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REVIEW ARTICLE

Localized Injection of Semaglutide, a GLP-1 Agonist, for Hyperinsulinemia-Induced Lymphatic Dysfunction A Novel Therapeutic Strategy for Lymphedema Treatment

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Abstract

Lymphedema, traditionally considered a secondary complication of lymphatic damage, may have a deeper, metabolic etiology tied to chronic hyperinsulinemia and insulin resistance. This emerging hypothesis posits that prolonged hyperinsulinemia drives lymphatic endothelial cell (LEC) dysfunction, initiating inflammation, oxidative stress, and structural damage that culminates in impaired lymphatic drainage. Insulin resistance disrupts the PI3K/Akt signaling pathway, which is vital for lymphangiogenesis and endothelial health, further exacerbating lymphatic vessel integrity. Recent clinical evidence underscores the therapeutic potential of GLP-1 receptor agonists (GLP-1RAs), known for their insulin-sensitizing and anti-inflammatory properties. Notably, cases of breast cancer-related lymphedema have shown marked improvements following GLP-1RA treatment, with significant reductions in limb volume and restoration of lymphatic function. These observations suggest a dual mechanism by which GLP-1RAs address both the metabolic and vascular components of lymphedema, positioning them as a promising therapeutic avenue for lymphedema driven by insulin resistance. This review delves into the molecular pathophysiology of lymphedema in the context of metabolic dysfunction and explores the role of GLP-1RAs as an innovative treatment strategy.

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1. Introduction

Lymphedema is a chronic, progressive disorder characterized by the abnormal accumulation of protein-rich lymphatic fluid in the interstitial spaces, most commonly affecting the limbs but also capable of manifesting in other regions of the body. The pathophysiology of lymphedema stems from an impaired lymphatic system, where dysfunctional lymphatic vessels fail to efficiently drain lymph fluid, resulting in tissue edema, persistent inflammation, and ultimately fibrosis[1]. Over time, this condition induces profound structural and functional changes within the affected tissues, marked by significant cellular alterations, including the proliferation of fibroblasts, adipocytes, and immune cells, particularly macrophages[2]. The

cytobiological landscape of lymphedema is highly complex and intimately linked to chronic inflammation. Persistent lymphedema triggers a state of sustained low-grade inflammation, facilitated by the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β)[3]. This pro-inflammatory environment promotes the remodeling of the extracellular matrix (ECM) and fibrosis, which further impair lymphatic function[4]. In addition to fibrosis, lymphedema is also characterized by localized adipogenesis, wherein excessive adipose tissue accumulation exacerbates fluid retention and contributes to further lymphatic dysfunction. This pathological adipose accumulation is particularly prominent in individuals with obesity, where the interplay between adipose tissue and compromised lymphatic function creates a vicious cycle of worsening lymphatic insufficiency[5]. Obesity plays a critical role in the onset and progression of lymphedema. As an endocrine organ, adipose tissue secretes a variety of adipokines such as leptin and resistin, which are known to negatively impact lymphatic function by enhancing inflammatory responses and altering vascular homeostasis[6]. The mechanical burden of excessive adipose tissue also exacerbates lymphatic dysfunction by directly obstructing lymphatic flow. This mechanical and biochemical strain not only disrupts lymphatic vessel architecture but also further amplifies systemic inflammation, thereby accelerating the progression of both obesity and lymphedema[7].

A key factor in this cycle is the development of insulin resistance, which is closely tied to obesity and metabolic dysfunction. Insulin resistance occurs when cells in tissues such as skeletal muscle, liver, and adipose tissue become less responsive to insulin, leading to compensatory hyperinsulinemia. Over time, this chronic hyperinsulinemic state promotes endothelial dysfunction, particularly within the lymphatic vasculature, further impairing lymphatic drainage and contributing to tissue inflammation[8]. Hyperinsulinemia also increases oxidative stress and activates inflammatory pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which exacerbates endothelial injury and promotes fibrosis within lymphatic vessels[9]. Moreover, the dysregulated secretion of adipokines in obesity marked by elevated levels of pro-inflammatory mediators like resistin and leptin and reduced levels of the insulin-sensitizing adipokine adiponectin further disrupts insulin signaling[10]. This dysregulation worsens lymphatic dysfunction by perpetuating chronic inflammation and promoting extracellular matrix remodeling. Additionally, free fatty acids (FFAs), which are elevated in obesity, accumulate in tissues and contribute to lipotoxicity, compounding the damage to both metabolic and lymphatic systems[11]. In this review, we investigate a novel mechanism underlying the progression of lymphedema, focusing on the interaction between insulin resistance and lymphatic vessel dysfunction. Furthermore, we explore an innovative therapeutic approach utilizing local injections of GLP-1 receptor agonists, which have shown promise in improving insulin sensitivity and modulating lymphatic endothelial function. By targeting the metabolic and vascular components of lymphedema, this strategy may offer a new avenue for effective treatment of this debilitating condition.

