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The Etiology of Pain in Lipedema Is Not Yet Fully Understood. An Integrative Synthesis of Inflammatory, Hypoxic-Hemorrhagic, Adipomyofascial, and Neuromolecular Mechanisms Based on Histopathological Evidences

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ABSTRACT

Lipedema is a chronic disease characterized by the accumulation of subcutaneous adipose tissue in the lower and upper limbs, sparing the trunk, hands and feet. Diagnosis is clinical, with the most frequent symptoms being pain, sensation of heaviness in legs, and spontaneous bruising. The understanding of the etiology of pain in this condition still lacks robust scientific evidence. Based on the integration of histopathological, biomechanical, and neurobiological findings, the authors propose a model that considers the convergence of four main mechanisms: inflammatory, hypoxic-hemorrhagic, adipomyofascial, and neuromolecular. Histopathological studies suggest a state of chronic inflammation in addition to ischemia, leading to the release of pro-nociceptive mediators capable of sensitizing peripheral nerve endings. Hypertrophy and

hyperplasia of adipose tissue promote progressive compression of the microcirculation, resulting in sustained hypoxia, venous congestion, and vascular remodeling. This environment may favor erythrocyte extravasation and the accumulation of hemoglobin degradation products, which are highly irritating to hypodermis. Pain may also arise from structural remodeling of the fascia, including thickening, increased disorganized collagen deposition, interstitial fibrosis, and reduced myofascial gliding. This mechanical dysfunction may lead to a chronic fasciitis-like condition. In addition, a synergistic interaction among these factors may result in structural and functional injury to nerve fibers, characterizing a state of painful peripheral neuropathy. Hypotheses inferred from the biology of pain (neuromolecular axis) related to adipose/fascial tissue are also presented, since direct measurements of specific tissue for lipedema are still limited. Adipose tissue, microcirculation, and the fascia act as an integrated system that may contribute to the generation and perpetuation of pain, establishing a pathophysiological vicious cycle. This model provides a basis for therapeutic development aimed at inflammatory modulation, restoration of perfusion, control of vascular leakage, optimization of fascial function, and neuroprotection.

1. INTRODUCTION

Lipedema is a chronic disease characterized by the accumulation of subcutaneous adipose tissue in the lower and upper limbs, sparing the trunk, hands, and feet. It affects approximately 12.3% of Brazilian women and is diagnosed clinically, with suggestive findings including pain on palpation and a tendency toward spontaneous bruising and ecchymoses [1]. Pain is the main clinical manifestation that leads patients to seek medical care; however, its pathophysiology remains poorly elucidated. Without a comprehensive understanding of its mechanisms, prospects for improvement are limited, as there are no specific therapies and treatment outcomes remain unsatisfactory.

To avoid conceptual ambiguity, operational definitions of the proposed axes are provided—1) the inflammatory axis, 2) the hypoxic-hemorrhagic axis, 3) the adipomyofascial axis and 4) the neuromolecular axis—causing peripheral neural injury and sensitization (clinical neuropathic features and molecular pathways of nociceptor hyperexcitability). Pain in this context refers to clinical features (allodynia, hyperalgesia, dysesthesia) with supporting neurophysiological or histological findings when available, because direct histological confirmation of lipedema remains short [2-4].

The inflammatory axis of lipedema demonstrates chronic low-grade inflammation, marked by macrophage infiltration, accompanied by the persistent release of pro-inflammatory cytokines that lower the threshold for peripheral nociceptive activation [4].

Within the hypoxic-hemorrhagic axis, increased pressure in the subcutaneous compartment leads to capillary compression and congestion, resulting in hypoxia and subsequent immature and fragile neoangiogenesis, which predisposes to erythrocyte extravasation [5, 6]. The presence of erythrocytes in the extravascular compartment leads to hemolysis and hemoglobin degradation, with the release of heme, free iron, and biliverdin—substances that are highly irritating to the hypodermis—thereby promoting sterile inflammation and prolonged nociceptive sensitization [6-8]. Hypoxia further intensifies oxidative stress through the release of reactive oxygen species (ROS) and the expression of hypoxia-inducible factor-1α (HIF-1α), perpetuating inflammation and resulting in ineffective vascular remodeling [9].

The adipomyofascial axis is centered on adipose tissue expansion and loss of elasticity, leading to fascial thickening, collagen reorganization, and reduced myofascial gliding. These changes result in continuous mechanical tension and a functional condition resembling chronic fasciitis, thereby exacerbating pain [10].

The neuromolecular axis represents the combined effect of the previously described mechanisms, which may promote structural injury to nerve fibers, including axonal degeneration and neural dysfunction,

culminating in painful peripheral neuropathy [11].

Thus, lipedema adipose tissue acts as an organ that generates and amplifies pain through the convergence of four pathophysiological axes: chronic inflammation, hypoxic-hemorrhagic changes, increased adipomyofascial tension, and neuromolecular damage [12].

