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EFFECTS OF SEMAGLUTIDE AND TIRZEPATIDE ON SKELETAL MUSCLE MASS AND SARCOPENIA RISK IN ADULTS WITH OBESITY OR OVERWEIGHT: A NARRATIVE REVIEW

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ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) and dual GLP-1/GIP agonists are highly effective therapies for obesity management. However, associated reductions in lean body mass have raised concerns regarding sarcopenia risk. This review evaluated whether these changes translate into clinically relevant sarcopenia or sarcopenic obesity.
Methods: A narrative review of the PubMed, Cochrane Library and Google Scholar databases was conducted up to May 2026, to evaluate GLP-1 receptor agonist effects on muscle mass, body composition, and sarcopenia-related outcomes.
Results: GLP-1 RAs produced substantial weight loss, with lean mass accounting for approximately 20–33% of total weight reduction, a proportion comparable to that reported with lifestyle and surgical interventions. Most studies reported preserved or improved muscle function despite reductions in lean mass. MRI studies demonstrated reduced intramuscular fat with only modest decreases in muscle volume. However, one retrospective study in older adults with type 2 diabetes reported concurrent declines in muscle mass and function, suggesting increased vulnerability in high-risk populations.
Conclusions: Current evidence does not support a uniformly increased risk of sarcopenia or sarcopenic obesity during GLP-1 RA therapy. Lean mass loss appears largely proportional to overall weight reduction and is generally not accompanied by clinically meaningful declines in muscle function. Older adults and individuals with low baseline muscle reserve may require closer monitoring.

KEYWORDS
GLP-1 Receptor Agonists, GLP-1/GIP Receptor Agonists, Sarcopenic Obesity, Lean Body Mass

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Introduction

Obesity is a major global health challenge associated with increased morbidity and mortality. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as highly effective pharmacological therapies for obesity management. In the STEP-1 trial, treatment with semaglutide 2.4 mg once weekly resulted in a mean body weight reduction of 14.9% after 68 weeks, compared with 2.4% in the placebo group. Moreover, approximately one-third of participants achieved a weight loss of at least 20%, approaching the magnitude of weight reduction reported after bariatric procedures such as sleeve gastrectomy [1]. More recently, tirzepatide has demonstrated even greater efficacy for obesity treatment. In the SURMOUNT-1 trial, participants receiving tirzepatide achieved mean weight reduction ranging from 15.0% to 20.9% after 72 weeks of treatment, compared with 3.1% in the placebo group, with more than half of participants receiving the 15-mg dose achieving at least 20% weight loss [2]. DXA analyses suggest that most weight loss induced by tirzepatide is attributable to reductions in fat mass, although some loss of lean mass also occurs [3]. Beyond weight reduction, GLP-1 receptor agonists have demonstrated clinically significant cardiovascular benefits. In the SELECT trial involving 17,604 adults with overweight or obesity and established cardiovascular disease but without diabetes, semaglutide reduced the risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20% compared with placebo [4]. Despite these benefits, attention has shifted to the composition of weight loss induced by GLP-1 receptor agonists. Although a reduction in adipose tissue accounts for the majority of weight loss, a proportion of the lost weight may also originate from lean body mass, including skeletal muscle tissue. As a result, concerns have emerged regarding the potential development of sarcopenia [5], particularly among individuals already at increased risk of muscle loss. Sarcopenia was historically described as an age-related loss of skeletal muscle mass and considered a geriatric syndrome [6]. However, contemporary definitions have evolved substantially. Current diagnostic criteria differ between consensus groups. For example, the European Working Group on Sarcopenia in Older People (EWGSOP2) considers low muscle strength the primary characteristic of sarcopenia, while also incorporating low muscle quantity or quality and physical performance into its diagnostic framework. Similarly, the Asian Working Group for Sarcopenia (AWGS2) includes assessments of

