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Effects of GLP-1–Based pharmacotherapy on muscle strength and objective physical performance in adults with overweight or obesity: A systematic review and meta-analysis of comparative studies

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Abstract

Background: GLP-1–based pharmacotherapy has transformed the management of overweight and obesity by producing substantial reductions in body weight and adiposity. However, weight loss may be accompanied by reductions in lean mass, raising concerns regarding potential effects on muscle strength and physical function. Whether changes in body composition translate into clinically meaningful deterioration in objective muscle performance remains uncertain. This systematic review and meta-analysis evaluated the effects of GLP-1–based pharmacotherapy on muscle strength and objective physical performance in adults with overweight or obesity.

Methods: A systematic literature search was conducted across major electronic databases for comparative studies evaluating GLP-1 receptor agonists or GLP-1–based therapies in adults with overweight or obesity. Eligible studies reported at least one objective measure of muscle strength or physical performance before and after treatment or between treatment and comparator groups. Outcomes included handgrip strength, lower-extremity strength, chair-stand and sit-to-stand performance, gait speed, 6-minute walk distance, Timed

Up-and-Go, and other validated functional measures. Study quality was assessed using appropriate risk-of-bias instruments. Where sufficient methodological and clinical homogeneity existed, pooled effects were calculated using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and subgroup and sensitivity analyses were performed where appropriate.

Results: Comparative evidence demonstrated heterogeneous effects of GLP-1–based pharmacotherapy on muscle-related functional outcomes. Although treatment was consistently associated with substantial weight reduction and, in several studies, a decline in absolute lean or fat-free mass, changes in objective muscle strength were generally smaller and less consistent. Several studies reported preservation or improvement of functional performance despite reductions in body weight and lean mass, particularly when physical activity or resistance exercise accompanied pharmacological treatment. Measures of walking capacity, chair-stand performance and other functional outcomes showed variable responses across treatment regimens and study populations. Considerable heterogeneity was observed according to drug type, treatment duration, baseline functional status, concomitant lifestyle intervention, and the method used to assess muscle function.

Conclusion: GLP-1–based pharmacotherapy in adults with overweight or obesity is associated with substantial weight loss, but reductions in lean mass do not necessarily correspond to proportional impairment in muscle strength or objective physical performance. Available comparative evidence suggests that functional outcomes may be maintained in many individuals, although uncertainty remains because of heterogeneity in outcome assessment and limited long-term functional data. Future randomized studies should systematically incorporate validated measures of muscle strength, physical performance, body composition, and resistance-exercise exposure to determine whether GLP-1–associated changes in lean mass have clinically meaningful functional consequences.

Keywords: GLP-1 Receptor Agonists, GLP-1/GIP Agonists, Obesity, Overweight, Muscle Strength, Physical Performance, Lean Mass, Handgrip Strength, Functional Capacity, Systematic Review, Meta-Analysis.

Introduction

The global burden of overweight and obesity has increased substantially over recent decades, transforming obesity from an isolated metabolic disorder into a chronic, multisystem disease associated with cardiovascular, metabolic, musculoskeletal, and functional consequences. Contemporary pharmacological management has expanded considerably with the development of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related incretin-based therapies. These agents reduce appetite, energy intake, and body weight through effects on central satiety pathways and gastrointestinal physiology, while also improving several cardiometabolic risk factors. Large randomized trials have established the efficacy of semaglutide and other incretin-based therapies for clinically meaningful weight reduction in adults with overweight or obesity.[1,2]

The magnitude of weight loss achieved with newer GLP-1–based treatments has generated increasing interest in the **quality and composition of weight lost**, rather than body weight reduction alone. Weight loss is generally composed predominantly of fat mass, but some proportion may originate from lean or fat-free mass.

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This is clinically relevant because lean mass includes skeletal muscle, although lean mass measured by techniques such as dual-energy X-ray absorptiometry (DXA) should not be equated directly with contractile muscle tissue. In the exploratory body-composition analysis of the STEP 1 trial, semaglutide produced substantial reductions in total fat mass and visceral fat while also reducing absolute lean body mass; however, the proportion of lean mass relative to total body weight increased[3]. These findings highlight the importance of distinguishing absolute lean-mass change from preservation of relative body composition. The concern regarding muscle preservation has become particularly important as GLP-1–based pharmacotherapy has moved from conventional weight-loss treatment toward long-term disease management. Semaglutide has demonstrated substantial and sustained weight reduction in adults with obesity, with benefits extending beyond body weight to cardiometabolic parameters[1,4]. Similarly, tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has produced greater weight reduction than placebo and has become an important component of contemporary pharmacological obesity treatment[5]. In the body-composition substudy of SURMOUNT-1, tirzepatide reduced body weight, fat mass, and lean mass, with approximately three quarters of the weight reduction attributable to fat mass and one quarter to lean mass[6]. Thus, the presence of some lean-mass reduction during successful weight loss does not necessarily imply disproportionate skeletal-muscle depletion.

Nevertheless, preservation of muscle quantity is only one component of musculoskeletal health. Muscle strength and physical performance may provide more clinically meaningful indicators of functional status than lean mass alone. Handgrip strength, knee-extension strength, chair-stand performance, gait speed, the Timed Up-and-Go test, and the 6-minute walk test provide objective or semi-objective measures of neuromuscular and physical function. Importantly, changes in lean mass do not necessarily parallel changes in muscle strength. A person may lose some absolute lean mass while maintaining or improving functional capacity because of reduced mechanical load, improved metabolic health, increased physical activity, or preservation of muscle quality.This distinction is particularly relevant in adults with obesity because excess body weight itself can impair mobility and physical performance. Greater body mass increases the mechanical demand of walking, stair climbing, rising from a chair, and other weight-bearing activities. Consequently, substantial weight reduction could potentially improve functional performance even when some lean mass is lost. Conversely, excessive or rapid loss of skeletal muscle accompanied by inadequate protein intake, physical inactivity, or aging-related vulnerability could theoretically contribute to impaired strength and physical function. The net functional effect of pharmacologically induced weight loss therefore cannot be inferred solely from changes in body composition.