The model proposed is a heuristic framework, intended to organize systematically the pathophysiological hypotheses in lipedema, while maintaining a descriptive and exploratory feature. The recognition of clinical heterogeneity of lipedema and methodological limitations of available literature—such as small sample sizes, predominance of observational study designs, and the absence of validated disease-specific biomarkers—avoid causal inferences in the absence of standardized quantitative measurements and robust mechanistic evidence. In this context, the associations described herein should be interpreted as plausible relationships grounded in the convergence of recurrent tissue-level patterns.

2. METHODOLOGY

A structured search was realized in PubMed/MEDLINE, LILACS, and Google Scholar. The PubMed search string was: ("lipedema" or "lipoedema") and ("pain" or "inflammation" or "macrophage" or "mast cell" or "hypoxia" or "ischemia" or "angiogenesis" or "hemorrhage" or "microcirculation" or "fascia" or "fibrosis" or "neuropathy" or "nociceptor" or "TRPV1" or "P2X3" or "ASIC3" or "transcriptomic" or "histopathology" or "biopsy"). Equivalent strategies were applied to LILACS and Google Scholar. The last search was conducted on October 29th, 2025; and reference lists of included articles were hand-searched.

Studies were included if participants had a clinical diagnosis of lipedema and at least one mechanistic assessment, including: histopathological, immunohistochemical, molecular/omics, microvascular, neurological, or biomechanical (fascia or subcutaneous adipose tissue) analyses. Studies focusing exclusively on therapeutic interventions or purely descriptive reports without structural or mechanistic analysis were excluded.

Each included study was critically appraised for—study design, population characteristics, methodological rigor, techniques employed, and reported pathophysiological findings—allowing assessment of the reliability of the evidence and the robustness of each mechanistic claim.

Data extraction was organized according to predefined domains: adipocyte morphology; immune markers (CD68/CD163, mast cells); vascular features; hemorrhagic markers; and extracellular matrix and fascial changes. Findings were synthesized narratively through a convergent analysis, integrating data across mechanistic domains, to provide a comprehensive overview of the main pathophysiological mechanisms underlying pain in lipedema; including the inflammatory, hypoxic-hemorrhagic, adipomyofascial, and neuromolecular axes.

3. RESULTS

Database search returned 10 biopsy based studies published between 2017 and 2025.

Inflammatory axis: adipocyte hypertrophy was reported in 7 of 10 studies. Diffuse or perivascular inflammatory infiltrates were observed in 5 of 10 studies. Macrophage enrichment was also noted in 5 of 10. Mast cell involvement was variably reported. Overall, the inflammatory axis demonstrated moderate to high strength of evidence.

Hypoxic-hemorrhagic axis: capillary dilation and dysfunctional angiogenesis were documented in 5 of 10 studies. Indirect evidence of hypoxia or oxidative stress was reported in 2 of 10 studies. Erythrocyte extravasation and interlobular hemorrhage were observed in 1 case report. Reporting moderate evidence for the hypoxic-hemorragic axis.

Adipomyofascial axis: interstitial fibrosis and extracellular matrix remodeling were described in 4 of 10 studies. Limited direct evidence of superficial fascia or septal thickening was observed in 1 of 10 studies. Confirm a low to moderate support for fascia axis.

Neuromolecular axis: dermal hypersensitivity, perineural involvement, and neurogenic inflammation were reported in 1 of 10 studies. Direct measurements of ion-channel activation (TRPV1, P2X3, ASIC3) in

lipedema tissue were not yet performed and remain as a “hypothetic theory”.

4. DISCUSSION

Recent histopathological and multi-omics studies aim to reveal the etiology of pain in lipedema, which is generated through profound structural and biochemical changes on adipose tissue: adipocyte hypertrophy and hyperplasia, edematous interstitial matrix, variable septal fibrosis, immature angiogenesis, increased macrophage and mast cell infiltration, and focal steatonecrosis with interlobular hemorrhage [6, 13, 14].

These findings support the hypothesis that lipedema is not merely a condition of passive fat accumulation, but rather an active disorder of adipose tissue with distinct inflammatory and vascular characteristics. Pain, therefore, appears to be a direct consequence of the convergence of simultaneously pro-inflammatory, pro-fibrogenic, and pro-nociceptive microenvironment [13].

This article proposes an integrative model encompassing four interdependent axes which will be detailed below: 1) chronic inflammation of adipose tissue; 2) progressive hypoxic-ischemic-hemorrhagic injury; 3) adipomyofascial remodeling; and 4) peripheral neuromolecular alterations [13]. The pathophysiological mechanism appears to primarily involve inflammation, which exacerbates hypoxia and fibrosis; fascial remodeling that alters biomechanics and reinforces nociceptive activation; and neuroinflammation that integrates signals originating from adipose tissue, vasculature, and fascia, resulting in multidimensional, persistent pain that is disproportionate to fat volume.

4.1. Inflammatory Axis (Initial Trigger)

In lipedema, subcutaneous adipose tissue is in a state of chronic low-grade inflammation, characterized by infiltration of the hypodermis by macrophages and perivascular mast cells [13, 15]. Sustained activation of these cells results in continuous release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), as well as vasoactive mediators and growth factors cells [16].