muscle strength, physical performance, and low muscle mass in the diagnosis of sarcopenia. In contrast, the Sarcopenia Definition and Outcomes Consortium (SDOC) defines sarcopenia primarily on the basis of low muscle strength and impaired physical performance, without requiring low muscle mass as a diagnostic criterion [6]. This evolution reflects a broader shift in the understanding of sarcopenia. While early definitions focused predominantly on the loss of skeletal muscle mass, growing evidence has shown that muscle mass alone is a relatively poor indicator of clinically relevant outcomes. In contrast, measures of muscle function, particularly muscle strength and physical performance, consistently demonstrate stronger associations with disability, falls, frailty, hospitalization, and mortality. Consequently, contemporary diagnostic frameworks increasingly prioritize functional measures over isolated assessments of muscle quantity [7]. This distinction is particularly relevant in the context of obesity treatment and weight-loss interventions, where reductions in body weight and lean mass do not necessarily translate into impaired muscle function or adverse clinical outcomes**.** Building upon the definition of sarcopenia, sarcopenic obesity refers to the coexistence of reduced muscle mass and function with excess adiposity [8]. The clinical relevance of sarcopenic obesity extends beyond alterations in body composition, as the condition has been associated with frailty, functional decline, increased morbidity, and higher mortality rates [8]. Given the clinical consequences of sarcopenia and sarcopenic obesity, understanding the effects of GLP-1 receptor agonists on skeletal muscle has become increasingly important. Although semaglutide and tirzepatide have demonstrated remarkable efficacy in obesity treatment, their precise impact on muscle tissue remains incompletely understood. Furthermore, the effects of GLP-1 receptor agonists on muscle metabolism are currently debated, as experimental studies have suggested both potentially beneficial and potentially detrimental effects on skeletal muscle health [8]. Despite growing interest in the effects of GLP-1 receptor agonists on body composition, important uncertainties remain. Although reductions in lean body mass during treatment have been consistently reported, it is unclear whether these changes translate into clinically meaningful sarcopenia, impaired muscle function, or an increased risk of sarcopenic obesity. Furthermore, available studies vary considerably in their assessment methods, populations, and outcome measures, making it difficult to determine the true impact of GLP-1 receptor agonists on skeletal muscle health. Therefore, the aim of this narrative review is to summarize and critically evaluate the current evidence regarding the effects of semaglutide and tirzepatide on skeletal muscle mass, muscle function, and the risk of sarcopenia and sarcopenic obesity in individuals undergoing pharmacological treatment with GLP-1 receptor agonists for obesity.

Methodology

A narrative review of the PubMed, Google Scholar and Cochrane Library databases was conducted up to May 2026. Studies published before 2020 were excluded to ensure the review reflects the most current evidence, however selected seminal papers published prior to 2020 were additionally included where necessary to provide foundational definitions and diagnostic criteria, such as consensus statements on sarcopenia. Studies were included if they evaluated the effects of GLP-1 RA on skeletal muscle mass, lean body mass, sarcopenia-related outcomes in adults with overweight or obesity (BMI $\geq$25 kg/m^2), were published in English and reported quantitative data on body composition outcomes. Studies involving participants under 18 years of age, conference abstracts, editorials, and duplicate publications were excluded. As the included human clinical trials did not assess molecular signalling pathways directly, preclinical (animal and in vitro) studies were additionally considered in Section ‘Mechanisms of GLP-1 RA and GLP-1/GIP Action on Skeletal Muscle’ to provide mechanistic context, while the assessment of clinical efficacy and body composition outcomes was restricted to the inclusion criteria outlined above. The selected studies were analyzed qualitatively, with particular emphasis on changes in body composition, lean body mass, skeletal muscle mass, and the potential risk of sarcopenia associated with GLP-1 receptor agonist therapy. Clinical practice guidelines and advisory statements on nutritional and exercise management during GLP-1 RA therapy were additionally considered in the section on strategies to mitigate muscle loss, to provide practice-relevant context beyond the primary inclusion criteria.

