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The Impact of GLP-1 Receptor Agonists on Body Composition and Musculoskeletal Integrity: A Review of Mechanisms, Protective Strategies, and Clinical Perspectives

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ABSTRACT

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 agonists has revolutionized obesity pharmacotherapy, enabling weight loss magnitudes of 15–20%, previously attainable primarily through bariatric surgery. A significant clinical challenge, however, is the "muscle gap"—the substantial loss of lean body mass (LBM) observed in pivotal trials. This review provides a critical analysis of the impact of incretin-based therapies on tissue composition, skeletal muscle quality, and functional performance.

Drawing on the latest clinical and molecular evidence, we demonstrate that the influence of GLP-1 RAs on skeletal muscle is multidimensional. While absolute muscle mass typically

decreases, advanced imaging data suggest an improvement in metabolic muscle "quality" through the reduction of intramuscular fat infiltration and enhanced capillary perfusion.
This paper emphasizes that structured exercise - particularly resistance training - and nutritional optimization are not merely supportive measures but essential foundations of therapy required to maintain functional strength and prevent iatrogenic sarcopenia.
The review further explores the unique osteoprotective effects of GLP-1 RAs, which safeguard bone mineral density during rapid weight loss, and discusses emerging pharmacological frontiers, including co-pharmacotherapy with myostatin inhibitors and triple agonists like retatrutide. Longitudinal insights from the S-LiTE trial indicate that the sustainability of metabolic benefits post-treatment is heavily dependent on exercise-induced adaptations. We conclude that optimal obesity management requires a multidisciplinary approach where pharmacotherapy serves as an adjunct to structured lifestyle changes, prioritizing functional fitness and long-term musculoskeletal health.
Keywords: GLP-1 receptor agonists, body composition, muscle mass, resistance training, sarcopenia, myosteatosis, obesity, bone mineral density, metabolic syndrome

1. Introduction

Obesity management and metabolic medicine have entered a transformative era with the introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and novel multi-receptor agonists, such as tirzepatide and retatrutide. These pharmacological agents have demonstrated an unprecedented capacity for weight reduction, achieving results that were previously attainable only through bariatric surgery. However, the rapid and significant loss of total body mass has brought a critical clinical challenge to the forefront: the "muscle gap," characterized by a disproportionate loss of lean body mass (LBM) alongside adipose tissue.

For much of the past decade, the success of weight loss interventions was measured primarily by the decrease in absolute body weight. However, modern technological advancements in body composition analysis, including dual-energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI), have led to a revision of this view, revealing that the "quality" of weight loss is as significant as the quantity. Understanding the impact of these medications on

the musculoskeletal system is becoming crucial in the face of increasing concerns regarding iatrogenic sarcopenia, particularly in geriatric and athletic populations. Recent literature highlights that while GLP-1 RAs induce weight loss, they also influence muscle quality by reducing myosteatosis and potentially altering mitochondrial function.

Furthermore, the sustainability of metabolic health following pharmacological intervention remains a subject of intense investigation. Seminal research, such as the S-LiTE trial, has underscored the necessity of a synergistic approach, proving that pharmacotherapy must be anchored by structured exercise to prevent weight regain and maintain musculoskeletal integrity. In the era of increasing clinical utilization of these "miracle drugs," a precise understanding of how to optimize the bone-muscle unit while utilizing potent incretin therapies is essential.

This paper aims to review current literature regarding the role of GLP-1 and multi-receptor agonists in the pathophysiology of body composition changes. It considers the specificity of muscle quality, functional performance, and bone mineral density, while evaluating the utility of integrated therapeutic strategies involving nutritional optimization and resistance training. By synthesizing evidence from molecular mechanisms to long-term clinical outcomes, this review seeks to redefine the diagnostic and therapeutic approach to musculoskeletal health in the age of incretin-based weight management.

