stratification and for identifying which abnormalities drive the pathological tissue state, which merely accompany it, and which interactions must be interrupted to restore regional adipose-tissue homeostasis.

Its longer-term value will depend on whether experimental studies identify reproducible AVU patterns or trajectories that predict progression, symptoms, reversibility, or treatment response.

8. Alternative Models, Limitations, and Boundaries of the AVU Hypothesis

The adipovascular unit (AVU) hypothesis integrates regional adipose expansion, reproductive physiology, vascular and stromal abnormalities, immune signaling, extracellular-matrix remodeling, and interstitial dysfunction. This integrative capacity should not be mistaken for evidence that the AVU is the unique or primary site of disease initiation. Several alternative or complementary models of lipedema remain biologically plausible. Moreover, much of the current evidence is cross-sectional, derived from relatively small cohorts, and obtained from established disease. Consequently, temporal sequence, necessity, and sufficiency cannot yet be assigned to most reported abnormalities. It should therefore be regarded as a testable systems-level hypothesis, not a definitive pathogenetic doctrine.

8.1. Competing cellular and tissue-level models

One alternative is that a primary abnormality resides predominantly within the adipocyte or adipose-progenitor lineage. Altered progenitor commitment, excessive adipogenesis, impaired lipid handling, resistance to lipolysis, or abnormal mature-adipocyte function could initiate regional tissue expansion, with vascular, immune, matrix, and lymphatic changes developing secondarily. Such a mechanism is compatible with the current framework. If a stable, cell-autonomous defect in the adipocyte/progenitor lineage proves sufficient to reproduce key disease-associated tissue phenotypes independently of vascular, immune, and ECM context, however, the AVU would become less compelling as the principal disease-maintaining unit.

A second possibility is that microvascular dysfunction represents the primary lesion. Capillary fragility, endothelial dysfunction, increased permeability, or abnormal angiogenic signaling could alter the local interstitial environment and subsequently influence progenitor recruitment, adipogenesis, immune-cell behavior, and matrix remodeling. Current functional evidence supports endothelial abnormalities but does not establish their temporal primacy. Vascular dysfunction may be initiating or secondary, and reciprocal vascular-stromal amplification remains plausible but unproven. A primary lymphatic mechanism has also been proposed. Impaired lymphatic transport could theoretically alter interstitial fluid homeostasis, promote tissue expansion, modify immune-cell trafficking, and stimulate fibrotic remodeling. Current evidence does not consistently establish primary lymphatic failure as a universal early feature of lipedema [27–34]. The AVU hypothesis therefore does not require primary lymphatic dysfunction, but neither does it exclude it. Altered collagen organization, tissue compliance, mechanical signaling, or perivascular support could precede adipose and vascular changes.

Within the AVU model, ECM remodeling may be a susceptibility factor, an amplifier, a consequence, or some combination of these [26,43]. If tissue-mechanical or ECM abnormalities precede all detectable cellular changes, the current emphasis of the model would need to shift accordingly. Immune abnormalities provide another possible point of entry. Macrophage populations are altered in lipedema tissue, and functional experiments demonstrate that modification of the macrophage-associated stromal environment can alter adipogenic differentiation [22,25].

The relevant pathological event may be a specific alteration in immune–stromal communication rather than generalized inflammation.

8.2. Systemic, endocrine, and genetic susceptibility

The marked female predominance and association with reproductive transitions make endocrine mechanisms unavoidable considerations. A purely systemic hormonal model, however, faces the regionality problem developed in Section 3. Endocrine mechanisms remain compatible with the model; the principal question shifts from whether a systemic endocrine abnormality is sufficient to explain lipedema to why anatomically distinct adipose tissue might respond differently to physiological endocrine change. Familial clustering strongly suggests a genetic contribution to lipedema, although no single causative gene has been established [45,46]. Genetic variation may determine regional susceptibility itself by affecting developmental patterning, progenitor-cell biology, vascular stability, ECM composition, steroid metabolism, immune regulation, or lymphatic capacity. The AVU is therefore best viewed as a candidate level of regional disease expression and maintenance, rather than necessarily the deepest etiological level.

8.3. Biological heterogeneity, obesity, and diagnostic uncertainty

Obesity represents one of the most important challenges in lipedema research because the two conditions frequently coexist and share changes in adipocyte size, inflammatory signaling, extracellular matrix, vascular biology, and metabolic function [2,3,47].