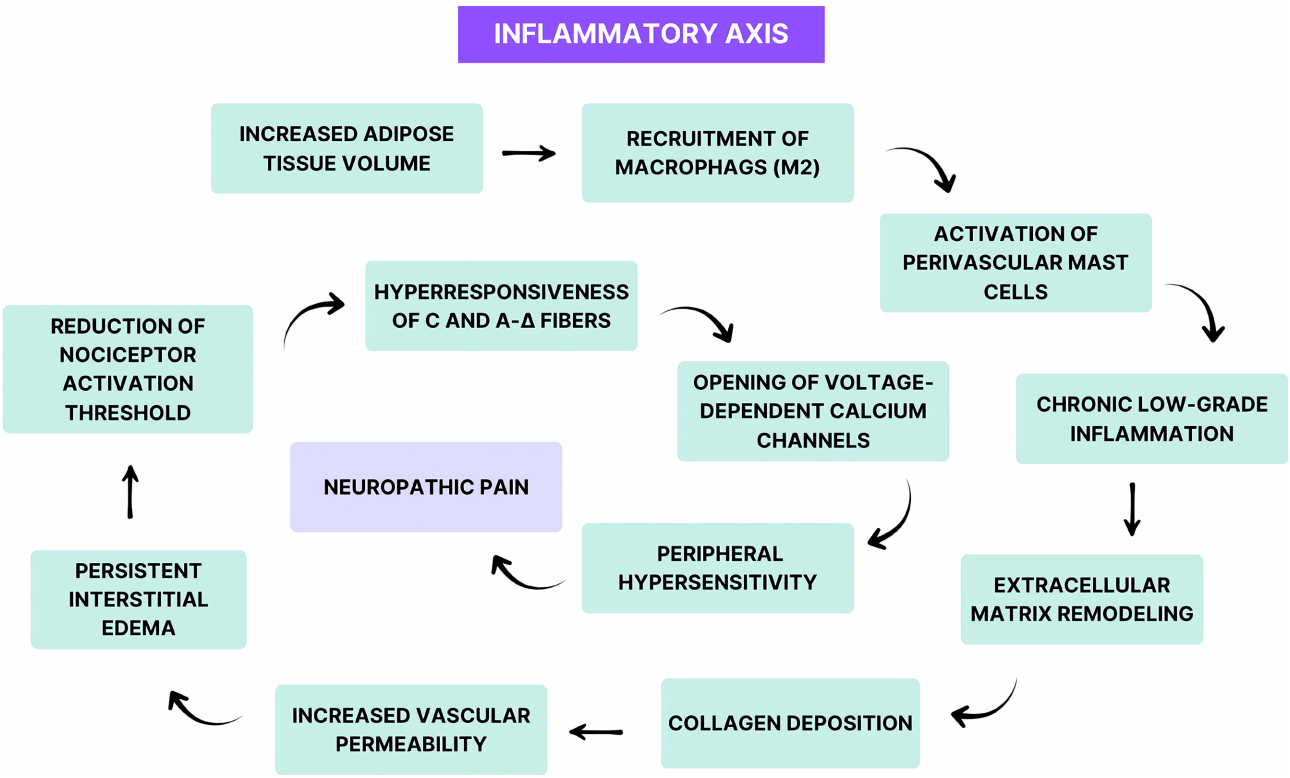

Figure 1. Inflammatory axis of the pain mechanism in lipedema.

This inflammatory microenvironment profoundly alters the architecture and physiology of adipose tissue, stimulating extracellular matrix remodeling, collagen deposition, increased vascular permeability, and protein-rich interstitial edema. This mechanism may explain the disproportionate pain in response to mechanical stimuli frequently reported by patients. From a nociceptive perspective, the persistent release of cytokines and algogenic mediators lowers the activation threshold of peripheral nociceptors in C and Aδ fibers, promoting peripheral sensitization, rendering subcutaneous tissue hyperresponsive to touch, compression, and changes in tissue pressure [13, 17]. However, the direct demonstration of these mediators acting on nociceptors in lipedema tissue is still being validated.

With maintenance of the inflammatory process, a progressive cycle develops: inflammation - tissue remodeling - pain - inflammatory exacerbation. In which tissue expansion and fibrosis further enhance immune cell activation. The result is a biologically active and inflamed adipose microenvironment, in which inflammation is not a secondary event but rather a primary mechanism in the genesis and perpetuation of pain in lipedema. This process is driven by chronic immune activation, leading to sustained release of cytokines and algogenic mediators and resulting in chronic, diffuse, deep pain that is disproportionate to the applied stimulus. A schematic illustration of these findings is shown in **Figure 1**.