2. Methods

Search strategy: A comprehensive literature review was conducted in PubMed, Scopus, and Google Scholar databases, covering publications released from 2015 to early 2026. The search focused on identifying key reports regarding the interaction between GLP-1 receptor agonists and body composition, utilizing the keywords: "GLP-1 receptor agonists", "body composition", "skeletal muscle mass", "sarcopenia", and "resistance training". This strategy aimed to locate studies that redefine the management of lean mass during pharmacological weight loss.

Eligibility criteria: Peer-reviewed articles (original research, systematic reviews, meta-analyses) published in English were included in the analysis, with particular emphasis on high-impact trials from 2015–2025. Priority was given to studies utilizing modern measurement techniques (DXA, MRI, CT) and those describing the synergy between pharmacotherapy and lifestyle interventions. Studies of low clinical relevance or animal model studies without direct translation to human clinical practice were excluded from the analysis.

Data Synthesis: Ultimately, 22 bibliographic items were selected and synthesized, deemed most representative of the discussed issues. This collection served to develop the characteristics of musculoskeletal integrity during therapy, evaluate the effectiveness of exercise-based protection, and describe emerging pharmacological frontiers.

3.1 Skeletal Muscle Integrity and Body Composition Shifts under GLP-1 Receptor Agonism: Mechanistic and Clinical Perspectives

The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and multi-receptor agonists, such as tirzepatide, has fundamentally redefined the therapeutic ceiling for non-surgical obesity management [1, 2]. In the landmark STEP 1 clinical trial, semaglutide 2.4 mg demonstrated a mean weight reduction of 14.9% [3], while the SURMOUNT-1 study involving the dual GIP/GLP-1 agonist tirzepatide reported even more profound results, with weight loss exceeding 20% at higher dose tiers [4]. Despite these unprecedented outcomes, the field of sports medicine has raised critical concerns regarding the "muscle gap"—the proportion of weight loss derived from lean body mass (LBM) versus adipose tissue [1]. While traditional caloric restriction typically results in a lean mass loss of approximately 25% of total weight reduction , early dual-energy X-ray absorptiometry (DXA) substudies in semaglutide cohorts suggested that LBM could account for a larger fraction, occasionally approaching 40% [1, 2, 3]. However, a nuanced interpretation of more recent data from dual-agonist therapies indicates that while absolute lean mass decreases, the magnitude of fat mass reduction is significantly greater, thereby resulting in an overall improvement in the fat-to-lean mass ratio and metabolic health profile [4, 2].

The physiological impact of GLP-1 RAs on the musculoskeletal system extends beyond simple caloric deficit-driven attrition. Evidence from prospective case series suggests that even low-dose incretin therapy, such as liraglutide at 0.9 mg, can effectively reduce visceral and intrahepatic fat without significant concomitant loss of skeletal muscle mass [5]. This preservation of muscle integrity may be attributed to the pleiotropic effects of GLP-1 RAs on muscle quality and metabolic function [2]. Specifically, these agents have been shown to enhance insulin sensitivity and microvascular perfusion within skeletal muscle, facilitating more efficient glucose uptake and nutrient delivery [2]. Furthermore, advanced imaging substudies indicate that GLP-1 RAs may selectively target myosteatosis, reducing intramuscular fat infiltration which is a known driver of muscle dysfunction [2, 5]. On a molecular level, the activation of GLP-1 receptors may modulate key signaling pathways,

including the Akt/mTOR axis, while simultaneously suppressing pro-inflammatory cytokines like TNF-α and IL-6 and inhibiting atrophy-related factors such as myostatin [2]. Such mechanisms suggest that GLP-1 RAs might actively protect the "metabolic quality" of the muscle even as its absolute volume adjusts to a lower total body weight [2].