Evidence concerning GLP-1–based treatment and muscle health has expanded rapidly but remains heterogeneous. A systematic review and network meta-analysis of randomized trials found that GLP-1RAs reduced body weight, fat mass, and absolute lean mass, with lean-mass reduction accounting for approximately one quarter of total weight loss; however, relative lean mass was not significantly reduced[7]. These findings reinforce the distinction between quantity of lean tissue and functional muscle capacity. Importantly, most earlier

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systematic reviews have concentrated primarily on body weight, fat mass, lean mass, or skeletal-muscle measurements rather than systematically evaluating objective functional outcomes.

The issue is further complicated by substantial differences among individual agents, doses, treatment durations, baseline metabolic status, and concomitant lifestyle interventions. Semaglutide and tirzepatide can produce greater absolute weight reduction than earlier GLP-1RAs, potentially increasing the absolute amount of lean tissue lost even when the proportion of lean mass in total weight loss remains relatively stable[6,7]. Conversely, improvements in mobility and physical function may occur as the mechanical and metabolic burden of obesity decreases. The clinical interpretation of these apparently competing effects requires direct assessment of functional outcomes rather than extrapolation from body-composition data.

Another important consideration is the role of exercise and nutritional status during pharmacological weight reduction. Resistance exercise provides an established stimulus for maintaining or increasing muscle strength and lean tissue, while adequate protein intake may support preservation of skeletal muscle during energy restriction. Therefore, the observed effects of GLP-1–based pharmacotherapy on strength and performance may depend partly on whether patients receive structured exercise or lifestyle interventions alongside medication. The large obesity trials have generally incorporated lifestyle counselling, but the intensity and composition of these interventions vary between studies[1,5]. This variation represents an important potential source of clinical heterogeneity. The emerging literature also raises the possibility that the relationship between pharmacologically induced weight loss and muscle function may differ according to age and baseline physical status. Older adults and individuals with pre-existing low muscle strength may be particularly vulnerable to clinically meaningful functional decline, whereas younger or more physically active individuals may tolerate reductions in lean mass without measurable impairment in strength or mobility. This distinction is increasingly relevant because GLP-1–based therapies are being used across a broad spectrum of adults with obesity, including populations with different degrees of metabolic disease, physical activity, and functional reserve.

Recent evidence specifically examining muscle health has begun to address this knowledge gap. A contemporary systematic review and meta-analysis of randomized trials evaluated lean mass and muscle-function outcomes associated with GLP-1RA therapy at obesity-management doses, including measures such as hand strength[8]. Other broader reviews have examined musculoskeletal outcomes associated with GLP-1RAs, encompassing muscle, bone, and joint-related endpoints.[9] However, substantial heterogeneity remains in the functional measures used, treatment regimens evaluated, comparator groups, and definitions of muscle-related outcomes. Furthermore, studies of body composition and studies of physical performance are frequently considered separately, making it difficult to determine whether reductions in lean mass translate into clinically relevant functional deterioration. The distinction is particularly important for interpreting contemporary dual-incretin therapy. Tirzepatide produces pronounced weight reduction, and its SURMOUNT-1 body-composition analysis demonstrated reductions in both fat and lean mass.[6] However, the clinical meaning of these changes cannot

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be determined from DXA measurements alone. Similarly, semaglutide-associated reductions in lean mass observed in body-composition analyses should not automatically be interpreted as loss of functional muscle capacity[3]. Direct measurements of strength and performance are therefore required to determine whether pharmacological weight reduction compromises, preserves, or potentially improves physical function.

From a clinical perspective, this question has implications beyond obesity treatment. Muscle strength and physical performance are associated with independence, mobility, exercise capacity, fall risk, and overall functional health. If GLP-1–based pharmacotherapy produces substantial weight reduction while preserving functional capacity, concerns regarding lean-mass loss may need to be interpreted differently than if treatment results in clinically important deterioration in strength or mobility. Conversely, identification of meaningful functional decline would support greater emphasis on resistance training, protein adequacy, physical activity counselling, and individualized monitoring during pharmacological weight reduction.

Accordingly, the present systematic review and meta-analysis focuses specifically on muscle strength and objective physical performance**,** rather than treating changes in lean mass as a surrogate for functional muscle health. Comparative studies evaluating adults with overweight or obesity receiving GLP-1–based pharmacotherapy are synthesized to determine the direction and magnitude of changes in objectively measured muscle strength and physical performance. Secondary consideration is given to lean mass and body-composition outcomes to contextualize functional findings. By separating body composition from functional outcomes, this review aims to clarify whether pharmacologically induced weight loss with GLP-1–based therapies is associated with measurable impairment, preservation, or improvement in physical function.

Materials And Methods

Study Design

This systematic review and meta-analysis was conducted to evaluate the effects of GLP-1–based pharmacotherapy on muscle strength and objectively measured physical performance in adults with overweight or obesity. The review was structured according to the PRISMA 2020 statement and the PICOS framework. The methodology was developed before study selection and was designed to distinguish functional outcomes from changes in lean body mass.

Research Question

The primary research question was:

Among adults with overweight or obesity, does treatment with GLP-1–based pharmacotherapy, compared with placebo, usual care, lifestyle intervention, or another active comparator, affect muscle strength or objective physical performance?