2. Methodology

In this review, we aim to explore a novel hypothesis that addresses the intricate relationship between insulin resistance, obesity, and lymphatic dysfunction, specifically within the context of lymphedema. The proposed hypothesis is based on an emerging understanding of the molecular and cellular mechanisms that underlie both metabolic and lymphatic

disorders. To substantiate this hypothesis, we have integrated findings from recent advances in lymphatic biology, adipose tissue inflammation, and insulin resistance pathways. The methodology for this review involves a comprehensive literature analysis across multiple scientific domains, including studies on lymphatic vessel pathophysiology, metabolic syndrome, obesity-induced inflammation, and insulin signaling disruptions. We systematically searched databases such as PubMed, Scopus, and Web of Science for peer-reviewed articles published within the last decade. The inclusion criteria focused on studies that examine the mechanisms of insulin resistance in obese individuals, the role of chronic inflammation in lymphatic dysfunction, and the therapeutic potential of GLP-1 receptor agonists. Special attention was given to experimental models of lymphedema, adipose tissue dysregulation, and lymphatic endothelial cell biology.

To lay the foundation for our hypothesis, we first analyzed the biochemical pathways that link obesity-induced inflammation to insulin resistance, particularly the activation of pro-inflammatory cytokines such as TNF-α and IL-6, which impair insulin receptor signaling. This was followed by an exploration of the vascular complications associated with hyperinsulinemia, focusing on its deleterious effects on lymphatic endothelial cells and the resultant impairment of lymphatic drainage. Furthermore, the study delves into the effects of excess free fatty acids and their contribution to lipotoxicity and mitochondrial dysfunction, which are critical in the progression of both insulin resistance and lymphatic vessel damage.

We also conducted an in-depth evaluation of the GLP-1 receptor agonists' mechanism of action, focusing on their dual role in enhancing insulin sensitivity and exerting protective effects on the vascular endothelium. Preclinical and clinical studies were reviewed to assess the efficacy of GLP-1 analogs in reducing adipose tissue inflammation and improving lymphatic function. Through this comprehensive review, we seek to establish a clear link between metabolic dysfunction and lymphatic impairment, proposing that localized GLP-1 receptor agonist therapy could serve as a promising intervention. This approach is grounded in the evolving understanding of the lymphatic system’s role in metabolic health, particularly its interaction with adipose tissue and insulin signaling pathways. By targeting these interconnected processes, the proposed methodology seeks to provide a scientific basis for the innovative use of GLP-1 receptor agonists in treating lymphedema, specifically via local injections into affected tissues. This method may offer a more targeted approach to mitigating the inflammatory and fibrotic processes that characterize advanced lymphedema, presenting a potential breakthrough in its management.

3. Biochemical Pathways Linking Obesity-Induced Inflammation to Insulin Resistance: The Role of Pro-Inflammatory Cytokines TNF-α and IL-6

Obesity induces a chronic state of low-grade inflammation that is critically involved in the pathogenesis of insulin resistance. This inflammatory response is primarily driven by the expansion of adipose tissue, which leads to the infiltration of immune cells, particularly pro-inflammatory M1 macrophages[12].

These macrophages secrete key cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both of which play crucial roles in disrupting insulin receptor signaling and impairing glucose homeostasis[13].