At the same time, lipedema cannot simply be equated with obesity. Future AVU studies therefore require carefully matched control groups including lipedema without obesity, lipedema with obesity, obesity without lipedema, and healthy anatomically matched controls. Matching by BMI alone may not fully control for differences in regional adiposity, metabolic status, or adipose-tissue distribution. Lipedema may encompass substantial biological heterogeneity. Patients differ in anatomical distribution, pain, bruising, swelling, tissue texture, progression, age of manifestation, obesity, metabolic status, and possible lymphatic involvement.

Different upstream perturbations may converge on overlapping tissue states. This possibility is one reason why AVU-state patterns or trajectories may ultimately prove more informative than a single universal biomarker. Existing lipedema studies use variable diagnostic criteria, patient-selection strategies, anatomical sampling sites, clinical stages, BMI distributions, and control populations [2,3].

Future mechanistic studies therefore require rigorous phenotyping, standardized tissue sampling, anatomically matched controls, and explicit documentation of obesity, reproductive status, medications, disease duration, symptoms, and comorbid vascular or lymphatic disease.

8.4. Limitations of current evidence

Most available tissue studies examine patients after lipedema has already become clinically established. Consequently, the presence of endothelial dysfunction, macrophage alterations, fibrosis, adipocyte hypertrophy, altered EV cargo, or progenitor abnormalities cannot determine whether that feature initiated disease, amplified disease, resulted from disease, or represents an adaptive response [9–13,19–25]. Until longitudinal human data and causal experimental reconstruction are available, the proposed transition from susceptibility through multicellular amplification to regenerative lock-in must remain a hypothesized trajectory rather than an established natural history. No current study has demonstrated that an AVU-level pathological state persists autonomously after withdrawal of a candidate initiating or amplifying stimulus. Regenerative lock-in should therefore be interpreted as a falsifiable hypothesis explaining how trigger dependence might evolve into tissue-state dependence. The term adipovascular unit is used here to describe a proposed spatially and functionally integrated regenerative niche. It should not imply that a new anatomically discrete organ or histological structure has been

discovered. If AVU components behave independently and spatial organization provides no additional explanatory or predictive information, the construct would add terminology without biological value.

8.5. Boundary conditions and falsifiability

A systems model carries the risk of accommodating almost any new finding after the fact. We therefore define explicit boundaries. The hypothesis does not claim that estrogen is the universal initiating cause; that endothelial dysfunction necessarily occurs first; that lymphatic impairment is obligatorily secondary; that macrophage activation initiates all disease; that altered EV cargo is sufficient to cause lipedema; that fibrosis is always a late event; that every patient follows the same biological sequence; that every clinical manifestation originates within the AVU; or that all abnormalities described in lipedema belong to one causal pathway.

Instead, the core claim is narrower: a regionally susceptible adipose regenerative niche may provide the tissue-level system in which different upstream susceptibilities converge, interact, and potentially become self-maintaining.

8.6. AVU as a convergence model

Lipedema could theoretically begin through different upstream routes, including genetic/developmental susceptibility, abnormal progenitor responsiveness, vascular instability, ECM/connective-tissue abnormalities, immune dysregulation, local endocrine processing, or lymphatic vulnerability.

The AVU need not be the site at which lipedema begins. It may instead represent the regional tissue system in which different biological susceptibilities converge and become clinically expressed.

The AVU hypothesis should be revised or rejected if future evidence demonstrates that regional tissue biology is not relevant to disease distribution; affected and spared depots are biologically equivalent; a single systemic abnormality independently explains the characteristic anatomical phenotype; one cell-autonomous defect is sufficient to explain the principal disease-associated

tissue phenotypes without meaningful contribution from multicellular context; or cross-compartment signaling is biologically negligible. Failure to demonstrate persistence after withdrawal of candidate initiating or amplifying stimuli would specifically argue against the regenerative lock-in component, but would not by itself invalidate regional AVU dysregulation.

Conversely, the model would gain support if affected tissue demonstrates a reproducible regional multicellular signature, if cross-compartment transfer experiments reproduce disease-associated phenotypes, if identical systemic signals generate different responses in affected and spared depots, and if perturbation of key interactions can destabilize an established pathological state.