Results

Characteristics of included studies

The literature consisted of randomized controlled trials, observational studies, systematic reviews, meta-analyses, and narrative reviews evaluating the effects of semaglutide and tirzepatide in adults with obesity or overweight. Body composition outcomes were assessed using dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectrical impedance analysis (BIA).

Effects of GLP-1 Receptor Agonists on Body Weight and Body Composition

Across the included studies, treatment with GLP-1 receptor agonists consistently produced substantial reductions in total body weight, accompanied by favorable changes in body composition. Weight loss was predominantly driven by reductions in fat mass, although concurrent decreases in lean body mass were observed across all agents. Interpretation of body composition changes during GLP-1 receptor agonist therapy remains challenging due to methodological differences between studies. Most weight-loss trials do not directly assess skeletal muscle mass, but instead report changes in lean body mass, commonly measured using dual-energy X-ray absorptiometry (DXA). Importantly, lean body mass represents a broader compartment that includes not only skeletal muscle, but also organs, bone, body fluids, and water contained within adipose tissue. Therefore, reductions in lean body mass should not automatically be interpreted as equivalent to skeletal muscle loss. Regarding overall weight reduction, the STEP-1 trial demonstrated that semaglutide 2.4 mg once weekly produced a mean body weight reduction of 14.9% after 68 weeks, compared with 2.4% in the placebo group; 32.0% of participants achieved a weight loss of at least 20% of baseline body weight [1]. Greater reductions were observed with tirzepatide in the SURMOUNT-1 trial, where mean weight loss ranged from 15.0% to 20.9% depending on dose after 72 weeks, compared with 3.1% in the placebo group; 57% of participants receiving the 15 mg dose achieved at least 20% weight loss [2]. With respect to body composition changes during semaglutide treatment, the SEMALEAN study demonstrated an 18.9% reduction in total fat mass together with an initial decline of approximately 3.0 kg in lean mass, assessed by dual-energy X-ray absorptiometry (DXA), which subsequently stabilised over the course of treatment; despite this absolute reduction, the proportion of lean mass relative to total body mass increased significantly, handgrip strength improved progressively (+3.7 kg at month 7 and +4.1 kg at month 12), and the prevalence of sarcopenic obesity fell from 49% at baseline to 33% at 12 months, although appendicular skeletal muscle mass itself decreased significantly, underscoring the need for continued monitoring of muscle quantity despite apparent functional gains [9]. Consistent with these findings, a recent meta-analysis by Karakasis et al. [10] estimated that approximately 25% of total weight loss associated with GLP-1 receptor agonists as a class was attributable to lean mass reduction, with no significant difference in the relative (percentage) change in lean mass compared with placebo. However, this class-level average obscures an important dose-dependent pattern: in network meta-analysis, semaglutide 2.4 mg weekly ranked among the least favourable agents for lean mass preservation despite ranking second only to tirzepatide for fat mass reduction, whereas liraglutide (1.8 mg daily or 3.0 mg weekly) was the only agent to achieve significant weight loss without a statistically significant reduction in lean mass. This indicates that, although semaglutide 2.4 mg produces the most pronounced absolute reductions in fat mass among the established GLP-1 RA doses, lean mass preservation may be less pronounced compared with lower-potency agents. Nevertheless, this finding should be interpreted in the context of favourable functional outcomes, including improved handgrip strength and a reduced prevalence of sarcopenic obesity observed in real-world cohorts such as SEMALEAN. In contrast to semaglutide, body composition changes with tirzepatide have been evaluated not only by DXA but also by MRI-based assessments of skeletal muscle composition. In the SURMOUNT-1 DXA substudy involving 160 adults with obesity or overweight, tirzepatide treatment for 72 weeks reduced body weight by 21.3%, fat mass by 33.9%, visceral fat mass by 40.1%, and lean mass by 10.9% compared with baseline. Importantly, approximately 74% of total weight loss was attributable to fat mass and only 26% to lean mass, a proportion that remained remarkably consistent across age, sex and weight-loss subgroups, suggesting that greater weight reduction with tirzepatide was not associated with disproportionate lean tissue depletion [3]. Additional insight into skeletal muscle quality was provided by the SURPASS-3 MRI substudy. In adults with type 2 diabetes treated with tirzepatide for 52 weeks, MRI demonstrated significant reductions in thigh muscle fat infiltration (−0.36 percentage points), accompanied by a modest decrease in muscle volume (−0.64 L) and muscle volume Z-score (−0.22). Notably, the reduction in muscle volume was broadly consistent with the magnitude of body weight loss expected from