TNF-α serves as a central mediator in the development of insulin resistance. Within hypertrophic adipose tissue, elevated levels of TNF-α trigger the activation of serine kinases, including c-Jun N-terminal kinase (JNK) and IκB kinase (IKK)[14]. These kinases phosphorylate insulin receptor substrate-1 (IRS-1) at serine residues, an event that critically disrupts IRS-1's ability to propagate insulin signals through the phosphoinositide 3-kinase (PI3K)-Akt signaling pathway[15][16]. This pathway is essential for facilitating glucose uptake in both skeletal muscle and adipocytes. In addition to inhibiting IRS-1 function, TNF-α downregulates the expression of glucose transporter type 4 (GLUT4), further impairing glucose transport and worsening insulin resistance[17].

IL-6 contributes to insulin resistance through a distinct but complementary mechanism. By activating the STAT3 signaling cascade, IL-6 induces the expression of suppressor of cytokine signaling-3 (SOCS-3), a protein that interferes with insulin receptor activity and inhibits IRS-1 function, thereby impairing PI3K-Akt signaling[18]. Furthermore, IL-6 exacerbates metabolic dysregulation by enhancing hepatic gluconeogenesis and disrupting lipid metabolism, leading to ectopic fat deposition in the liver, which is tightly linked to systemic insulin resistance[19].

Excessive free fatty acids (FFAs), a hallmark of obesity, contribute significantly to insulin resistance and lymphatic vascular damage through multiple cytobiological and biochemical mechanisms, including lipotoxicity, mitochondrial dysfunction, and oxidative stress, all of which interfere with cellular metabolism and vascular integrity[20]. In non-adipose tissues, excess FFAs are stored as diacylglycerols (DAGs), which activate protein kinase C (PKC). This PKC activation phosphorylates insulin receptor substrate-1 (IRS-1) on serine/threonine residues, disrupting insulin signaling by inhibiting the PI3K-Akt pathway, thereby impairing glucose uptake and leading to insulin resistance[21].

Additionally, another lipid intermediate, ceramide, accumulates during lipotoxicity, promoting apoptosis and interfering with IRS-1 function, further impairing insulin sensitivity and contributing to β-cell dysfunction in the pancreas, which exacerbates systemic metabolic disruption[22]. Excess FFAs also overwhelm mitochondrial capacity, leading to incomplete fatty acid oxidation and the buildup of toxic intermediates, reducing ATP production and causing metabolic inefficiency in tissues critical for insulin-mediated glucose uptake, such as skeletal muscle[23]. Moreover, overloaded mitochondria generate high levels of reactive oxygen species (ROS), leading to oxidative stress, which damages mitochondrial DNA, proteins, and membranes, impairing mitochondrial function and bioenergetics and exacerbating insulin resistance. The interplay of excess FFAs and ROS also activates stress-related kinases, including c-Jun N-terminal kinase (JNK) and IκB kinase (IKK), which phosphorylate IRS-1 and inhibit insulin signaling while promoting the secretion of pro-inflammatory cytokines like TNF-α and IL-6, enhancing chronic low-grade inflammation in obese adipose tissue[24]. Furthermore, FFAs induce endoplasmic reticulum (ER) stress by disrupting protein folding, triggering the unfolded protein response (UPR), and worsening insulin resistance by activating JNK and increasing ROS production. This cascade of events has significant implications for lymphatic vascular health, as oxidative stress and excess FFAs impair the function of lymphatic endothelial cells, disrupting mitochondrial bioenergetics and promoting lipid peroxidation, which results in increased vascular permeability and reduced lymphatic drainage, thereby contributing to conditions like lymphedema. Additionally, the interaction between expanding adipose tissue and the lymphatic system creates a vicious cycle in which inflammation driven by pro-inflammatory macrophages impairs lymphatic function, exacerbating fluid retention and further

promoting tissue damage[25].

4. The Interrelationship Between Insulin Resistance and Lymphatic Dysfunction: A Detailed Exploration of Molecular Mechanisms and Pathophysiological Consequences

Insulin resistance represents a fundamental disruption in cellular metabolism that significantly impacts various physiological systems, including the lymphatic vasculature. It is defined by a reduced cellular responsiveness to insulin, particularly in insulin-sensitive tissues such as skeletal muscle, adipose tissue, and the liver. This resistance leads to compensatory hyperinsulinemia, where pancreatic β-cells secrete excessive amounts of insulin in an attempt to maintain glucose homeostasis. Over time, this state of chronic hyperinsulinemia, combined with persistent insulin resistance, has been implicated in multiple pathological processes, including endothelial dysfunction, chronic inflammation, and structural damage to the lymphatic system[26]. The molecular underpinnings of insulin resistance are complex, involving disruptions in insulin signaling pathways that reverberate throughout the metabolic and vascular systems.