4.2. Hypoxic-Hemorrhagic Axis (Cyclical Amplification)

Lipedema is characterized by adipocyte hyperplasia and hypertrophy. The expansion of the subcutaneous compartment volume leads to compression of the microcirculation, resulting in ischemia and consequent increased blood demand findings of a subclinical subcutaneous compartment syndrome [18]. The increased blood demand promotes neovascularization, which, under compressive conditions, results in immature and fragile capillaries, predisposing to hemorrhage [5-7]. Microcirculatory compression affects not only the arterial side but also venous and lymphatic pathways, contributing to edema and congestion.

Erythrocyte extravasation and hemoglobin degradation release free iron and biliverdin—molecules that are highly irritating to the hypodermis—thereby recruiting inflammatory cells that amplify nociception and promote septal fibrosis. Ischemia is also associated with increased release of hypoxia-inducible factor-1α (HIF-1*α*), which intensifies pathological angiogenesis and fibrosis, establishing a self-perpetuating cycle of hypoxia, inflammation, and structural damage [9, 13].

Histopathological findings reported by Vargas *et al.* demonstrate that subcutaneous adipose tissue in lipedema-affected areas exhibits microvascular alterations that define a microenvironment of chronic perfusion impairment. These include dilated capillaries, immature angiogenesis, increased permeability, erythrocyte extravasation, and interlobular hemorrhage, frequently accompanied by protein-rich interstitial edema and stromal fibrotic deposition. Collectively, these features characterize dysfunctional microangiopathy [6].

Immature and permeable angiogenesis, together with capillary fragility identified in biopsies, results in recurrent erythrocyte extravasation and interstitial hemoglobin release. Subsequent heme and iron degradation activates CD163+ macrophages and triggers the production of reactive oxygen species (ROS), promoting oxidative damage, interstitial edema, and fibrotic stimulation [12-17, 19, 20]. This inflammation-hemorrhage-fibrosis cycle progressively compromises oxygen transport and nutrient diffusion, leading to persistent tissue hypoxia.

Hypoxia, in turn, precipitates robust metabolic and nociceptive responses: adipocytes, endothelial cells, and matrix cells release algogenic mediators (extracellular ATP, lactate, NGF), which lower the activation threshold of peripheral nociceptors (C and Aδ fibers) [13, 17]. In addition, protein-rich interstitial edema and fibrosis resulting from dysfunctional angiogenesis increases local interstitial pressure, exerting mechanical compression on nerve endings and connective tissue structures. This increase in subcutaneous compartment pressure, combined with microvascular ischemia, generates pain through simultaneous compression and ischemic mechanisms [18].

As the condition progresses, subcutaneous tissue exhibits increasing cicatricial remodeling, with greater collagen density and reduced stromal compliance. Decreased tissue pliability alters microvascular flow

dynamics and perpetuates ischemia, establishing a self-reinforcing cycle of vascular injury, fibrosis, and pain. This tissue chronicity also explains the poorer clinical response observed in intermediate and advanced stages of lipedema, in which pain becomes more persistent and disproportionate to mechanical stimuli. A schematic illustration of the hypoxic-hemorrhagic mechanism is shown in Figure 2.

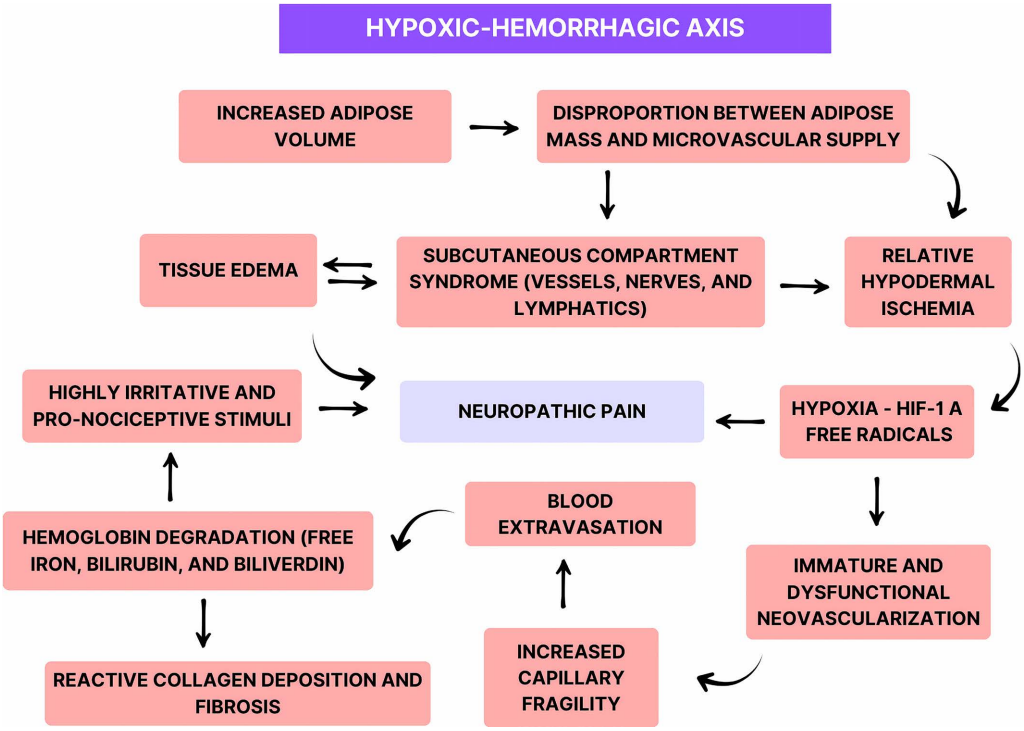

Figure 2. Hypoxic-hemorrhagic axis in the pain mechanism of lipedema.

