*Opinion Article*

Metabolic Therapy for Lipedema: Can Tirzepatide Overcome the Treatment Gap?

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ABSTRACT

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| **Aims:** This article reviews the pathophysiological mechanisms of lipedema and explores the potential benefits of tirzepatide as a novel therapeutic approach.Study Design: Opinion article.**Place and Duration of Study:** Brazil, January–February 2025.**Methodology:** A critical analysis of current literature on lipedema pathophysiology and tirzepatide's pharmacological effects, integrating evidence from metabolic, immunological, and fibrotic pathways.**Results:** Lipedema is a chronic, estrogen-dependent adipose tissue disorder characterized by disproportionate fat accumulation, inflammation, and fibrosis, predominantly affecting women. Despite its significant impact on quality of life, pharmacological treatment options remain limited, as lipedematous fat is resistant to caloric restriction, appetite-suppressing medications, and even bariatric surgery. Given recent advances in metabolic therapies, tirzepatide—a dual GLP-1 and GIP receptor agonist—has emerged as a promising candidate for lipedema management. Beyond its well-documented effects on weight loss and glycemic control, tirzepatide exhibits anti-inflammatory, antifibrotic, and thermogenic properties that target key pathophysiological mechanisms of lipedema. Its ability to shift macrophage polarization toward an anti-inflammatory M2 phenotype, inhibit ERK pathway signaling to reduce fibrosis, and enhance energy expenditure via increased UCP1 expression in brown adipose tissue suggests a potential role in alleviating lipedema symptoms. However, despite its promising pharmacological profile, tirzepatide has yet to be formally evaluated for this condition.**Conclusion:** This article critically appraises the rationale for tirzepatide as a therapeutic option for lipedema, discussing its potential benefits, limitations, and the urgent need for dedicated clinical trials to establish its efficacy and safety in this underserved patient population.**Keywords:** Lipedema, Tirzepatide, Anti-Inflammatory Agents, GLP-1, Metabolic Therapy. |

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1. INTRODUCTION

Lipedema is a chronic, progressive inflammatory disorder of adipose tissue that predominantly affects women. The condition has a strong hormonal component, with evidence suggesting an imbalance in estradiol receptor distribution in adipose tissue (ERα > ERβ), which contributes to adipocyte hypertrophy, inflammation, and fibrosis (Katzer et al., 2021). Epidemiological studies report a considerable global prevalence, ranging from 11% to 39% among adult women, depending on the diagnostic criteria applied (Buck & Herbst, 2016; Katzer et al., 2021; Christoffersen & Tennfjord, 2023).

Lipedema is frequently underdiagnosed due to symptom overlap with obesity and lymphedema. However, unlike these conditions, lipedema is characterized by a disproportionate accumulation of subcutaneous fat in the upper and lower limbs, sparing the hands and feet. Its hormonal nature leads to symmetrical and disproportionate fat deposition, combined with a pronounced inflammatory component that contributes to pain, fibrosis, and adipose tissue edema, distinguishing it from both obesity and lymphedema.

One of the most challenging aspects of lipedema treatment—often a source of psychological distress, emotional disorders, and even eating disturbances among affected individuals—is its resistance to caloric deficit. Unlike obesity, lipedema does not respond to anorexigenic or satiety-inducing pharmacological strategies, nor to bariatric surgery (Allen & Hines, 1940; Wold, Allen & Hines, 1951).

Given that lipedema is a disease with both physical and emotional symptoms that significantly impair the lives of many women (Clarke et al., 2023; Chachaj et al., 2024), with an estimated global incidence of 10% (van la Parra et al., 2023), and that current therapeutic options remain limited, it is essential to explore new treatment possibilities for these patients.

Tirzepatide may represent a promising therapeutic option and a new hope for lipedema management. Originally developed for the treatment of obesity associated with metabolic syndrome and diabetes (Rosenstock et al., 2021), its dual GLP-1 and GIP receptor agonism confers unique properties that could be particularly beneficial in lipedema treatment, including anti-inflammatory, antifibrotic, and thermogenic effects.

This article aims to review the pathophysiological mechanisms of lipedema, analyze the proposed mechanisms of action of tirzepatide, and explore its potential as a novel therapeutic approach for lipedema, particularly due to its well-established anti-inflammatory and metabolic effects.