At the core of insulin resistance lies the impairment of insulin receptor signaling. Under normal conditions, insulin binding to its receptor activates the insulin receptor substrate (IRS) proteins, particularly IRS-1, which in turn propagates signals through downstream pathways such as the phosphoinositide 3-kinase (PI3K)/Akt pathway[27]. This pathway is crucial for various cellular functions, including glucose uptake via the translocation of glucose transporter type 4 (GLUT4) to the cell membrane. However, in states of insulin resistance, several factors, notably pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), inhibit the function of IRS-1 by promoting its serine phosphorylation[28]. This modification blocks the ability of IRS-1 to engage with PI3K, thereby disrupting the Akt signaling cascade, leading to decreased glucose uptake and the worsening of hyperglycemia. The failure of this critical signaling pathway is a major contributor to the development of metabolic complications associated with insulin resistance[29].

Chronic hyperinsulinemia, a direct consequence of insulin resistance, further exacerbates endothelial dysfunction, particularly within the lymphatic system. Lymphatic endothelial cells (LECs), which form the structural basis of lymphatic vessels, are highly sensitive to insulin signaling under physiological conditions[30]. Normally, insulin promotes lymphangiogenesis and supports the proliferation and migration of LECs through the PI3K/Akt and extracellular signal-regulated kinase (ERK) pathways[31]. However, in an insulin-resistant state, dysregulated insulin signaling impairs the normal function of these cells. As a result, there is a significant reduction in lymphangiogenesis, impaired lymphatic drainage, and an increased susceptibility to inflammation within lymphatic vessels. This is further compounded by the activation of protein kinase C (PKC) and the generation of reactive oxygen species (ROS), which contribute to endothelial damage. ROS, in turn, activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that plays a central role in orchestrating inflammatory responses. This inflammatory cascade not only exacerbates local endothelial dysfunction but also contributes to systemic inflammation, creating a feedback loop that accelerates the progression of insulin resistance[32].

The dysfunction of the lymphatic system in insulin resistance is further amplified by adipose tissue dysfunction, which is a

hallmark of obesity a major driver of insulin resistance. Adipose tissue, particularly in its hypertrophic state, becomes a source of pro-inflammatory mediators, including cytokines and free fatty acids (FFAs). These FFAs can directly impair lymphatic function by activating Toll-like receptors (TLRs), especially TLR4, on LECs. This activation promotes the production of inflammatory cytokines and chemokines, leading to lymphatic vessel leakage, fibrosis, and reduced fluid clearance. Moreover, the inflammatory environment induced by adipose tissue dysfunction contributes to the breakdown of the lymphatic barrier, further promoting tissue edema and metabolic dysregulation[33].

Recent evidence suggests that advanced glycation end products (AGEs), which accumulate in insulin-resistant states due to chronic hyperglycemia, further compromise lymphatic function. AGEs are proteins or lipids that become glycated after exposure to sugars, and they exert pathological effects by crosslinking with extracellular matrix components in vascular tissues, including the lymphatics[34]. These AGEs engage with the receptor for AGEs (RAGE), triggering a signaling cascade that involves NF-κB activation and the subsequent release of pro-inflammatory mediators[35]. The activation of the RAGE-NF-κB axis within lymphatic vessels perpetuates chronic inflammation, endothelial cell apoptosis, and fibrosis, all of which contribute to the progressive impairment of lymphatic function. This chronic inflammatory state not only leads to local lymphatic vessel dysfunction but also contributes to systemic insulin resistance, as the lymphatic system plays a crucial role in maintaining interstitial fluid balance and immune cell trafficking[36].

Thus, the interplay between insulin resistance and lymphatic dysfunction is multifactorial and involves a complex network of biochemical and cytobiological mechanisms. Pro-inflammatory cytokines, oxidative stress, adipose tissue dysfunction, and AGE accumulation all contribute to a cycle of worsening metabolic and vascular health. The disruption of insulin signaling pathways at the molecular level directly impairs lymphatic endothelial cell function, while chronic inflammation and oxidative stress further exacerbate lymphatic vessel damage. This intricate interplay underscores the need for therapeutic strategies targeting not only glucose metabolism but also the inflammatory and vascular complications associated with insulin resistance. By addressing these interconnected pathways, it may be possible to mitigate the broader systemic effects of insulin resistance and improve both metabolic and lymphatic health[37].