4.3. Adipomyofascial Axis (Mechanical Amplification)

Recent reviews describe lipedema as an adipofascial disorder, in which chronic pain, edema, and nodularity are associated with profound structural alterations of the connective tissue [16]. The pathogenesis and development of lipedema may result from alterations in adipogenesis, inflammation, and extracellular matrix remodeling that lead to fibrosis and edema formation, and transcriptomic studies of subcutaneous tissue from patients have identified differentially expressed genes involved in these processes—including adipogenesis-related PRKG2, MEDAG, and BICC1; inflammation and macrophage polarization markers CD68, CD163, and TREM2; and pain-modulating genes such as SHTN1, SCN7A, and SLC12A2 [19].

Fascial remodeling with progressive thickening is thought to occur secondary to adipose tissue expansion, as a compensatory response to loss of tissue elasticity [21]. Fascial thickening is associated with collagen reorganization and reduced myofascial gliding, resulting in continuous mechanical tension, vascular compression, and deformation of septal tunnels that conduct neurovascular bundles [22, 23].

Several recent studies reinforce the concept of lipedema as an adipofascial disorder, characterized by progressive connective tissue fibrosis and thickening of septa and fascia [21-24]. These findings support the notion that, beyond the adipocytic component, there is marked thickening and remodeling of the superficial fascia and fibrous septa (retinacula cutis) in affected areas, creating a mechanically "stiffer" and less compliant tissue environment.

This mechanical dysfunction contributes both to the progression of fibrosis—leading to a functional condition resembling chronic fasciitis—and to neural entrapment, which increases pain even in the absence of overt edema. The fascia is now recognized as a highly innervated tissue, containing a rich network of nociceptive, proprioceptive, and autonomic fibers, and is capable of actively participating in pain modulation

[17].

At the microscopic level, the collagen pattern within the fascia is critical. Alterations in collagen and elastic fiber composition modify the biomechanical properties of the fascia and plausibly represent a source of myofascial dysfunction in women. Histological studies demonstrate that in human fascia, low hormonal exposure (such as during menopause) leads to a relative increase in type I collagen with a reduction in type III collagen and fibrillin, rendering the fascia stiffer and less elastic. In lipedema, recent reviews emphasize that the disease is hormone-related and marked by extracellular matrix (ECM) remodeling, fibrosis, and altered tissue elasticity. Accordingly, collagen reorganization (increased type I collagen, denser fibers, reduced type III collagen) within the fascia and septa increases mechanical stiffness, reduces the ability to dissipate mechanical stress, and facilitates microtrauma, small nerve injury, and chronic pain during movement or compression [21-23].

Gliding between fascial planes and between muscle-fascia-adipose tissue depends on a matrix rich in low-viscosity hyaluronic acid (HA). Increased HA viscosity within the fascia is directly associated with myofascial pain; when HA becomes more concentrated and structured ("densification"), sliding between fascial layers is reduced and mechanoreceptors are activated, generating pain [23, 24]. Stecco *et al.* have demonstrated that increased HA viscosity within fascia is directly linked to myofascial pain, as densification impairs fascial gliding and activates mechanosensitive receptors [23]. Matteini *et al.* showed that highly concentrated HA solutions form stable "superstructures," with abrupt changes in rheological properties (increased viscosity), which can be reversed by temperature elevation (gel-fluid transition) [24].