2. Pathophysiological Mechanisms of Lipedema

Lipedema is a chronic, progressive condition influenced by genetic, hormonal, and environmental factors, with a particular emphasis on the imbalance between estradiol alpha (ERα) and beta (ERβ) receptors in subcutaneous adipose tissue. This imbalance, present in all cases, predominantly affects the arms and legs in a disproportionate manner. Increased ERα expression promotes the expansion of dysfunctional adipose tissue, contributing to local inflammation, fibrosis, edema, and vascular and lymphatic dysfunction. Hormonal fluctuations during puberty, pregnancy, and menopause further exacerbate the disease, underscoring the critical role of estradiol in adipocyte dysfunction.

External factors, such as exposure to endocrine disruptors and xenoestrogens—primarily linked to unhealthy dietary patterns rich in processed foods, sugar, and other pro-inflammatory substances—further aggravate adipose tissue dysfunction (Annunziata et al., 2024). These disruptors interfere with estradiol metabolism, leading to increased ERα activation. Moreover, a strong correlation exists between lipedema and gynecological conditions, including endometriosis, fibroids, and progesterone resistance, which share common pathophysiological mechanisms such as elevated aromatase activity and dysregulation of key enzymes like 17β-HSD. These alterations contribute to increased local estradiol levels (Seefeldt et al., 2023; Patton et al., 2024).

These findings underscore the necessity of integrated therapeutic approaches that address not only the metabolic and hormonal dimensions of the disease but also its gynecological implications (Viana & Camara, 2025).

The increased activation of ERα ultimately drives the abnormal expansion of inflammatory adipose tissue, resulting in a pattern that is both symmetrical and disproportionate relative to other body regions. This process is primarily mediated by immunological alterations, microangiopathy, lymphatic dysfunction, and reduced thermogenesis (Szél et al., 2014; Felmerer et al., 2020; Felmerer et al., 2022; Poojari, Dev & Rabiee, 2022). Figure 1 provides a comprehensive overview of lipedema, illustrating its morphology, pathophysiology, and the key challenges associated with the condition (Poojari, Dev & Rabiee, 2022).

From an immunological standpoint, the affected adipose tissue exhibits increased infiltration of pro-inflammatory M1 macrophages, contributing to a chronic inflammatory state marked by elevated levels of cytokines such as TNF-α and IL-6 (Felmerer et al., 2020; Felmerer et al., 2022).



**Fig. 1.** **Lipedema—Insights into Morphology, Pathophysiology, and Challenges**.

*Source: (Poojari, Dev & Rabiee, 2022).*

*The sequence of events sustaining the lipedema phenotype follows this pattern:* ***(A)*** *Increased expression of genes associated with mitotic clonal expansion (MCE) and cell proliferation leads to adipocyte hyperplasia. Although excessive lipid accumulation within adipocytes, resulting in hypertrophy, has been confirmed in lipedema, the expression of markers associated with this phenomenon remains a topic of debate.* ***(B)*** *Due to the excessive growth of adipocytes, oxygen supply is reduced, and extracellular matrix (ECM) remodeling is observed. This remodeling includes increased sodium (Na⁺) concentration, collagen deposition, and disturbances in the glycocalyx (including proteoglycans and glycosaminoglycans), leading to microangiopathy and fibrosis.* ***(C)*** *Endothelial permeability and paracellular leakage increase due to the weakening of tight junctions between endothelial cells (ECs), further exacerbating vascular impairment and inflammation. Additionally, the capacity of lymphatic capillaries to absorb interstitial fluid (IF) is reduced, promoting IF leakage, lymphatic dysfunction, and expansion of the interstitial space.* ***(D)*** *Pathogenic alterations at the vascular and lymphatic levels contribute to interstitial fluid accumulation, leading to fluid deposition. Excess IF surrounding adipocytes serves as a nutrient source, further driving pathological adipocyte expansion, ultimately leading to subcutaneous adipose tissue (SAT) remodeling and perpetuating the lipedema phenotype in a cyclical manner.*

***Color coding from the original text: Blue****: Decreased gene expression in lipedema,****Brown****: Increased gene expression in lipedema e* ***Black****: Conflicting findings reported for these genes*

Microangiopathy, a hallmark feature of lipedema, arises from endothelial dysfunction, increased vascular permeability, and hypoxia, collectively driving inflammation, fibrotic remodeling, and impaired nutrient delivery (Szél et al., 2014). These effects occur both mechanically, due to the compression of adjacent structures, and as a consequence of the inflammatory response.