The present evidence is sufficient to justify testing an integrated regional model, but not to establish it. The field remains constrained by small cohorts, heterogeneous diagnostic definitions, obesity-related confounding, predominantly cross-sectional sampling, limited longitudinal evidence, and incomplete replication [2,3].

The principal contribution of the AVU hypothesis is not to resolve lipedema pathogenesis, but to reorganize it into experimentally separable questions: where susceptibility resides; which compartment initiates dysregulation; which interactions amplify it; which changes merely accompany established disease; what maintains the tissue state after the initiating signal has passed; and whether restoration of coordinated regional adipose-tissue homeostasis can reverse the pathological phenotype.

8. Conclusion

Lipedema is increasingly recognized as a biologically complex disorder of subcutaneous adipose tissue, yet available evidence does not identify a single cellular abnormality or tissue compartment that can presently be assigned a universal initiating role. Instead, disease-associated alterations have been reported across adipose progenitor, vascular, immune, extracellular-matrix, adipocyte and interstitial–lymphatic compartments, with substantial heterogeneity between experimental systems and disease stages.

We propose the adipovascular unit (AVU) as a spatial and functional framework through which these observations can be integrated. In this model, adipose stem and progenitor cells, endothelial and mural cells, immune populations, extracellular matrix and mature adipocytes

form a reciprocally regulated regenerative niche. Lipedema may arise when an otherwise physiological, female hormone-responsive program of subcutaneous adipose remodeling encounters a regionally susceptible AVU in which regenerative activity is insufficiently constrained in space, magnitude or duration. Progressive cross-compartment remodeling could subsequently amplify and stabilize the altered tissue state and contribute to the characteristic regional expansion, vascular and interstitial manifestations, pain and structural remodeling of the disease.

This framework does not establish the AVU as the primary site of disease initiation, nor does current evidence demonstrate regenerative lock-in. Genetic susceptibility, adipocyte-intrinsic abnormalities, vascular or lymphatic dysfunction, extracellular-matrix alterations and immune dysregulation may act upstream, downstream or in parallel and remain legitimate alternative or complementary mechanisms.

The principal value of the AVU hypothesis is therefore experimental rather than explanatory alone. It predicts measurable biological differences between affected and spared depots, context-dependent responses to physiological endocrine signals, functional cross-talk among AVU compartments and, potentially, persistence of disease-associated cellular states after removal of the initiating stimulus. Testing these predictions in paired-depot, spatially resolved and multicellular experimental systems should determine whether the AVU represents a causal organizing principle of lipedema biology or merely a useful descriptive framework.

Figure 1. The adipovascular unit in lipedema: multicellular architecture and reciprocal communication

The adipovascular unit (AVU) is proposed as a spatially organized regenerative niche of subcutaneous adipose tissue comprising adipose stem and progenitor cells (ASPCs), microvascular endothelial cells, mural cells, mature adipocytes, immune populations and extracellular matrix. These compartments interact through direct cell–cell contacts and paracrine communication, including soluble mediators and extracellular vesicles; solid arrows indicate established or directly supported interactions, whereas dashed arrows denote additional context-dependent or incompletely tested relationships. The figure is intended to emphasize the AVU as a reciprocal multicellular network rather than a linear sequence and does not imply that a new anatomically discrete structure has been demonstrated.

Figure 2. From physiological endocrine context to regional AVU dysregulation and the lipedema phenotype: a working model

The hypothalamic–pituitary–ovarian axis provides a physiological reproductive endocrine context across puberty, pregnancy, perimenopause and menopause. In a resilient AVU, these signals are accommodated by controlled regenerative responses and tissue homeostasis; in a regionally susceptible AVU, the same physiological context may encounter a lower threshold for regenerative activation, leading to dysregulated progenitor recruitment and differentiation, endothelial–stromal and immune cross-talk, extracellular-matrix remodeling and reciprocal AVU amplification. Progressive tissue remodeling may contribute to the characteristic regional adipose expansion, pain, tenderness, easy bruising, heaviness or swelling and nodularity or fibrosis. Persistence of an altered AVU state after withdrawal of a candidate initiating or amplifying stimulus is shown as a hypothetical regenerative lock-in and remains to be experimentally demonstrated.

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