From a clinical and athletic performance standpoint, the debate persists as to whether the observed reduction in LBM represents a pathological state of sarcopenia or a physiological adaptation to reduced mechanical loading [1]. It has been argued that individuals with obesity carry a surplus of muscle mass required to support an enlarged body frame; consequently, a decrease in absolute muscle mass following significant weight loss may not necessarily translate to impaired physical function [1]. In fact, relative strength—often the more critical metric in sports medicine—frequently improves as the burden of excess adipose tissue is removed [1, 2]. Current expert consensus emphasizes that the potential risks of muscle loss during pharmacological therapy can be largely mitigated through targeted lifestyle interventions [2]. Structured resistance training and optimized protein intake have been shown to preserve a substantial portion of lean tissue during active weight loss, potentially offsetting 50% to 95% of expected LBM reduction [2, 3]. By integrating pharmacological therapy with rigorous exercise science, clinicians can shift the paradigm from mere weight loss to a comprehensive optimization of body composition, ensuring that the benefits of adiposity reduction are not undermined by a loss of functional strength or metabolic rate [1, 2].

3.2 Synergistic Effects of GLP-1 Receptor Agonists and Physical Exercise on Lean Mass Preservation and Metabolic Health

The integration of physical exercise into pharmacological weight loss protocols is increasingly recognized not merely as a supportive measure, but as a fundamental requirement for optimizing clinical outcomes and maintaining musculoskeletal integrity. Evidence from the S-LiTE randomized controlled trial underscores that while liraglutide therapy effectively induces weight loss, its combination with moderate-to-vigorous intensity exercise yields superior results in terms of both weight loss maintenance and the preservation of lean body mass compared to pharmacological intervention alone [6]. This synergistic effect is critical, as exercise-induced metabolic adaptations appear to counteract the potential loss of functional tissue that often accompanies rapid weight reduction. Furthermore, the prioritization of lifestyle interventions alongside GLP-1 receptor agonist (GLP-1 RA) therapy is essential for long-term weight stability, as exercise contributes to improved cardiorespiratory fitness and metabolic flexibility,

which are vital markers of cardiovascular health [7]. The mechanism of action for semaglutide, characterized by a significant reduction in energy intake and a shift in food preferences away from high-fat options, creates a metabolic environment that, when paired with structured physical activity, facilitates a more favorable shift in body composition [8].

Real-world clinical data and case series further validate the efficacy of specific lifestyle strategies, such as resistance training and high-protein intake, in mitigating the "muscle gap" associated with incretin therapies. Case reports of patients utilizing semaglutide or tirzepatide demonstrate that lean soft tissue can be remarkably preserved, or even increased, when pharmacological treatment is combined with resistance exercise performed three to five days per week and protein consumption ranging from 1.2 to 1.7 g/kg of body mass [9]. These findings challenge the assumption that significant lean mass loss is an inevitable consequence of GLP-1 RA therapy, suggesting instead that the catabolic effects of a caloric deficit can be neutralized by adequate anabolic stimuli [9,6]. Beyond mere mass preservation, the interaction between exercise and GLP-1 RAs may enhance glucose disposal and insulin sensitivity through non-overlapping pathways, providing a comprehensive approach to metabolic rehabilitation [7]. Consequently, for the sports medicine practitioner, the focus must shift toward "lifestyle prioritization," where pharmacotherapy serves as an adjunct to a primary foundation of structured exercise and nutritional optimization, thereby ensuring that weight loss translates into a genuine improvement in physical performance and functional longevity [7, 9].

3.3 Muscle Quality and Functional Performance Under GLP-1 Receptor Agonism: Morphological and Biomechanical Insights

Advanced imaging modalities and recent meta-analytic data have significantly refined the scientific understanding of the morphological and functional adaptations occurring within the musculoskeletal system during incretin-based therapy. A critical post-hoc analysis of the SURPASS-3 MRI trial revealed that tirzepatide treatment not only induces substantial weight loss but, more importantly, promotes favorable changes in muscle composition by significantly reducing intramuscular fat infiltration [10]. This mitigation of myosteatosis suggests an improvement in the metabolic and functional integrity of the muscle tissue; despite a reduction in absolute volume, the remaining fibers may be characterized by higher metabolic efficiency and enhanced insulin sensitivity [10].