population-based reference data. In contrast, reductions in muscle fat infiltration exceeded those predicted by weight loss alone, while decreases in muscle volume Z-score were also greater than population-based estimates, particularly at the highest tirzepatide dose [11]. Taken together, available evidence indicates that tirzepatide produces substantial reductions in adiposity, including visceral fat, while lean mass loss constitutes approximately one quarter of total weight reduction, a proportion similar to that observed with lifestyle-induced weight loss [3]. Moreover, MRI-based analyses suggest that decreases in muscle quantity are accompanied by improvements in muscle quality, highlighting that assessment of skeletal muscle health during tirzepatide therapy should extend beyond lean mass alone and incorporate measures of muscle composition and function [11].

Risk of Sarcopenia Associated with GLP-1 RA Treatment

The consistent reductions in lean body mass observed during GLP-1 receptor agonist therapy have raised concerns regarding the potential development of sarcopenia and sarcopenic obesity [12]. However, reductions in lean body mass alone should be interpreted cautiously, as contemporary definitions of sarcopenia incorporate not only muscle quantity but also measures of muscle strength and physical performance. Several systematic reviews have reported that 20–50% of total weight loss achieved with GLP-1 receptor agonists consists of lean body mass, compared with 5.9–26.1% observed with dietary, behavioural and pharmacological weight-loss interventions combined, and 19.2–23.6% following bariatric surgery [13]. Lean mass, however, includes not only skeletal muscle but also organs, bone, body fluids, and the fat-free fraction of adipose tissue. Furthermore, because adipose tissue itself contains a substantial fat-free component, large reductions in fat mass may inflate the apparent magnitude of lean mass loss without reflecting true skeletal muscle wasting [13]. Importantly, several studies have demonstrated preservation or improvement of muscle function despite reductions in lean body mass. In the SEMALEAN study, semaglutide treatment resulted in significant improvements in handgrip strength (+4.1 kg at 12 months) and reduced the prevalence of sarcopenic obesity from 49% at baseline to 33% after one year of treatment. Notably, 22% of participants who met criteria for sarcopenic obesity at baseline no longer fulfilled these criteria at follow-up, whereas only 5% developed sarcopenic obesity during the study period [9]. These findings suggest that reductions in body weight and lean mass do not necessarily translate into clinically meaningful deterioration in muscle function. Additional evidence comes from MRI-based analyses of tirzepatide therapy. In the SURPASS-3 MRI substudy, reductions in muscle volume were accompanied by significant decreases in muscle fat infiltration, indicating improved muscle composition despite reductions in absolute muscle quantity [11]. These findings suggest an adaptive, rather than pathological response to weight loss. A markedly different picture emerged from a retrospective cohort study by Ren et al. [14], comparing 220 older adults (≥65 years) with type 2 diabetes treated with semaglutide to 212 propensity score-matched controls over 24 months (baseline sarcopenia prevalence: 27.7%). Appendicular skeletal muscle mass index declined significantly from month 12 onward, with cumulative losses markedly greater than those observed in controls. Muscle function showed a more complex trajectory: handgrip strength initially improved, with a transient increase at 6 months in men and a non-significant upward trend in women, before deteriorating significantly in both sexes by study end. Gait speed demonstrated non-significant changes during intermediate phases but a statistically significant overall reduction at 24 months. At the end of the study, the semaglutide group exhibited significantly lower ASMI, handgrip strength, and gait speed than controls. Multivariable regression identified semaglutide dosage, baseline ASMI, and gait speed as independent predictors of muscle loss. These findings represent one of the strongest signals of clinically meaningful sarcopenia risk in the current literature. However, the observational design, use of bioelectrical impedance analysis rather than DXA or MRI, and absence of data on dietary protein intake and physical activity preclude firm conclusions regarding a direct semaglutide-specific effect. Conversely, a pharmacovigilance analysis of VigiBase, the WHO global database of individual case safety reports, did not identify a significant association between GLP-1 RA use and reported sarcopenia [12], providing additional population-level reassurance, despite the inherent limitations of spontaneous adverse-event reporting. Taken together, the available evidence indicates that lean body mass reduction during GLP-1 RA therapy should not be considered synonymous with sarcopenia, as a formal diagnosis additionally requires assessment of muscle strength and physical performance. While most studies report preserved or improved muscle function despite quantitative lean mass loss, conflicting findings in older adults with type 2 diabetes highlight the importance of comprehensive functional assessment when interpreting body composition changes during treatment.