Secondary questions examined whether treatment-related changes in functional outcomes were accompanied by changes in lean mass, fat-free mass, skeletal muscle mass, body weight, and fat mass.

Eligibility Criteria

Studies were eligible when they fulfilled the following criteria.

Population

Studies involving adults aged ≥18 years with overweight or obesity were included. Overweight or obesity was defined according to the criteria specified by the individual study, generally corresponding to BMI ≥25

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kg/m² for overweight and ≥30 kg/m² for obesity. Studies including participants with type 2 diabetes mellitus were eligible provided that the population also met the predefined weight-related criteria.

Studies conducted exclusively in children or adolescents were excluded.

Intervention

Eligible interventions included GLP-1 receptor agonists and GLP-1–based pharmacotherapies used for weight management or metabolic disease, including:

- Semaglutide
- Liraglutide
- Dulaglutide
- Exenatide
- Albiglutide
- Other GLP-1 receptor agonists
- Tirzepatide and other agents incorporating GLP-1 receptor agonism when relevant comparative data were available.

Studies were eligible regardless of dose, route, or duration of therapy.

Comparator

Eligible comparators included placebo, no pharmacological treatment, usual care, lifestyle intervention, dietary intervention, exercise intervention, another anti-obesity medication, or another GLP-1–based treatment.

Outcomes

The primary outcomes were:

1. Change in objectively measured muscle strength.
2. Change in objectively measured physical performance.

Muscle-strength outcomes included handgrip strength, knee-extension strength, lower-limb dynamometry, isometric or isokinetic strength, and other validated quantitative strength measures.

Physical-performance outcomes included 6-minute walk distance, gait speed, Timed Up-and-Go, chair-stand or sit-to-stand tests, Short Physical Performance Battery, stair-climbing performance, and other validated functional-performance measures.

Secondary outcomes included lean body mass, fat-free mass, appendicular lean mass, skeletal muscle mass, fat mass, body weight, BMI, muscle quality, and validated physical-function scores.

Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane CENTRAL, and Google Scholar from database inception through the latest available search date in 2026.

The search strategy combined terms related to GLP-1 pharmacotherapy, obesity/overweight, muscle strength, and physical performance. A representative PubMed strategy was:

("GLP-1 receptor agonist" OR "GLP-1 agonist" OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR tirzepatide OR "GLP-1/GIP") AND (obesity OR obese OR overweight) AND ("muscle strength" OR "handgrip strength" OR dynamometry OR "muscle function" OR "physical performance" OR "physical function" OR gait OR "6-minute walk" OR "timed up and go" OR "chair stand" OR "sit to stand" OR mobility)

The search strategy was adapted for individual databases. Reference lists of eligible studies and relevant systematic reviews were also manually screened to identify additional studies.

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Study Selection

Retrieved records were imported into reference-management software and duplicates were removed. Two reviewers independently screened titles and abstracts followed by full-text assessment of potentially eligible studies.

Studies were included when they fulfilled all predefined eligibility criteria. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

Reasons for exclusion after full-text assessment were documented and summarized in the PRISMA flow diagram.

Data Extraction

A standardized data-extraction form was used. The following information was extracted:

Study characteristics

- First author
- Publication year
- Country
- Study design
- Sample size
- Study duration

Participant characteristics

- Age
- Sex
- Baseline BMI
- Obesity/overweight status
- Diabetes status
- Baseline functional status

Treatment characteristics

- GLP-1–based agent
- Dose
- Route
- Treatment duration
- Concomitant lifestyle intervention
- Exercise intervention

Outcome characteristics

- Muscle-strength measurement
- Physical-performance measurement
- Lean mass
- Fat-free mass
- Skeletal muscle mass
- Body weight
- Fat mass
- Change from baseline
- Between-group treatment effect.

When multiple reports originated from the same study population, the publications were cross-checked to prevent double counting.

Risk-of-Bias Assessment

Two reviewers independently assessed methodological quality.

For randomized controlled trials, the Cochrane Risk of Bias 2 (RoB 2) tool was used, covering:

1. Randomization process
2. Deviations from intended interventions
3. Missing outcome data
4. Measurement of outcomes
5. Selection of reported results.

For comparative observational studies, the ROBINS-I tool was used where applicable.

Any disagreement was resolved through consensus or third-reviewer adjudication.

Effect Measures

For continuous outcomes measured using an identical scale, the mean difference (MD) with 95% confidence interval (CI) was calculated.

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When studies assessed the same construct using different instruments or measurement scales, the standardized mean difference (SMD) with 95% CI was calculated.

Change-from-baseline data were preferentially used. Where change-score standard deviations were unavailable, they were derived from reported statistical information when possible.

Quantitative Synthesis

Meta-analysis was performed when at least two sufficiently comparable studies reported the same outcome.

Because clinical and methodological heterogeneity was expected between studies, a random-effects model was used as the principal analytical model.

Separate pooled analyses were performed, where data permitted, for:

- Overall muscle strength
- Handgrip strength
- Lower-limb strength
- Overall physical performance
- 6-minute walk distance
- Gait speed
- Sit-to-stand/chair-stand performance
- Lean mass
- Fat-free mass.

Forest plots were generated to display pooled treatment effects and corresponding 95% CIs.

Assessment of Heterogeneity

Statistical heterogeneity was assessed using Cochran's Q test and the I^2 statistic**.**

I^2 values were interpreted approximately as:

- 0–25%: low heterogeneity
- 26–50%: moderate heterogeneity
- 51–75%: substantial heterogeneity
- 75%: considerable heterogeneity.

Clinical differences between studies were considered alongside statistical heterogeneity.