5. Exploring the Therapeutic Approach of Local GLP-1 Agonist Injections as a Promising Treatment for Lymphedema

The therapeutic potential of glucagon-like peptide-1 (GLP-1) receptor agonists has recently garnered attention in the treatment of metabolic and vascular dysfunctions, particularly in conditions associated with insulin resistance, such as lymphedema. GLP-1 receptors are widely expressed in multiple tissues, including pancreatic beta cells, the vascular endothelium, and lymphatic endothelial cells (LECs). The dual role of GLP-1 receptor activation in enhancing insulin sensitivity and exerting protective effects on the vasculature presents a promising avenue for treating lymphatic disorders[38].

At the molecular level, GLP-1 receptor agonists, such as semaglutide and liraglutide, exert their insulin-sensitizing effects by enhancing glucose-stimulated insulin secretion and promoting beta-cell survival via the activation of cyclic AMP

(cAMP)-dependent signaling pathways. This cascade leads to the phosphorylation of protein kinase A (PKA) and the subsequent activation of key transcription factors, such as cAMP response element-binding protein (CREB), which supports insulin production and prevents beta-cell apoptosis[39]. Additionally, GLP-1 enhances insulin sensitivity in peripheral tissues by improving glucose uptake through the PI3K/Akt pathway[40], thus ameliorating hyperglycemia and reducing compensatory hyperinsulinemia, a significant factor contributing to lymphatic endothelial dysfunction[41].

From a vascular perspective, GLP-1 receptor agonists have demonstrated vasoprotective properties that may mitigate lymphatic endothelial damage. Activation of the GLP-1 receptor on endothelial cells has been shown to stimulate nitric oxide (NO) production through endothelial nitric oxide synthase (eNOS), which promotes vasodilation and reduces oxidative stress[42]. This is particularly relevant in insulin-resistant states, where endothelial cells experience increased oxidative stress and inflammation. GLP-1 agonists counteract these effects by inhibiting the production of reactive oxygen species (ROS)[43] and reducing the activation of pro-inflammatory pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[44]. By attenuating inflammation and oxidative damage, GLP-1 agonists may preserve lymphatic vessel integrity and improve lymphangiogenesis, the formation of new lymphatic vessels, which is crucial for proper lymphatic drainage.

Clinical and preclinical studies have further highlighted the role of GLP-1 receptor agonists in reducing adipose tissue inflammation, a key contributor to lymphatic dysfunction. In obese and insulin-resistant individuals, adipose tissue releases pro-inflammatory cytokines and free fatty acids (FFAs) that impair lymphatic function[45]. GLP-1 agonists have been shown to suppress the release of these inflammatory mediators, thereby improving the structure and function of lymphatic vessels. Notably, GLP-1 receptor activation reduces the expression of Toll-like receptors (TLRs), particularly TLR4, on LECs, which are typically upregulated in response to excess FFAs[46]. This reduction in TLR4 signaling dampens the inflammatory response within the lymphatic system, thereby preventing lymphatic vessel leakage, fibrosis, and impaired fluid clearance[47].

Moreover, GLP-1 receptor agonists have been implicated in reducing the accumulation of advanced glycation end products (AGEs) within vascular tissues[48]. AGEs are known to disrupt endothelial cell function by crosslinking extracellular matrix proteins and activating the receptor for AGEs (RAGE), which perpetuates NF-κB signaling and chronic inflammation[49]. Additionally, GLP-1 agonists have been reported to decrease the expression of pro-fibrotic markers, such as transforming growth factor-beta (TGF-β)[50], which is often elevated in lymphatic dysfunction[51].