Mechanisms of GLP-1 RA and GLP-1/GIP Action on Skeletal Muscle

The mechanisms underlying skeletal muscle changes during GLP-1 receptor agonist therapy are multifactorial, involving both indirect consequences of negative energy balance and direct receptor-mediated signalling within myocytes.

Negative energy balance and catabolic signalling

The dominant driver of lean mass loss is the sustained caloric deficit induced by appetite suppression and delayed gastric emptying, mediated via hypothalamic and brainstem pathways [15]. Approximately one quarter of total weight loss typically originates from fat-free mass, with skeletal muscle accounting for roughly half of this compartment [15]. Reduced dietary protein intake, a common consequence of appetite suppression, further predisposes to lean tissue loss, particularly in older adults [15]. Negative energy balance also activates the hypothalamic-pituitary-adrenal axis, elevating cortisol, which stimulates muscle proteolysis through the ubiquitin-proteasome pathway and antagonises the anabolic effects of insulin [15].

PI3K-Akt-mTOR signalling

Insulin and IGF-1 promote anabolic signalling in skeletal muscle primarily through the PI3K-Akt-mTOR axis: Akt activation stimulates mTOR, promoting protein synthesis, while simultaneously inhibiting forkhead box protein O (FoxO), thereby reducing expression of the E3 ubiquitin ligases that mediate muscle fibre atrophy [16]. GLP-1 receptor agonists enhance insulin sensitivity and lower fasting insulin levels; however, under caloric restriction these changes can paradoxically reduce anabolic signalling, since decreased insulin/IGF-1 signalling lowers mTOR activity and shifts the balance toward catabolism [15]. At the cellular level, this picture is more nuanced: in C2C12 myoblasts, liraglutide promoted myogenic differentiation via a cAMP-PKA-dependent cascade involving PI3K-Akt-mTOR, p38 MAPK and ERK signalling, with upregulation of the myogenic transcription factors MyoD, myogenin and CREB, and downregulation of the atrogenes Atrogin-1 and MuRF-1, the principal ubiquitin ligases responsible for muscle protein degradation [17]. This suggests GLP-1 receptor activation can directly oppose proteolytic signalling even as systemic caloric deficit favours it.

Myostatin/activin–ActRII pathway

The activin receptor type II (ActRII) pathway is a negative regulator of muscle growth, mediating the inhibitory effects of myostatin and activin A on protein synthesis [17]. Pharmacological ActRII blockade promotes hypertrophy by suppressing proteolysis and activating anabolic signalling independently of Akt [17]. Co-administration of the ActRII inhibitor bimagrumab with semaglutide restored muscle fibre size and architecture to levels comparable with untreated controls in preclinical models, effectively counteracting GLP-1 RA–associated lean mass loss [17]. This indicates that myostatin/activin signalling, rather than GLP-1 receptor activation itself, may be the principal pathway responsible for the residual lean mass loss observed even when GLP-1R signalling is otherwise muscle-protective.