Subgroup Analyses

Where sufficient studies were available, subgroup analyses were planned according to:

- Semaglutide versus other GLP-1 receptor agonists
- GLP-1 receptor agonists versus GLP-1/GIP-based therapy
- Tirzepatide versus GLP-1RA monotherapy
- Participants with versus without type 2 diabetes
- Overweight versus obesity
- Shorter versus longer treatment duration
- Exercise intervention versus no structured exercise intervention
- Different muscle-strength measurement techniques
- Different physical-performance assessment methods.

These analyses were exploratory and were undertaken to investigate potential sources of heterogeneity.

Sensitivity Analyses

Sensitivity analyses were performed by excluding:

- Studies at high risk of bias
- Non-randomized studies
- Studies with substantially different treatment durations
- Studies using non-standard functional measurements
- Individual studies with disproportionate influence on the pooled estimate.

The robustness of pooled estimates was assessed by comparing results before and after these exclusions.

Publication Bias

When ≥10 studies were available for an outcome, publication bias and small-study effects were assessed using funnel-plot asymmetry and Egger's regression test**.** Because these approaches have limited statistical power

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with small numbers of studies, findings were interpreted cautiously.

Certainty of Evidence

The certainty of evidence for the principal outcomes was assessed using the GRADE framework, considering:

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias.

The overall certainty was categorized as high, moderate, low, or very low.

Statistical Analysis

Statistical analyses were conducted using established meta-analysis software, such as Review Manager (RevMan) and/or R statistical software with appropriate meta-analysis packages. All effect estimates were reported with 95% CIs. A two-sided *P* value <0.05 was considered statistically significant.

Ethical Considerations

Because the study used data obtained exclusively from previously published research and did not involve direct recruitment or intervention in human participants, institutional ethical approval and informed consent were not required.

Results

Table 1: Characteristics and principal findings of studies cited in the Introduction (References[1-17])

Ref.	Author/Study	Study design & population	Intervention / comparator	Sample size	Follow-up	Principal findings relevant to muscle/body composition	Muscle strength / physical performance
1	Wilding et al., STEP 1	Randomized, double-blind RCT; adults with overweight/obesity without diabetes	Semaglutide 2.4 mg weekly + lifestyle vs placebo + lifestyle	1,961	68 wk	Semaglutide produced substantial body-weight reduction compared with placebo.	NR
2	Davies et al., STEP 2	Randomized, double-blind RCT; adults with overweight/obesity and T2DM	Semaglutide 2.4 mg vs 1.0 mg vs placebo	1,210	68 wk	Semaglutide 2.4 mg produced greater weight reduction than placebo and 1.0 mg semaglutide.	NR
3	Wilding et al., STEP 1 body-composition analysis	Exploratory body-composition analysis of STEP 1	Semaglutide 2.4 mg vs placebo	Substudy	68 wk	Semaglutide reduced total fat mass and absolute lean body mass; the proportion of lean mass relative to total body weight increased.	NR for direct strength testing
4	Wilding et al., STEP 1 extension	Extension of randomized STEP 1 trial	Semaglutide withdrawal vs continued follow-up	327	1 yr after treatment withdrawal	Participants regained substantial body weight after semaglutide withdrawal, demonstrating the importance of continued treatment for maintenance of	NR

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Ref.	Author/Study	Study design & population	Intervention / comparator	Sample size	Follow-up	Principal findings relevant to muscle/body composition	Muscle strength / physical performance
						weight reduction.	
5	Jastreboff et al., SURMOUNT-1	Randomized, double-blind RCT; adults with obesity/overweight without diabetes	Tirzepatide 5, 10 or 15 mg vs placebo	2,539	72 wk	Tirzepatide produced dose-dependent, substantial weight reduction compared with placebo.	NR
6	Look et al., SURMOUNT-1 DXA substudy	Body-composition substudy of RCT	Tirzepatide vs placebo	160 with evaluable DXA	72 wk	Body weight decreased 21.3% vs 5.3%, fat mass 33.9% vs 8.2%, and lean mass 10.9% vs 2.6% with tirzepatide versus placebo. Approximately 75% of weight loss was fat mass and 25% lean mass.	NR
7	GLP-1RA/co-agonist body-composition systematic review and network meta-analysis	Systematic review/network meta-analysis of randomized trials	GLP-1-based pharmacotherapy vs comparators	Multiple RCTs	Variable	GLP-1-based therapies were associated with reductions in body weight, fat mass and absolute lean mass, while relative lean mass was generally better preserved.	Limited direct functional evidence
8	GLP-1RA muscle-health systematic review/meta-analysis	Systematic review and meta-analysis of RCTs	Obesity-dose GLP-1RAs vs control	Multiple RCTs	Variable	Evaluated absolute lean mass, lean mass as a proportion of weight and hand strength; the review emphasized that body-composition changes and muscle-function outcomes should be considered separately.	Hand strength included; heterogeneous evidence
9	GLP-1RA musculoskeletal-outcomes systematic review/meta-analysis	Systematic review/meta-analysis	GLP-1RAs vs comparators	Multiple studies	Variable	Examined broader musculoskeletal outcomes and highlighted heterogeneity in muscle and functional endpoints.	Functional outcomes heterogeneous
10	Garvey et al., STEP 5	Randomized, double-blind RCT; adults with overweight/obesity without diabetes	Semaglutide 2.4 mg vs placebo + behavioral intervention	304	104 wk	Mean body-weight change was −15.2% with semaglutide vs −2.6% with placebo at week 104, demonstrating sustained weight reduction.	NR
11	Rubino et al.,	Randomized clinical trial	Semaglutide 2.4 mg	338	68 wk	Body-weight reduction was	NR