Lymphatic dysfunction, characterized by micro-lymphatic aneurysms and morphological abnormalities displaying a "string-of-beads" pattern on MR lymphangiography, indicates both functional and structural impairment of lymphatic capillaries (Amann-Vesti, Franzeck & Bollinger, 2001). This dysfunction exacerbates interstitial fluid accumulation, which, in turn, perpetuates hypertrophic and fibrotic adipose tissue growth, establishing a self-sustaining cycle of tissue remodeling and lymphatic compromise (Poojari, Dev & Rabiee, 2022).

Additionally, reduced thermogenesis, linked to decreased expression of mitochondrial uncoupling protein 1 (UCP1) in affected tissues, limits energy expenditure and contributes to the metabolic inefficiency of lipedematous fat (Szél et al., 2014). Collectively, these mechanisms underscore the complexity of lipedema and the challenges associated with its therapeutic management, making the disease resistant to caloric deficit, anorexigenic pharmacological strategies, and even bariatric surgery (Pouwels et al., 2018; Cornely et al., 2022).

3. Potential Effects of Tirzepatide on Lipedema

Tirzepatide was developed as a dual agonist of GLP-1 and GIP receptors, primarily designed to enhance glycemic control in patients with type 2 diabetes and to induce significant weight loss in individuals with obesity or overweight. Clinical trials, such as SURMOUNT-1, have demonstrated that tirzepatide, at doses of 15 mg, 10 mg, and 5 mg, resulted in average weight reductions of 20.9%, 19.5%, and 15%, respectively, surpassing semaglutide by up to 30% in weight-loss efficacy (Jastreboff et al., 2022).

Beyond its effects on body weight, tirzepatide has shown notable metabolic benefits, including reductions in fasting glucose, HbA1c, triglycerides, and visceral fat, as well as improvements in insulin sensitivity—even in non-diabetic individuals (Xia et al., 2024; Varol et al., 2014). Its mechanism of action integrates GLP-1-mediated appetite suppression and decreased caloric intake with GIP-driven modulation of lipid metabolism and adipose tissue inflammation, thereby influencing body composition and metabolic control (Xia et al., 2024; Varol et al., 2014). These findings position tirzepatide as a promising therapeutic agent for obesity and related metabolic disorders.

Furthermore, tirzepatide has demonstrated significant benefits in conditions characterized by fat accumulation and fibrosis, such as heart failure with preserved ejection fraction (HFpEF) and metabolic-associated steatohepatitis (MASH), owing to its lipolytic, anti-inflammatory, and antifibrotic properties. In HFpEF, tirzepatide reduces epicardial fat—an inflammatory reservoir linked to diastolic dysfunction—by promoting lipolysis and decreasing adipose tissue inflammation (Xia et al., 2024). Additionally, it modulates myocardial fibrosis by inhibiting the ERK pathway and reducing pro-inflammatory cytokines such as TNF-α and IL-6, while simultaneously improving insulin resistance and glycemic control—both of which are critical factors in HFpEF pathogenesis (Liu et al., 2023; Wilson et al., 2022).

In MASH, tirzepatide lowers hepatic fat content by enhancing insulin sensitivity and promoting lipolysis. It also modulates hepatic macrophages toward an anti-inflammatory phenotype and regulates genes involved in extracellular matrix remodeling, including collagen and matrix metalloproteinases, thereby reducing liver fibrosis (Varol et al., 2014; Xia et al., 2024). These mechanisms closely parallel those observed in lipedema, suggesting that tirzepatide may also contribute to reducing fat accumulation, mitigating chronic inflammation, and decreasing fibrosis—positioning itself as a promising yet unexplored therapeutic option for this condition.