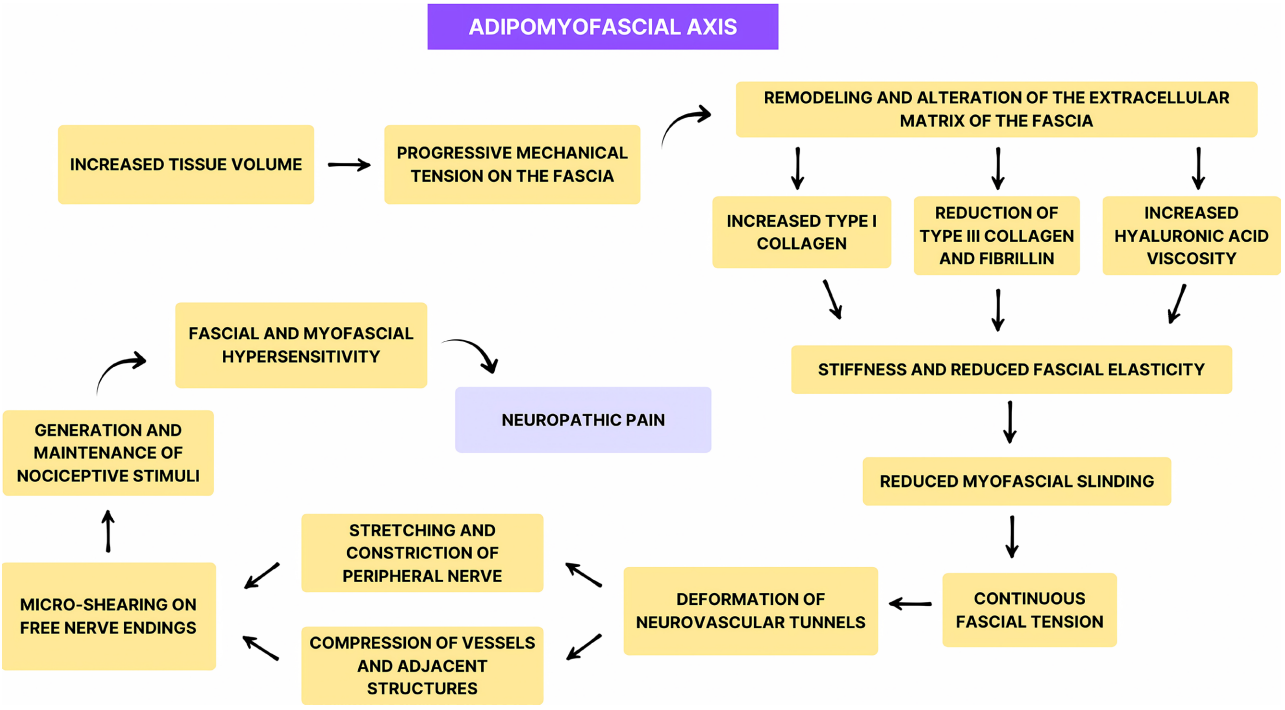

Figure 3. Adipomyofascial axis in the pain mechanism of lipedema.

In lipedema, chronic inflammation of adipose tissue promotes interstitial and fascial fibrosis, with collagen accumulation and thickening of septa and superficial fascia. Collagen remodeling (increased type I collagen and reduced type III collagen) renders fascia and septa stiffer and less elastic, particularly in a hormonally dependent female context. Alterations in the HA-rich matrix within the fascia increase viscosity (densification), impairing sliding between muscle, fascia, and adipose tissue. The combination of fascial thickening and matrix densification alters force transmission [25], generates focal stress points and microshear forces on free nerve endings and neurovascular plexuses, and facilitates hypersensitivity to superficial

palpation, deep pain, sensations of heaviness and burning under load, and mechanical allodynia (e.g., light touch or clothing compression). A schematic illustration of the adipomyofascial mechanism is shown in Figure 3.

4.4. Neuromolecular Axis (Pain Perpetuation)

The environment characterized by inflammation, fibrosis, increased subcutaneous compartment pressure, hypoxia, and oxidative stress induces structural damage to sensory nerve fibers, including axonal degeneration and partial demyelination. In parallel, biochemical alterations activate transient receptor potential vanilloid 1 (TRPV1), purinergic receptor P2X3, and acid-sensing ion channel 3 (ASIC3), maintaining neuronal hyperexcitability and persistent ectopic discharges [11, 26]. Clinically, this manifests as allodynia, hyperalgesia, and deep pain disproportionate to the applied stimulus.

Narrowing of neural tunnels, compression, and oxidative stress lead to axonal degeneration and demyelination, while sustained activation of TRPV1, P2X3, and ASIC3 channels maintains hyperexcitability, resulting in persistent pain, although these channels have not been directly identified in adipose tissue in lipedema, since such analyses remain scarce. The molecular basis of pain in lipedema involves the integration of inflammatory, hypoxic, tissue remodeling, and mechanic transduction pathways, which together modulate the adipose microenvironment and neuronal excitability.