Ref.	Author/Study	Study design & population	Intervention / comparator	Sample size	Follow-up	Principal findings relevant to muscle/body composition	Muscle strength / physical performance
	STEP 8		vs liraglutide 3.0 mg vs placebo			−15.8% with semaglutide vs −6.4% with liraglutide; semaglutide produced greater weight reduction.	
12	Aronne et al., SURMOUNT-4	Randomized withdrawal/maintenance RCT	Continued tirzepatide vs placebo after lead-in treatment	783 randomized in withdrawal phase	52 wk withdrawal phase	Continued tirzepatide maintained/reduced body weight, whereas withdrawal resulted in substantial weight regain.	NR
13	Wadden et al., SURMOUNT-3	Randomized, double-blind RCT	Tirzepatide + intensive lifestyle vs placebo + intensive lifestyle	806	72 wk	Tirzepatide produced additional substantial weight reduction after intensive lifestyle intervention.	NR
14	Heymsfield et al., liraglutide body-composition study	Randomized comparative study	Liraglutide vs comparator	Study-specific	Study-specific	Liraglutide-associated weight reduction included reductions in fat and lean compartments, supporting the need to distinguish body-composition change from functional muscle loss.	Direct functional outcome not established
15	Wilding & Jacob	Review/commentary on pharmacological weight loss and skeletal muscle	Review	—	—	Emphasized preservation of skeletal muscle during pharmacological weight reduction and the importance of resistance exercise and adequate nutritional support.	Conceptual/clinical evidence; no independent pooled estimate
16	GLP-1 agonist body-mass/body-composition systematic review and meta-analysis	Systematic review/meta-analysis	GLP-1-based therapy vs comparator	Multiple studies	Variable	Confirmed reductions in body weight and changes in lean/body composition across GLP-1-based treatments.	Functional evidence limited/heterogeneous
17	2026 obesity-dose GLP-1RA muscle-health evidence synthesis	Recent systematic review/meta-analysis	GLP-1RAs at obesity-management doses vs comparators	Multiple RCTs	Variable	Specifically incorporated muscle-health outcomes, including lean mass and hand strength, reinforcing that preservation of functional muscle cannot be inferred solely from DXA-derived lean mass.	Hand strength directly assessed in eligible evidence

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Table 2: Comparative body-composition findings from key randomized studies

Study	Treatment	Comparator	Body-weight finding	Lean-mass finding	Interpretation for muscle
STEP 1	Semaglutide 2.4 mg	Placebo	Marked reduction	Absolute lean mass decreased in DXA substudy	Lean-mass reduction did not establish functional impairment
STEP 2	Semaglutide 2.4 mg	Placebo/1.0 mg	Greater weight loss with 2.4 mg	Body-composition/function not primary endpoint	Functional effect cannot be inferred
STEP 1 DXA	Semaglutide 2.4 mg	Placebo	Major weight reduction	Fat mass declined substantially; absolute lean mass also declined	Relative lean proportion increased
SURMOUNT-1 DXA	Tirzepatide	Placebo	−21.3% vs −5.3%	−10.9% vs −2.6% lean mass	Approximately 25% of weight loss was lean mass
STEP 5	Semaglutide 2.4 mg	Placebo	−15.2% vs −2.6% at 104 wk	Body composition not primary endpoint	Long-term weight reduction demonstrated
STEP 8	Semaglutide 2.4 mg	Liraglutide 3.0 mg	−15.8% vs −6.4%	Body composition not primary endpoint	Greater weight reduction does not itself establish greater muscle loss
SURMOUNT-4	Continued tirzepatide	Withdrawal/placebo	Continued treatment maintained weight reduction	Muscle outcome not primary endpoint	Demonstrates importance of treatment continuation
SURMOUNT-3	Tirzepatide + lifestyle	Placebo + lifestyle	Additional major weight reduction	Functional muscle outcome not primary endpoint	Lifestyle intervention may influence body-composition preservation

Table 3: Evidence specifically relevant to muscle strength and physical performance

Outcome	Evidence identified	Overall observation
Handgrip strength	Recent GLP-1RA muscle-health systematic review	Directly evaluated in a subset of studies; findings were heterogeneous.
Lower-limb strength	Limited comparative evidence	Insufficient consistent data for a definitive pooled conclusion
6-minute walk distance	Limited evidence among major obesity RCTs	Not routinely included as a primary endpoint
Gait speed	Limited	Insufficient comparable data

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Outcome	Evidence identified	Overall observation
Timed Up-and-Go	Limited	Insufficient comparable data
Chair-stand/sit-to-stand	Limited	Insufficient standardized comparative evidence
Short Physical Performance Battery	Limited	Not consistently reported in major GLP-1 obesity trials
Lean/fat-free mass	Relatively extensive evidence	Consistent reduction in absolute lean mass with substantial pharmacological weight loss
Relative lean mass	Several body-composition analyses	Generally preserved or increased as a proportion of total body weight
Muscle quality	Emerging evidence	Requires further standardized investigation

Across the cited literature, the most consistent finding was substantial pharmacological weight loss accompanied by a reduction in absolute lean mass. For example, the SURMOUNT-1 DXA substudy found a 21.3% reduction in body weight and a 10.9% reduction in lean mass with tirzepatide over 72 weeks, with approximately 75% of weight lost attributable to fat mass and 25% to lean mass. Semaglutide similarly produced substantial weight reduction in STEP 1, STEP 2, STEP 5 and STEP 8, while body-composition analyses indicated reductions in absolute lean mass.

However, the major obesity trials were primarily designed around body weight and metabolic outcomes rather than muscle strength or objective physical performance. Consequently, the evidence base for direct functional outcomes is considerably smaller than the evidence base for lean mass. The newer muscle-health evidence synthesis specifically incorporating hand strength supports the need to analyze muscle function separately from DXA-derived lean mass.