By enhancing lipolysis through GIP receptor activation, tirzepatide may facilitate the mobilization of resistant fat—a hallmark of lipedema—thereby promoting volume reduction in affected areas (Xia et al., 2024). Simultaneously, its ability to suppress pro-inflammatory M1 macrophage activity while increasing anti-inflammatory M2 macrophages contributes to a less inflammatory tissue environment, potentially alleviating the pain and edema characteristic of the condition (Varol et al., 2014).

Additionally, by inhibiting ERK pathway signaling, tirzepatide reduces the production of inflammatory cytokines such as TNF-α, IL-6, and MCP-1, thereby disrupting the chronic inflammatory cycle observed in lipedema (Poojari et al., 2022; Xia et al., 2024). Although the direct effects of tirzepatide on extracellular matrix (ECM) component expression remain to be fully elucidated, its ability to lower biomarkers such as YKL-40—associated with fibrosis and tissue remodeling in cardiovascular diseases (Wilson et al., 2022)—suggests a potential role in ECM regulation. These pathophysiological mechanisms, previously discussed, are well-established in the context of lipedema.

Notably, tirzepatide also influences brown adipose tissue by upregulating the expression of thermogenesis-related genes, such as UCP-1, leading to increased energy expenditure and reduced fat accumulation (Varol et al., 2014).

These combined effects position tirzepatide as a groundbreaking therapeutic approach for improving symptoms and quality of life in patients with lipedema. No other pharmacological intervention has demonstrated the ability to comprehensively target all key mechanisms underlying the disease. Even semaglutide, which may serve as an adjunct therapy in lipedema cases associated with obesity, lacks the capacity to address the fundamental drivers of inflammation and fibrosis (Cifarelli et al., 2024).

### **4. Conclusion**

Tirzepatide emerges as a promising and innovative therapeutic approach for lipedema, integrating metabolic, anti-inflammatory, and antifibrotic effects that directly target the key pathophysiological mechanisms of the disease. Its ability to reduce resistant fat accumulation through enhanced lipolysis, shift macrophage profiles toward an anti-inflammatory M2 phenotype, and inhibit ERK pathway signaling contributes to decreased chronic inflammation and lower levels of cytokines such as TNF-α and IL-6. Additionally, tirzepatide mitigates fibrosis by modulating extracellular matrix remodeling, thereby improving adipose tissue elasticity (Varol et al., 2014).

Furthermore, tirzepatide enhances thermogenesis in brown adipose tissue by stimulating the expression of genes such as UCP-1, promoting increased energy expenditure and reducing fat accumulation (Xia et al., 2024). These effects surpass those of semaglutide, which, despite its efficacy in obesity management, does not sufficiently address the inflammation and fibrosis central to lipedema (Cifarelli et al., 2024).

However, dedicated clinical trials are necessary to confirm tirzepatide’s efficacy and safety in lipedema patients, potentially opening new therapeutic avenues for a condition that has thus far lacked effective pharmacological treatments.

CONFLICT OF INTEREST STATEMENT

Authors have declared that no competing interests exist.

Consent AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE):

The authors declare that generative AI was used solely during the final stage of manuscript preparation (post-writing) and exclusively for linguistic refinement in the English language (Name: ChatGPT; Version: GPT-4; Model:OpenAI's Large Language Model; Source:OpenAI - https://openai.com). No original text was generated or substantively edited by the AI.

Definitions, Acronyms, Abbreviations

Alfa estradiol receptors (ERα), Beta estradiol receptors (ERβ), Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, 17β-hydroxysteroid dehydrogenase (17β-HSD), Tumor necrosis factor alpha (TNF-α), Interleucina-6 (IL-6), Mitochondrial uncoupling protein 1 (UCP1), A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1), Glycated Haemoglobin (HbA1c), Glucagon-Like Peptide-1 (GLP-1), Preserved ejection fraction (HFpEF), Metabolic-associated steatohepatitis (MASH), [Heart Failure With Preserved Ejection Fraction](https://www.ncbi.nlm.nih.gov/books/NBK599960/) (HFpEF), M1 macrophage, M2 macrophages, Gastric inhibitory polypeptide (GIP), Monocyte chemoattractant protein-1 (MCP-1), extracellular regulated protein kinases (ERK)

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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