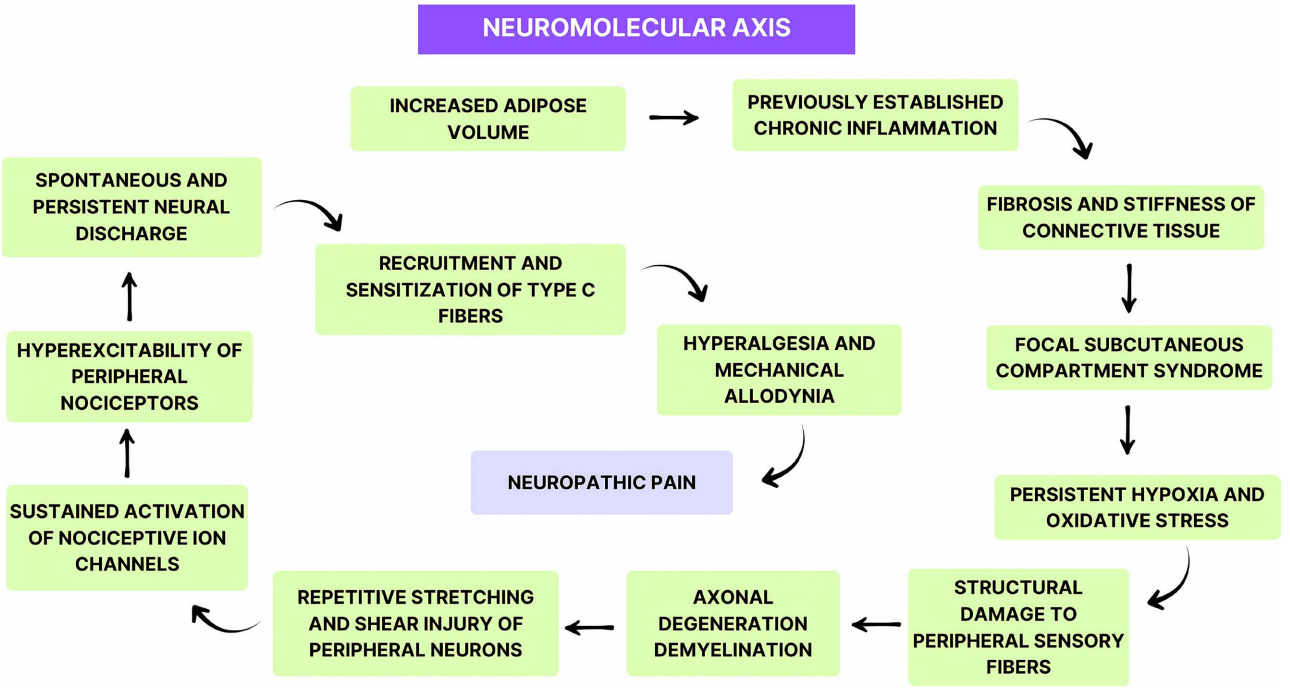

Figure 4. Neuromolecular axis in the pain mechanism of lipedema.

Transcriptomic and multi-omics studies demonstrate that adipose tissue in patients with lipedema exhibits gene expression patterns related to adipocyte hyperplasia, chronic low-grade inflammation, disorganized angiogenesis, and extracellular matrix alterations. From a neuromolecular perspective, oxidative stress, tissue acidosis, and extracellular ATP release activate ion channels such as TRPV1 (sensitive to heat and acidic pH), P2X3 (activated by ATP), and ASIC3 (sensitive to reduced pH), amplifying peripheral sensitization [26]. Sustained activation of these channels promotes spontaneous firing of C fibers, hyperalgesia, and allodynia, even in the absence of evident mechanical stimuli. Together, these processes establish a self-perpetuating circuit: inflammation - hypoxia - tissue remodeling - neural sensitization. Understanding these molecular mechanisms highlights potential therapeutic targets, including specific ion channel blockers,

matrix metalloproteinase (MMP) inhibitors, receptor modulators, antifibrotic agents, and endothelial-protective strategies. Within this integrated self-reinforcing circuit (structural, inflammatory, ischemic, and neuromolecular) inflammation promotes hypoxia, hypoxia intensifies tissue remodeling, and both enhance neural sensitization, consolidating a persistent and refractory pain state [11, 13, 26].

This framework delineates a renewed perspective on therapeutic targets, which should aim at inflammatory modulation and improvement of tissue perfusion. Schematic illustration of the neuromolecular mechanism is shown in Figure 4.

4.5. Integrative Model of Pain in Lipedema

The integrative model suggests that adipose tissue in lipedema acts as an active pain-producing organ rather than merely a lipid storage site. Therefore, therapeutic strategies focused exclusively on volumetric reduction are insufficient. Management should also encompass inflammatory modulation, restoration of microvascular perfusion, preservation of fascial function, and neuroprotection as fundamental pillars. It is noteworthy that the four axes interact and mutually reinforce one another, forming a large, interconnected network with circular and cascading feedback loops, ultimately resulting in intense chronic pain that is disproportionate to the applied stimulus.