DISCUSSION

The present systematic review and meta-analysis examined whether GLP-1–based pharmacotherapy influences muscle strength and objective physical performance in adults with overweight or obesity. The central finding is that GLP-1–based treatment consistently produces substantial weight reduction and is frequently accompanied by a reduction in absolute lean mass; however, the available evidence does not establish a proportional or clinically meaningful deterioration in muscle strength or objective physical performance. This distinction is important because lean mass is a composite measurement and cannot be regarded as a direct surrogate for functional skeletal muscle. Recent evidence similarly emphasizes that the clinical consequences of GLP-1-associated lean-mass reduction remain uncertain because relatively few trials directly assess strength or physical performance.

The findings are consistent with the pivotal STEP 1 trial by Wilding et al. [1], in which once-weekly semaglutide produced substantial weight reduction in adults with overweight or obesity. Although the trial was primarily designed to assess weight and cardiometabolic outcomes rather than muscle function, its results established the magnitude of weight loss achievable with GLP-1-based pharmacotherapy. The absence of systematic muscle-

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strength testing in such a large trial highlights an important evidence gap addressed by the present review.

The STEP 2 trial by Davies et al.[2] further demonstrated that semaglutide 2.4 mg produced greater weight reduction than lower-dose semaglutide and placebo among adults with overweight or obesity and type 2 diabetes. However, functional muscle outcomes were not a principal endpoint. Thus, these findings support the efficacy of GLP-1 therapy for weight reduction but cannot by themselves determine whether the accompanying weight loss affects muscle function.

The exploratory body-composition analysis of STEP 1[3] provides a more direct context for the present findings. Semaglutide reduced both fat mass and absolute lean body mass, while the proportion of lean mass relative to total body weight increased. This is an important distinction: an absolute decline in lean mass does not necessarily mean that skeletal-muscle function has deteriorated. The present review therefore supports interpreting lean-mass changes alongside direct measures of strength and physical performance rather than treating lean mass as a functional endpoint.

The STEP 1 extension[4] demonstrated substantial weight regain following withdrawal of semaglutide, emphasizing that obesity pharmacotherapy is generally a chronic treatment strategy rather than a short-term intervention. From a muscle-health perspective, repeated cycles of weight loss and regain may have implications for body composition and physical function, although available evidence remains insufficient to establish whether weight cycling caused by treatment withdrawal produces clinically important muscle consequences.

The SURMOUNT-1 trial by Jastreboff et al.[5] expanded the evidence base by demonstrating substantial, dose-dependent weight reduction with tirzepatide. Because tirzepatide combines GIP and GLP-1 receptor activity, its effects cannot necessarily be assumed to be identical to those of conventional GLP-1 receptor agonists. Nevertheless, the trial again primarily addressed body weight rather than direct muscle performance.

The SURMOUNT-1 DXA substudy by Look et al.[6] provides particularly relevant evidence. Tirzepatide treatment produced reductions in body weight, fat mass, and lean mass, with approximately 75% of the weight lost attributable to fat mass and 25% to lean mass. Specifically, body weight decreased by 21.3%, fat mass by 33.9%, and lean mass by 10.9% with tirzepatide, compared with smaller changes with placebo. These findings demonstrate that absolute lean-mass loss accompanies substantial pharmacological weight reduction, but they do not demonstrate impaired muscle function.

The systematic review and network meta-analysis evaluating GLP-1-based therapies and body composition[7] similarly reported reductions in absolute lean mass alongside reductions in total body weight. Importantly, the relative preservation or increase in lean mass as a proportion of total body weight suggests that the majority of weight lost is derived from fat rather than lean tissue. This reinforces the interpretation that the absolute amount of lean mass lost should be considered in the context of the much larger reduction in adipose tissue.

The recent systematic review and meta-analysis specifically examining GLP-1 receptor agonists at obesity-management doses[8] provides particularly important support for the present analysis. Seven randomized trials involving 821 participants demonstrated an increase in lean mass as a proportion of total body weight but a significant reduction in absolute

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lean mass. The pooled absolute reduction was approximately 1.74 kg, while substantial heterogeneity was observed, particularly for absolute and percentage lean-mass outcomes. The inclusion of hand-strength outcomes in this newer evidence base is important because it moves the field beyond body composition toward functional assessment.

The broader systematic review of GLP-1 receptor agonists and musculoskeletal outcomes[9] similarly found a significant reduction in lean body mass/fat-free mass, with considerable statistical heterogeneity. Across 28 studies, the pooled standardized mean difference indicated reduced lean mass/fat-free mass, although the certainty of evidence was low and the authors emphasized that whether these changes translate into clinically meaningful impairment of muscle function or physical performance remains uncertain. This conclusion closely corresponds to the principal finding of the present review.

The STEP 5 study by Garvey et al.[10] demonstrated that semaglutide could maintain substantial weight reduction over two years. Although long-term body-weight reduction is clinically important, the lack of systematic muscle-strength endpoints again illustrates that duration of weight loss does not automatically provide evidence regarding preservation of functional muscle.

The STEP 8 trial[11] compared semaglutide with liraglutide and demonstrated greater weight reduction with semaglutide. These findings are relevant because differences in the magnitude of weight reduction may influence the absolute amount of lean mass lost. However, a greater reduction in body weight should not automatically be interpreted as greater functional muscle impairment. Functional endpoints need to be measured directly.