6. Promising Clinical Evidence

Recent clinical findings have provided encouraging insights into the potential therapeutic role of GLP-1 receptor agonists (GLP-1RAs) in the management of breast cancer-related lymphedema, as evidenced by a case report published in Frontiers in Oncology[52]. The case report detailed the significant resolution of lymphedema symptoms in a patient following the initiation of GLP-1RA therapy, originally prescribed for weight loss. This patient, who developed severe lymphedema after breast cancer surgery and adjuvant therapy, experienced substantial improvements in lymphatic

function, with a reduction in limb volume from 10.3% to 3.4% after 13 months of GLP-1RA treatment. This was accompanied by a 24% reduction in body weight, and a notable return of lymphatic pumping function, as confirmed by imaging. The patient's quality of life was also markedly improved, and she no longer required the use of compression garments.

These findings align with the hypothesis that GLP-1RAs may offer significant benefits in conditions where insulin resistance contributes to vascular and lymphatic dysfunction. As insulin resistance is known to impair lymphatic endothelial cell (LEC) function through mechanisms involving chronic inflammation, oxidative stress, and the disruption of insulin signaling pathways, the use of GLP-1RAs could address these pathological changes. The weight loss observed in the patient likely improved overall insulin sensitivity, reducing the chronic hyperinsulinemia that exacerbates lymphatic vessel dysfunction.

Mechanistically, GLP-1RAs could exert direct effects on the lymphatic system beyond their metabolic benefits. GLP-1 receptors are present on vascular endothelial cells, including LECs, and their activation may enhance lymphangiogenesis and lymphatic vessel repair. Through pathways involving nitric oxide (NO) production and the inhibition of reactive oxygen species (ROS), GLP-1RAs may restore normal endothelial function, promoting effective lymphatic drainage and reducing vessel inflammation. Additionally, by modulating the immune response, particularly the downregulation of pro-inflammatory cytokines and Toll-like receptor (TLR) signaling, GLP-1RAs may further protect lymphatic vessels from fibrosis and functional deterioration.

This case supports the notion that GLP-1RAs offer a promising therapeutic approach for managing lymphedema, particularly in patients with underlying metabolic disturbances like insulin resistance. It also opens up the possibility of a dual action of GLP-1RAs in improving both metabolic and lymphatic health, potentially reducing the need for more invasive interventions, such as lymphovenous bypass or vascularized lymph node transplantation, by restoring the function of the existing lymphatic network. Future studies are needed to explore the precise mechanisms by which GLP-1RAs influence lymphatic endothelial cells and to confirm their long-term efficacy in larger cohorts of patients with secondary lymphedema[52].

7. Localized Administration of GLP-1 Receptor Agonists: A Promising Therapeutic Strategy for Lymphedema

Recent advancements in the treatment of lymphedema, particularly secondary lymphedema following breast cancer surgery, have highlighted the potential of GLP-1 receptor agonists (GLP-1RAs) as a novel therapeutic intervention. Given their established metabolic benefits, localized injection of GLP-1RAs into affected lymphatic tissues presents a promising approach to not only improve metabolic disturbances but also directly target lymphatic dysfunction. This strategy capitalizes on the ability of GLP-1RAs to restore insulin signaling, reduce inflammation, and promote lymphangiogenesis the formation and repair of lymphatic vessels. By inhibiting the production of reactive oxygen species (ROS) and modulating nitric oxide (NO) pathways[53], GLP-1RAs enhance endothelial cell function and reduce vascular permeability,

thereby improving lymphatic drainage[54]. Based on current pharmacokinetic data, we propose a localized administration protocol where an initial dose of 0.6 mg of liraglutide or 0.25 mg of semaglutide is administered once weekly via subcutaneous injection directly into the affected lymphatic region. This targeted approach ensures higher drug concentrations in the affected area while minimizing systemic exposure, thereby reducing the risk of side effects. Over the course of 12 weeks, the dosage can be titrated up to 1.8 mg of liraglutide or 1 mg of semaglutide, depending on patient response and clinical improvements such as a reduction in limb volume. This localized administration could enhance lymphatic vessel repair and stimulate lymphatic pumping by directly activating the GLP-1 receptors expressed on lymphatic endothelial cells (LECs), effectively addressing the core dysfunction in lymphedema[55]. The proposed treatment should be combined with conventional lymphedema care, such as compression therapy and physical exercise, to maximize therapeutic outcomes. Monitoring through imaging studies like lymphoscintigraphy or MRI can be employed to track the progression of lymphatic repair and drainage function, offering valuable insights into treatment efficacy[56].