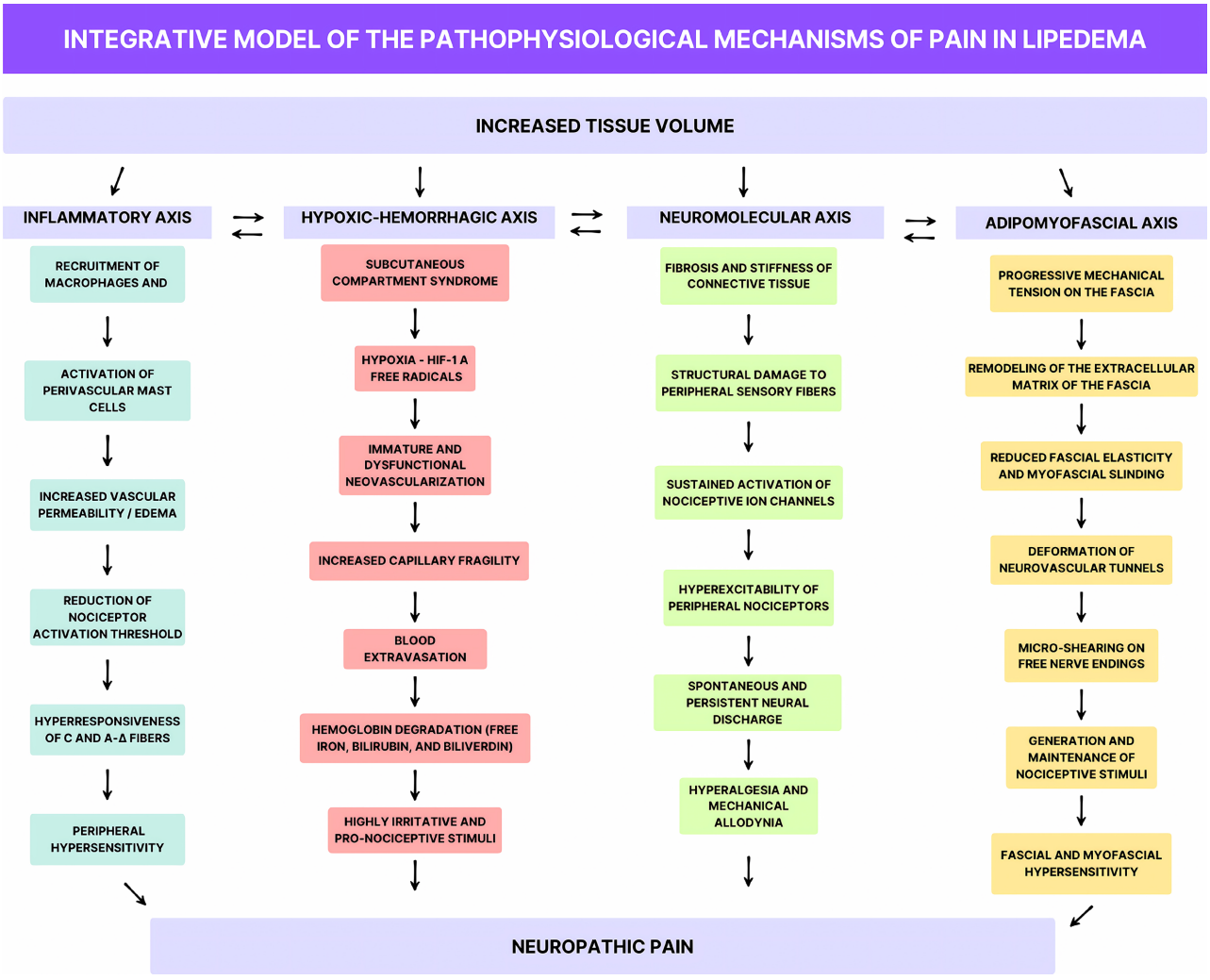

Figure 5. Schematic illustration of the integration of pathophysiological axes in the pain mechanism of lipedema.

The authors propose a multifactorial model of pain in lipedema (**Figure 5**): inflammation intensifies hypoxia and fibrosis; fascial remodeling alters biomechanics and amplifies nociceptive signaling; and neuroinflammation integrates inputs from adipose tissue, the vasculature, and fascia, producing persistent, multidimensional neuropathic pain often disproportionate to adipose volume.

Obesity, venous disease, lymphedema, age, menopausal status and analgesic administration may cause confusion; affecting independently inflammation, microcirculation, fascia stiffness, and pain in lipedema. Most of the studies included are lacked matched controls or adjustments for these factors, limiting the ability to attribute observed alterations, specifically to lipedema. Therefore, while the current evidence suggests plausible pathophysiological mechanisms, the findings should be interpreted with caution.

5. CONCLUSIONS

Despite the increasing recognition of lipedema and the growing body of research in recent years, its main clinical manifestation—pain—remains poorly understood and inadequately treated. By subdividing its pathophysiology into distinct components, a clearer understanding can be achieved. These components, referred to as axes, include inflammatory, hypoxic-hemorrhagic, adipomyofascial, and neuromolecular mechanisms.

The axes interact synergistically within the subcutaneous tissue, establishing direct and cyclic correlations between tissue damage and nociceptive hyperexcitability. This interaction results in intense pain that is disproportionate to the stimulus and ultimately evolves into chronic pain.

Given this complexity, therapeutic approaches centered exclusively on fat reduction are insufficient for effective pain control. Novel pain-directed therapies may prove transformative if they are targeted toward inflammatory modulation, mitigation of oxidative stress, reduction of vascular permeability, improvement of microvascular perfusion, preservation of myofascial function, and neuroprotection. Future studies—with well-characterized cohorts, appropriate control groups, and multivariate analyses—are needed to distinguish lipedema-specific changes from those related to comorbidities or age-related factors. Such investigations are essential to strengthen causal inference, clearing relative contribution of each mechanistic axis, and guide targeted therapeutic strategies for pain management in lipedema.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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