The SURMOUNT-4 trial[12] demonstrated that continued tirzepatide treatment maintained or further reduced body weight, whereas treatment withdrawal was associated with weight regain. These findings reinforce the importance of treatment continuation but also raise a clinically relevant question regarding whether repeated treatment and withdrawal cycles influence lean mass and muscle function. Current evidence does not adequately answer this question.

The SURMOUNT-3 trial[13] is particularly relevant because tirzepatide was evaluated after intensive lifestyle intervention. The additional weight reduction achieved with pharmacotherapy demonstrates the potential for combined lifestyle and pharmacological management. From a muscle-preservation perspective, this model is important because structured physical activity and nutritional support may help mitigate reductions in muscle tissue during pharmacologically induced energy restriction.

The liraglutide body-composition study by Heymsfield et al.[14] also demonstrated that pharmacological weight reduction can involve changes in both fat and lean compartments. These findings are consistent with the broader observation that some lean-mass reduction is expected during substantial weight loss, irrespective of whether weight reduction is achieved through pharmacotherapy or lifestyle intervention.

Wilding and Jacob[15] emphasized the importance of preserving skeletal muscle during pharmacological weight reduction. Their discussion supports the concept that resistance exercise, adequate protein intake, and appropriate nutritional management should accompany pharmacological treatment when preservation of muscle is a priority. This is particularly relevant because the present review suggests that body-composition changes

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alone are insufficient to determine functional consequences.

The systematic review and meta-analysis represented by reference 16 further supports the observation that GLP-1-based therapies produce substantial changes in body weight and body composition. However, the relatively limited number of studies incorporating direct functional measures reinforces the need for trials specifically designed around muscle strength and physical performance.

Reference 17, representing the emerging 2026 muscle-health evidence, further strengthens this interpretation. Contemporary evidence increasingly distinguishes lean-mass loss from functional muscle loss, recognizing that DXA-derived lean mass includes non-contractile tissues and therefore cannot by itself establish sarcopenia or functional deterioration. The recent meta-analysis found an improvement in lean mass as a proportion of total weight despite a reduction in absolute lean mass.

Recent evidence published beyond the principal trials provides additional context for interpreting the present findings. Mechanick et al.[15] emphasized strategies for minimizing muscle loss during incretin-mimetic treatment, particularly resistance exercise, adequate protein intake, and nutritional optimization. Their analysis noted that lean-mass reductions observed during semaglutide and tirzepatide treatment warrant attention but should be interpreted within the overall magnitude of weight loss.

The SURMOUNT-1 body-composition analysis[19] provides further evidence that tirzepatide-associated lean-mass reduction is not disproportionate to the overall weight reduction. Approximately three quarters of the weight lost was fat mass and one quarter lean mass, and this proportion remained relatively consistent across several clinically relevant subgroups. Thus, although absolute lean mass decreases, the dominant component of weight reduction remains adipose tissue.

The comprehensive 2026 musculoskeletal meta-analysis[20] is particularly important because it included 60 studies involving more than 1.2 million individuals and found a significant reduction in lean body mass/fat-free mass with GLP-1 receptor agonists. However, the authors emphasized that the certainty of evidence was low and that the observed changes appeared largely related to overall weight loss. Most importantly, they concluded that it remains uncertain whether these changes translate into clinically meaningful impairment in muscle function or physical performance.

A 2026 systematic review focused specifically on GLP-1 receptor agonists in metabolic dysfunction-associated steatotic liver disease[21] similarly highlights the distinction between muscle mass, strength, and muscle quality. This distinction is particularly relevant because metabolic disease populations may have pre-existing muscle dysfunction, making changes in lean mass difficult to interpret without concurrent strength or performance measurements.

Finally, recent clinically oriented literature addressing lean-mass and musculoskeletal preservation[22] has emphasized that pharmacological weight reduction should ideally be accompanied by nutritional optimization, resistance exercise, and functional monitoring. This supports an integrated approach in which successful obesity treatment is judged not only by kilograms lost but also by preservation of functional capacity.

Clinical Interpretation

Taken together, the evidence suggests that GLP-1–based pharmacotherapy does not necessarily produce

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functional muscle deterioration despite measurable reductions in absolute lean mass. The distinction is clinically important. A reduction in body weight reduces the mechanical burden imposed by obesity during walking and other weight-bearing activities, potentially allowing patients to perform physical tasks more efficiently. Consequently, a patient may lose some lean mass while maintaining or even improving functional performance.

At the same time, the available evidence should not be interpreted as demonstrating that muscle loss is clinically irrelevant. The recent literature indicates that absolute lean-mass reduction can be substantial in some patients, particularly during large or prolonged weight loss. Individuals who are older, physically inactive, nutritionally vulnerable, or already have low muscle strength may have a smaller physiological reserve. For these groups, preservation of muscle quality and strength may be particularly important.

Implications for clinical practice

The findings support an approach in which weight loss and muscle preservation are considered complementary rather than competing goals. GLP-1-based pharmacotherapy should not be assessed solely according to the amount of lean mass lost. Instead, clinicians should consider changes in muscle strength, physical activity, dietary protein adequacy, and functional performance alongside body-composition measurements.

Resistance exercise may be particularly important because pharmacological weight reduction creates a negative energy balance, whereas mechanical loading provides a direct stimulus for muscle maintenance. Nutritional strategies, including adequate protein intake, may also be useful in selected patients. Current evidence therefore supports integrating pharmacotherapy with lifestyle measures rather than viewing medication as an isolated intervention.

Strengths of the present evidence synthesis

A major strength of this review is its focus on clinically meaningful functional endpoints rather than relying exclusively on lean mass as a surrogate for muscle health. Another strength is the consideration of different GLP-1-based agents, including conventional GLP-1 receptor agonists and dual GIP/GLP-1 therapy. The review also distinguishes objective physical performance from body-composition outcomes, allowing a more clinically relevant interpretation of pharmacological weight loss.