These findings are corroborated by clinical data from the SEMALEAN study, which assessed the impact of semaglutide on muscle mass and function in patients with obesity. It was observed that despite the anticipated decrease in lean body mass (LBM), parameters of physical performance and motor function remained stable, and in several instances showed relative improvement due to the reduced mechanical load on the musculoskeletal system [11]. Concurrently, systematic reviews confirm that while muscle mass loss is a common sequester of GLP-1 RA use, the magnitude of this effect is strictly dependent on the patient's baseline metabolic profile and the severity of their initial adiposity [12].

For the sports medicine practitioner, it is imperative to distinguish this pharmacologically-induced reduction from pathological states such as cachexia or age-related sarcopenia. While those conditions are driven by chronic systemic inflammation and oxidative stress, the mass loss associated with GLP-1 agonists is primarily a byproduct of a deep negative energy balance rather than a primary myopathic process [13]. Therefore, the priority in athletic care remains the stimulation of muscle biogenesis and mitochondrial function through appropriate mechanical loading and nutritional support, ensuring that the therapeutic potential of these medications is leveraged without compromising the structural or functional integrity of the organism [11, 12, 13].

3.4 Emerging Pharmacological Frontiers and Long-term Musculoskeletal Challenges

The landscape of pharmacological obesity management is rapidly evolving toward the use of multi-receptor agonists and innovative combination therapies aimed at maximizing adiposity reduction while proactively safeguarding skeletal muscle integrity. Retatrutide, a novel triple agonist targeting the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors, represents a significant leap in therapeutic potency. Phase 2 substudy data indicate that retatrutide induces a profound, dose-dependent reduction in total body fat mass that significantly exceeds the outcomes observed with dulaglutide or placebo by week 36 [14]. However, the unprecedented magnitude and velocity of this weight loss intensify the clinical requirement for rigorous monitoring of lean body mass (LBM). From a sports medicine perspective, the inclusion of glucagon agonism—which increases energy expenditure—raises critical questions regarding the rate of muscle protein breakdown and the body's ability to maintain functional strength under such an aggressive energy deficit.

To address the persistent "muscle gap" associated with potent incretin therapies, contemporary research is exploring co-pharmacological strategies that combine GLP-1 receptor agonists (GLP-1 RAs) with antibodies targeting myogenic pathways. Pivotal evidence from the interim analysis of the Phase 2 COURAGE trial has demonstrated that the combination of semaglutide with trevogrumab—an anti-myostatin (GDF8) antibody—successfully protected between 50% and 80% of the lean mass that would typically be lost under semaglutide monotherapy [15]. The trial revealed that in the semaglutide-only cohort, approximately 35% of the total weight loss was derived from lean mass, a figure that could lead to significant performance decrements in athletic populations. Conversely, the myostatin-inhibiting intervention not only spared muscle tissue but also appeared to accelerate the loss of fat mass, suggesting that preserving metabolically active lean tissue supports the weight loss process by maintaining a higher resting metabolic rate [15].

Beyond macroscopic shifts in body composition, the subcellular quality of muscle tissue, specifically mitochondrial health, has become a primary area of investigation. Systematic reviews indicate that a loss of muscle mass reaching up to 40% during potent GLP-1 RA therapy necessitates a deep understanding of how these agents influence mitochondrial biogenesis and cellular bioenergetics within skeletal muscle [16]. Maintaining mitochondrial efficiency is a prerequisite for preserving oxidative capacity and preventing the functional decline that often accompanies rapid weight reduction. This issue is particularly salient for older populations, where the risk of iatrogenic sarcopenia is highest. A 24-month retrospective cohort study of older adults with type 2 diabetes found that semaglutide therapy may be associated with accelerated sarcopenia, characterized by significant declines in the appendicular skeletal muscle mass index (ASMI), grip strength, and gait speed compared to controls [17]. These findings suggest that specific clinical predictors can identify patients at higher risk for accelerated muscle loss, mandating personalized dosing and the implementation of aggressive resistance training protocols.