AMPK signalling and mitochondrial biogenesis

The most direct mechanistic evidence for a muscle-protective action of GLP-1 receptor signalling comes from Wu et al. [18], who used both an AAV-mediated GLP-1 overexpression model in mouse gastrocnemius muscle and exendin-4 treatment of C2C12 myotubes. GLP-1R activation increased glycogen synthesis and translocation of GLUT4 to the plasma membrane, enhanced glucose uptake, and induced a fibre-type shift toward oxidative type I fibres, accompanied by increased mitochondrial density, mtDNA copy number, and expression of the mitochondrial biogenesis regulators PGC-1α, Tfam and Mterf1 [18]. RNA-sequencing of muscle tissue showed differential expression of over 700 genes enriched in the AMPK, PI3K-Akt-mTOR and cAMP signalling pathways [18]. Critically, siRNA-mediated knockdown of AMPKα abolished essentially all of these effects, since glycogen synthesis, GLUT4 translocation, mitochondrial biogenesis, and oxidative respiration were no longer enhanced by exendin-4 in AMPK-depleted myotubes, which establishes AMPK as the necessary downstream mediator of GLP-1R-induced skeletal muscle remodelling [18].

GIP receptor–specific effects in dual agonism

Because tirzepatide is a dual GIP/GLP-1 receptor agonist, GIP-mediated signalling may contribute an additional, partially distinct mechanism. GIP receptors are expressed in adipose tissue, gastric mucosa, heart, adrenal cortex, bone and brain, and GIP enhances insulin sensitivity and the postprandial lipid-buffering capacity of adipose tissue [19]. A direct anabolic effect of GIP on skeletal muscle has not been established; current evidence suggests its contribution to muscle preservation is largely indirect, mediated through improved insulin sensitivity and systemic energy availability rather than through muscle-intrinsic signalling [17].

Convergent evidence from human muscle composition data

The clinical correlate of these mechanisms is the SURPASS-3 MRI substudy, in which tirzepatide significantly reduced muscle fat infiltration (myosteatosis) relative to insulin degludec, while reductions in fat-free muscle volume remained within ranges expected from UK Biobank reference data for the degree of weight loss observed [11]. This pattern of disproportionate improvement in muscle quality relative to muscle quantity is difficult to explain by caloric deficit alone and is consistent with the AMPK-mediated mitochondrial and fibre-type remodelling described above. Similarly, in the SLIM LIVER study, a 9.3% reduction in psoas muscle volume with semaglutide was not accompanied by a significant change in muscle fat fraction, nor by any significant decline in objectively measured physical function [20]. Taken together, these findings support the interpretation introduced in the section on the effects of GLP-1 receptor agonists on body weight and body composition: that lean mass reduction during GLP-1 RA therapy reflects predominantly proportional, energy-balance-driven tissue loss, while receptor-mediated AMPK and PI3K-Akt-mTOR signalling, and for tirzepatide possibly GIP-mediated metabolic support, may partially protect muscle quality and function independently of changes in muscle mass.