Remaining evidence gaps

The principal limitation of the current evidence base is the relatively small number of studies directly measuring muscle strength and objective physical performance compared with the large number assessing body weight or lean mass. The recent musculoskeletal meta-analysis similarly identified the need for future studies specifically evaluating muscle function and physical performance.

Future randomized trials should therefore incorporate standardized handgrip strength, lower-limb strength, gait speed, chair-stand performance, 6-minute walk distance, and validated physical-function batteries alongside DXA or MRI-derived body composition. Long-term studies should also determine whether resistance exercise and adequate protein intake modify the relationship between pharmacological weight loss and muscle function.

Overall, the available evidence indicates that absolute lean-mass reduction is a reproducible component of GLP-1–associated weight loss, but its translation into clinically meaningful loss of muscle strength or physical

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performance remains insufficiently demonstrated. This distinction should remain central when interpreting the musculoskeletal consequences of modern incretin-based obesity pharmacotherapy.

Conclusion

GLP-1–based pharmacotherapy produces substantial and clinically meaningful weight reduction in adults with overweight or obesity and is consistently associated with reductions in absolute lean body mass. However, the available comparative evidence does not demonstrate that these changes in lean mass necessarily translate into clinically important reductions in muscle strength or objective physical performance. Functional outcomes appear more heterogeneous than body-composition outcomes and remain inadequately assessed in many major obesity trials.

The findings emphasize that lean-mass loss should not be interpreted as equivalent to functional muscle loss. Improvements in mobility and physical performance may occur as the mechanical and metabolic burden of excess body weight decreases, despite some reduction in absolute lean mass. Nevertheless, individuals with advanced age, low baseline muscle strength, physical inactivity, or nutritional vulnerability may require particular attention to muscle preservation.

Future trials should routinely incorporate standardized measurements of handgrip and lower-limb strength, gait speed, chair-stand performance, 6-minute walk distance, muscle quality, and body composition, with sufficiently long follow-up to determine the long-term functional consequences of GLP-1–based therapy. Combining pharmacotherapy with resistance exercise, adequate nutritional support, and functional monitoring may help optimize weight loss while preserving physical capacity.

Limitations

Limited direct functional evidence: Most GLP-1–based obesity trials primarily evaluated body weight and body composition, while standardized measures of muscle strength and objective physical performance were not routinely reported.

Substantial heterogeneity: Differences in GLP-1 agents, doses, treatment duration, participant characteristics, comparator interventions, and methods used to assess muscle and physical performance contributed to between-study heterogeneity.

Lean mass is an imperfect surrogate: DXA-derived lean mass or fat-free mass cannot be equated directly with skeletal-muscle mass or muscle function, limiting interpretation of studies that reported body-composition outcomes without strength testing.

Variation in functional measurements: Handgrip strength, gait speed, chair-stand tests, 6-minute walk distance, and other performance measures assess different aspects of physical function, making direct pooling difficult.

Limited long-term data: Follow-up beyond the duration of most randomized trials remains limited, particularly regarding sustained effects on muscle strength and physical performance.

Potential confounding by lifestyle interventions: Dietary counseling, physical activity, and resistance exercise varied among studies and may have influenced muscle outcomes independently of pharmacological treatment.

Drug-class heterogeneity: Conventional GLP-1 receptor agonists and dual GIP/GLP-1 agonists such as tirzepatide may have different effects, while the number of directly comparable studies for individual agents remains limited.

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Population heterogeneity: Differences in age, sex, baseline obesity severity, diabetes status, baseline physical activity, and pre-existing functional status may limit.

Future Prospects

Long-term functional studies: Future randomized controlled trials should evaluate the effects of GLP-1–based therapies on muscle strength and physical performance over several years rather than focusing predominantly on short-term weight and body-composition changes.

Standardized muscle-function assessment: Trials should routinely include validated measures such as handgrip strength, knee-extension strength, gait speed, chair-stand performance, Timed Up-and-Go, 6-minute walk distance, and Short Physical Performance Battery.

Better characterization of muscle tissue: DXA should be complemented by techniques such as MRI, CT, ultrasound, or bioimpedance where appropriate to distinguish skeletal-muscle tissue from other components of lean mass and to assess muscle quality.

Integration of resistance exercise: Future studies should directly evaluate whether structured resistance training can preserve or improve muscle strength during GLP-1–associated weight loss.

Nutritional optimization: Trials should investigate the role of adequate protein intake and individualized nutritional strategies in preserving lean tissue and functional capacity during pharmacological weight reduction.

Drug-specific comparisons: Head-to-head studies should compare semaglutide, liraglutide, tirzepatide, and other incretin-based therapies to determine whether their effects on muscle quantity, strength, and performance differ.

Identification of vulnerable populations: Particular attention should be given to older adults, individuals with low baseline muscle strength, sarcopenia, physical inactivity, or metabolic disease, who may have greater functional vulnerability during weight loss.

Assessment of muscle quality: Future research should move beyond measuring muscle quantity and investigate muscle strength relative to muscle mass, contractile quality, intramuscular fat, and neuromuscular function.

Combination-treatment strategies: Studies should determine whether combining GLP-1–based pharmacotherapy with resistance exercise, adequate protein intake, and physical-activity programs produces better functional outcomes than pharmacotherapy alone.

Patient-centered outcomes: Future research should evaluate whether changes in muscle strength and physical performance translate into meaningful improvements in mobility, independence, quality of life, exercise capacity, and long-term health outcomes.

Declarations

Consent for publication: There is consent for the publication of this Article.

Authors' contributions: All authors contributed equally.

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