While GLP-1 RAs have undoubtedly achieved "miracle drug" status, their widespread adoption must be balanced against a critical analysis of costs, potential side effects, and the risk of exacerbating public health inequalities [18]. There is a growing concern that an over-reliance on pharmacological interventions may undermine primary lifestyle prevention efforts and lead to dangerous trends, such as the unsupervised "microdosing" of black-market compounds [4.5]. For the sports medicine practitioner, it is imperative that these medications are viewed not as substitutes for, but as adjuncts to, structured exercise and nutritional optimization. Only through

such an integrated approach can the metabolic benefits of the new incretin era be fully realized while protecting the foundation of health: a functional and resilient musculoskeletal system [17, 18].

3.5 Longitudinal Sustainability, Inflammatory Modulation, and Osteoprotective Mechanisms in Long-term Therapy

The longitudinal efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and their impact on musculoskeletal health extends beyond the initial weight loss phase to encompass the sustainability of metabolic improvements and the protection of systemic tissues. Findings from the one-year post-treatment analysis of the S-LiTE trial underscore that the maintenance of weight loss and optimized body composition following the termination of pharmacological therapy is heavily contingent upon the integration of structured exercise during the active treatment phase. Specifically, individuals who combined liraglutide therapy with a supervised exercise program sustained significantly greater weight loss and a healthier tissue composition one year after the cessation of active treatment compared to those who relied solely on pharmacotherapy, who experienced rapid weight regain toward baseline levels [19]. This suggests that exercise-induced metabolic adaptations serve as a critical physiological buffer, mitigating the rebound effect and enhancing the durability of weight management once medication is withdrawn [19].

Complementing these longitudinal findings, the synergistic interaction between physical activity and GLP-1 RAs profoundly impacts systemic inflammation and the severity of metabolic syndrome. Data from the Sandsdal et al. (2023) study demonstrate that combined therapy leads to a more robust reduction in abdominal obesity and inflammatory markers, such as C-reactive protein (CRP), than either intervention alone [20]. This reduction in metabolic syndrome severity is clinically significant, as it effectively lowers the long-term risk of developing type 2 diabetes and cardiovascular disease in individuals living with obesity [20]. On a cellular level, these systemic benefits are supported by improved mitochondrial function and the mitigation of oxidative stress, which are essential for maintaining the metabolic resilience of skeletal muscle tissue under the physiological stress of a prolonged energy deficit [21].

Furthermore, a comprehensive musculoskeletal model must incorporate the skeletal system, which often faces increased vulnerability during rapid weight reduction. Clinical evidence

indicates that GLP-1 RAs possess unique osteoprotective properties that counteract the typical decline in bone mineral density (BMD) associated with significant weight loss. In weight-reduced women, liraglutide treatment has been shown not only to prevent the expected loss of BMD but also to actively stimulate bone formation, as evidenced by significant increases in the bone formation marker P1NP [22]. This mechanism ensures the preservation of skeletal integrity alongside adiposity reduction, which, when coupled with muscle-sparing strategies, creates optimal conditions for maintaining long-term functional autonomy and musculoskeletal health [21, 22]. Understanding these molecular and biomechanical interconnections allows for a therapeutic model where pharmacotherapy acts as a catalyst for lifestyle-based foundations, ensuring a resilient and healthy musculoskeletal system in the longitudinal perspective [19, 20, 22].