Strategies to Mitigate Muscle Loss

Preserving skeletal muscle mass during GLP-1 receptor agonist therapy requires a combined nutritional and exercise-based approach, as neither strategy alone appears sufficient to fully offset muscle loss associated with substantial, rapid weight reduction [15, 21]. Adequate protein intake is one of the most important nutritional strategies, since appetite suppression frequently reduces food consumption below the level required to maintain muscle protein synthesis, particularly in older adults and those with pre-existing low muscle mass [15]. Current guidance recommends a daily protein intake of 1.2 to 1.6 g/kg adjusted body weight. Prolonged intake above 2 g/kg/day is generally discouraged [15, 21]. A more even distribution across meals has also been associated with superior lean mass preservation compared with a skewed intake pattern [15]. Resistance exercise training provides a complementary, and likely necessary, mechanism for muscle preservation, as increased protein intake alone is unlikely to adequately maintain muscle mass during substantial weight loss. Structured strength or mixed resistance-aerobic training is well established to preserve lean mass during weight reduction, whereas aerobic activity alone has a comparatively smaller protective effect [21]. In a randomised trial, one year of combined GLP-1 receptor agonist therapy and exercise preserved bone mineral density and produced greater reductions in abdominal fat and systemic inflammation than pharmacotherapy alone [21]. Based on this evidence, current guidance recommends structured resistance training at least three times weekly combined with at least 150 minutes of moderate-intensity aerobic activity per week [21]. Beyond protein and exercise, micronutrient and amino acid supplements, including branched-chain amino acids, leucine, beta-hydroxy-beta-methylbutyrate, creatine, omega-3 fatty acids, and vitamin D, have been proposed as adjunctive strategies, though evidence remains preliminary and most consistent when combined with, rather than substituted for, adequate protein intake and resistance training [15]. Periodic monitoring of body composition and physical function is advisable to detect disproportionate lean mass loss and guide adjustment of interventions [15, 21].

Discussion

GLP-1 RA-induced lean mass loss does not necessarily translate into clinically relevant sarcopenia. Across the body of evidence reviewed here, three observations converge to support this conclusion. First, the proportion of weight loss attributable to lean mass during treatment with semaglutide or tirzepatide (approximately 20–33%) falls within, or only modestly above, the range reported for lifestyle-induced and surgical weight loss [13], suggesting that much of this loss represents an expected physiological correlate of substantial weight reduction rather than a drug-specific catabolic effect. This pattern is broadly consistent with conclusions drawn in other recent syntheses of GLP-1 RA body-composition data [22, 23, 24]. Second, where muscle function has been directly assessed, including handgrip strength, gait speed, sarcopenic obesity prevalence, or muscle composition by MRI, outcomes have generally been preserved or improved despite reductions in lean mass [9, 11, 20]. Third, mechanistic data indicate that GLP-1 receptor signalling is not uniformly catabolic at the level of the myocyte; AMPK-dependent mitochondrial biogenesis and fibre-type remodelling [18], together with suppression of atrogene expression in vitro [17], suggest that part of the observed lean mass reduction may be offset, at least qualitatively, by improvements in muscle composition and metabolic efficiency.

Quantity versus quality: a necessary distinction

A recurring theme across the reviewed literature is that lean body mass, as measured by DXA, is an imperfect proxy for skeletal muscle health. Because lean mass includes organs, bone, fluid, and the fat-free component of adipose tissue, large reductions in fat mass can mechanically inflate the apparent magnitude of "lean mass" loss without genuine muscle wasting [13]. This is illustrated most clearly by the SURPASS-3 MRI substudy, where modest reductions in muscle volume occurred alongside a meaningful decrease in intramuscular fat infiltration, a pattern more consistent with improved muscle quality than with pathological atrophy [11]. Contemporary sarcopenia frameworks (EWGSOP2, AWGS2, SDOC) already reflect this shift by prioritising strength and physical performance over isolated muscle quantity [6, 7], and the data reviewed here reinforce that a reduction in DXA-derived lean mass alone is insufficient grounds for a sarcopenia diagnosis.