8. Discussion

The emerging hypothesis that chronic hyperinsulinemia, secondary to insulin resistance, plays a pivotal role in the pathogenesis of lymphedema offers a transformative perspective on this traditionally mechanical disorder. Historically, lymphedema has been primarily attributed to physical lymphatic damage or obstruction, commonly following cancer-related surgeries or radiotherapy. However, positioning lymphedema as a vascular complication of metabolic dysfunction, particularly insulin resistance, sheds light on the broader impact of systemic metabolic disturbances on the lymphatic system. This redefinition aligns with evidence that insulin resistance significantly impairs lymphatic endothelial cell (LEC) function, promoting vessel inflammation, structural damage, and impaired lymphatic drainage.

At the molecular level, insulin resistance disrupts the PI3K/Akt signaling pathway, which is critical for maintaining endothelial function, glucose uptake, and promoting lymphangiogenesis. Normally, this pathway supports the repair and growth of lymphatic vessels, ensuring fluid homeostasis. However, in the insulin-resistant state, pro-inflammatory mediators such as TNF-α and IL-6 inhibit these signaling mechanisms, leading to oxidative stress, endothelial dysfunction, and exacerbation of hyperglycemia. These cytokines promote the activation of protein kinase C (PKC) and the generation of reactive oxygen species (ROS), which collectively compromise LEC integrity. This dysfunction not only impairs the ability of lymphatic vessels to regulate fluid balance but also exacerbates lymphatic vessel permeability and inflammation, hallmark features of lymphedema.

Further compounding the issue, insulin resistance accelerates the formation of advanced glycation end products (AGEs), which crosslink extracellular matrix proteins and activate receptors for AGEs (RAGE). This pathway triggers chronic inflammatory responses via NF-κB signaling, leading to endothelial cell apoptosis and fibrosis. Such endothelial degradation perpetuates a cycle of inflammation and damage, impairing the lymphatic system's capacity to clear excess interstitial fluid, thus manifesting as clinical lymphedema.

The therapeutic potential of GLP-1 receptor agonists (GLP-1RAs) in targeting this metabolic-driven pathophysiology is

particularly promising. Beyond their established role in managing type 2 diabetes, GLP-1RAs demonstrate the ability to restore insulin sensitivity by enhancing PI3K/Akt signaling and reducing pro-inflammatory cytokine activity. This restoration is vital for promoting lymphangiogenesis and preserving LEC functionality, which are both compromised in insulin-resistant states. Additionally, GLP-1RAs exert antioxidative effects, reducing ROS production and oxidative stress, which further protects the endothelial lining of lymphatic vessels from ongoing damage.

Clinical evidence, including case reports, supports the potential dual benefit of GLP-1RAs in lymphedema management improving metabolic health and exerting direct lymphatic repair mechanisms. Notably, GLP-1RAs can mitigate the chronic hyperinsulinemia that drives lymphatic vessel dysfunction, while simultaneously promoting endothelial repair through pathways involving nitric oxide (NO) and the suppression of ROS. Case studies have shown significant clinical improvements in lymphedema, such as reductions in limb volume and enhanced lymphatic function following GLP-1RA therapy, particularly in patients with metabolic disorders contributing to lymphatic dysfunction. This underscores the potential of GLP-1RAs to revolutionize lymphedema management by addressing both the underlying metabolic disorder and its vascular manifestations.

The introduction of GLP-1RAs as a targeted therapeutic option for lymphedema, particularly through localized administration, presents a compelling clinical strategy. By directly delivering these agents to affected lymphatic regions, clinicians can enhance drug concentration in the target tissue, optimize lymphatic vessel repair, and reduce systemic side effects.

9. Conclusion

The hypothesis that lymphedema may arise from metabolic dysfunction, particularly insulin resistance and hyperinsulinemia, offers a fresh perspective on the disease's etiology. By linking vascular endothelial damage with chronic metabolic stress, this model underscores the importance of addressing underlying insulin resistance to improve lymphatic health. The therapeutic potential of GLP-1 receptor agonists in treating this form of lymphedema is compelling, given their role in enhancing insulin sensitivity, reducing inflammation, and promoting vascular integrity. Future research should focus on validating these findings through clinical trials, as this could revolutionize the management of lymphedema by targeting its metabolic roots.

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