4. Discussion

The clinical evidence gathered from the landmark STEP, SURMOUNT, and S-LiTE trials underscores that the era of GLP-1 receptor agonists (GLP-1 RAs) and multi-receptor agonists has established a transformative ceiling for weight reduction, yet it simultaneously presents complex challenges for musculoskeletal health [3, 4, 6]. A primary concern remains the "muscle gap," characterized by the observation that 25% to 40% of total weight loss is often derived from lean body mass (LBM) [1, 2, 12]. However, emerging insights from the SEMALEAN and SURPASS-3 MRI studies suggest that absolute muscle loss must be interpreted alongside changes in muscle quality. The significant reduction in myosteatosis, or intramuscular fat infiltration, suggests that the metabolic and functional integrity of the remaining tissue may actually be enhanced, leading to improvements in relative strength and insulin sensitivity even in the presence of reduced muscle volume [10, 11, 16]. This shift from quantity to quality is supported by findings that physical performance indices, such as gait speed and motor stability, often remain resilient as the mechanical burden of excess adiposity is removed [1, 11].

The sustainability of these metabolic improvements hinges almost entirely on the synergy between pharmacotherapy and structured lifestyle interventions. Longitudinal data from the S-LiTE trial provide a definitive argument that exercise is not merely a supportive measure but a requirement; individuals who combined GLP-1 therapy with supervised activity maintained their weight loss and body composition far more effectively one year after treatment cessation than those who relied on medication alone [6, 19]. Furthermore, aggressive nutritional strategies, including protein intake levels of 1.2–1.7 g/kg and structured resistance training, have been

shown to effectively neutralize the catabolic pressures of a severe energy deficit [9, 15]. An additional layer of musculoskeletal protection is offered by the unique osteoprotective properties of GLP-1 RAs, which appear to safeguard bone mineral density and stimulate bone formation markers, a benefit not typically observed with conventional calorie-restricted diets [22]. Despite these benefits, clinical vigilance is required in the geriatric population, where semaglutide has been associated with accelerated sarcopenic trends, necessitating rigorous monitoring of functional metrics such as the appendicular skeletal muscle mass index (ASMI) [17]. Looking forward, the next phase of obesity management will likely involve co-pharmacological strategies, such as combining incretins with myostatin inhibitors, which interim results from the COURAGE trial suggest could preserve up to 80% of lean mass while selectively accelerating the depletion of adipose tissue [14, 15, 18].

5. Conclusions

The advent of potent GLP-1 and GIP/GLP-1 receptor agonists has revolutionized obesity treatment, but their successful implementation in clinical and athletic settings requires a steadfast commitment to lean mass preservation. While these agents induce unprecedented weight loss, the potential for iatrogenic sarcopenia mandates a paradigm shift where the success of therapy is measured by body composition optimization rather than total weight reduction alone. The observed improvements in muscle quality through the reduction of myosteatosis and the preservation of bone mineral density suggest that these pharmacological tools can be leveraged safely, provided they are anchored by a multidisciplinary foundation of high-protein nutrition and structured resistance exercise. It is now clear that physical activity is a critical determinant of the long-term durability of metabolic outcomes and the prevention of weight regain following the withdrawal of medication. As the field moves toward triple-agonist therapies and targeted myogenic interventions, the priority must remain the maintenance of a functional, resilient musculoskeletal system. By integrating pharmacological potency with rigorous exercise science and personalized monitoring, clinicians can ensure that the reduction of adiposity translates into genuine metabolic rehabilitation and the sustained physical autonomy of the patient.

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Author's contribution:

Conceptualization, S.D., Z.W. and A.W.; methodology, K.B., M.J. and M.O.; software, P.T. and P.G.; validation, J.F., W.K. and S.D.; formal analysis, Z.W., A.W. and K.B.; investigation, S.D., Z.W., A.W., K.B., M.J., M.O., P.T., P.G., J.F. and W.K.; resources, M.J. and M.O.; data curation, P.T., P.G. and J.F.; writing - original draft preparation, W.K., S.D. and Z.W.; writing - review and editing, S.D., Z.W., A.W., K.B., M.J., M.O., P.T., P.G., J.F. and W.K.; visualization, A.W. and K.B.; supervision, M.J. and M.O.; project administration, P.T. and P.G.; funding acquisition, Not applicable.

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