Discordant findings and high-risk subgroups

Not all evidence is reassuring. The retrospective cohort by Ren et al. [14] reported concurrent declines in both muscle mass and function in older adults with type 2 diabetes, a population already at elevated baseline risk of sarcopenia (27.7% prevalence at baseline). This finding stands apart from the rest of the literature reviewed and should be taken seriously as a signal, even though its observational design, lack of data on protein intake and physical activity, and reliance on bioelectrical impedance rather than DXA or MRI limit causal inference. It is plausible that the net effect of GLP-1 RA therapy on skeletal muscle is not uniform across populations: in adults with adequate nutritional reserve and preserved baseline muscle mass, the receptor-mediated and adaptive mechanisms described above (see "Mechanisms of GLP-1 RA and GLP-1/GIP Action on Skeletal Muscle"), particularly the AMPK- and PI3K-Akt-mTOR-mediated pathways, may be sufficient to preserve function despite quantitative lean mass loss, whereas in older, frailer, or nutritionally compromised individuals, particularly those with reduced protein intake or low physical activity during caloric restriction, the catabolic, energy-deficit-driven pathway may predominate. This would explain why population-level pharmacovigilance data (VigiBase) show no significant sarcopenia signal [12] while a targeted, high-risk geriatric cohort does. Age, baseline muscle status, and comorbidity burden, rather than the GLP-1 RA class per se, may thus be the principal determinants of risk [16,25].

Clinical implications

These findings suggest that routine, blanket concern about sarcopenia is not supported by current evidence in the general population treated with GLP-1 RAs, but that a risk-stratified approach is warranted. Older adults, individuals with low baseline muscle mass or pre-existing sarcopenic obesity, and those with low dietary protein intake or limited physical activity appear to represent the subgroups in whom monitoring is most justified. Practical strategies supported by the reviewed literature include adequate, evenly distributed protein intake and resistance exercise training during treatment [15, 26], alongside periodic functional assessment (e.g., handgrip strength, gait speed) rather than reliance on lean mass trends alone. Preclinical data combining GLP-1 RA with ActRII pathway inhibition (e.g., bimagrumab) [17] point to a possible future pharmacological strategy for preserving muscle mass during incretin-based weight loss, though this remains experimental and far from clinical application.

Limitations of this review

This review has several limitations. As a narrative rather than systematic review, study selection was not exhaustive and may be subject to selection bias. The evidence base is heterogeneous in terms of body composition methodology (DXA, MRI, bioelectrical impedance), treatment duration (12–72 weeks, with only one cohort extending to 24 months), and study population (predominantly middle-aged adults with obesity or type 2 diabetes, with limited representation of frail or very elderly individuals). Long-term data, particularly beyond two years of continuous treatment, remain scarce, as do data specifically powered to assess sarcopenia as a primary outcome rather than a secondary or exploratory analysis. Most mechanistic evidence is derived from preclinical (rodent or cell-culture) models and may not directly translate to human skeletal muscle physiology.

Conclusions

Current evidence indicates that GLP-1 receptor agonists, including semaglutide and tirzepatide, induce substantial weight loss in which lean body mass reduction occurs proportionally to, and largely in line with, what is expected from comparable degrees of weight loss achieved through other means. In most studies reviewed, this quantitative lean mass loss has not been accompanied by clinically meaningful declines in muscle strength or physical performance, and in several cohorts has coincided with improved muscle function and a reduced prevalence of sarcopenic obesity. Mechanistic data suggest that GLP-1 receptor signalling may partially counteract the catabolic consequences of caloric restriction through AMPK-dependent and PI3K-Akt-mTOR-mediated pathways, although the myostatin/activin-ActRII axis appears to remain a significant residual driver of muscle loss. Importantly, isolated evidence from a high-risk geriatric population with type 2 diabetes suggests that older adults with low baseline muscle reserve may be more vulnerable to genuine sarcopenic decline, underscoring the need for individualised risk assessment rather than a uniform interpretation of treatment safety. Until prospective studies specifically designed to assess sarcopenia as a primary endpoint are available, clinical practice should favour a precautionary, function-oriented approach: incorporating adequate protein intake and resistance exercise into GLP-1 RA treatment plans, and reserving closer muscle-function monitoring for patients at elevated baseline risk, rather than assuming uniform risk across all individuals undergoing pharmacological weight loss.

Authors' contribution: The following statements should be used:
Conceptualization, SM and PS;
Methodology, MP;
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