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EDITORIAL

Glucagon-like peptide-1 receptor agonists and muscle: interpreting lean mass changes in clinical care

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Abstract

Skeletal muscle supports mobility and metabolic reserve. Low muscle reserve is common in obesity, type 2 diabetes mellitus (T2DM), and metabolic-associated steatotic liver disease, where myosteatosis and insulin resistance are linked to poorer strength and physical performance. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve weight and glycemic control, but body composition studies often report reductions in measured lean mass alongside fat mass loss. Interpretation is complicated because lean mass and fat-free mass are not direct measures of contractile muscle and are sensitive to hydration and measurement modality, particularly with dual-energy X-ray absorptiometry and bioelectrical impedance analysis. A network meta-analysis of 22 randomized trials (n=2258) reported mean reductions of 3.55 kg in body weight, 2.95 kg in fat mass, and 0.86 kg in lean mass, with lean tissue contributing about one-quarter of total weight loss. A recent meta-analysis of 38 studies (n=1735) found smaller muscle changes in T2DM (mean reduction: 0.74 kg) than in populations without T2DM (mean reduction: 1.41 kg). In addition, imaging cohorts involving computed tomography show modest declines in muscle area and attenuation after semaglutide. More recently, SEMALEAN study reported 13% weight loss and 19% fat mass loss at 12 months, with early lean mass decline followed by stability, and improved handgrip strength. Clinical decisions should prioritize function over lean mass alone and pair GLP-1RA therapy with resistance training and adequate protein intake, with closer monitoring in older adults and other high-risk phenotypes.

Key words: glucagon-like peptide-1 receptor agonists, receptor agonists, body composition.

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Introduction

Skeletal muscle is not only a structural tissue for movement, but also a fundamental determinant of physiological reserve. Skeletal muscle supports mobility, protects against falls and disability, and provides metabolic capacity during illness and recovery.[1] Reduced muscle reserve is highly prevalent in the setting of cardiometabolic multimorbidity and contributes to impaired exercise tolerance, diminished functional capacity, and increased risk of disability, particularly among older adults with sarcopenia.[2-4] In obesity, type 2 diabetes mellitus (T2DM), and metabolic-associated steatotic liver disease (MASLD) changes in lean mass warrant careful interpretation. Metabolic disease–related alterations in muscle composition, including myosteatosis, impaired mitochondrial function, and insulin resistance, are closely associated with reduced muscle strength, impaired physical performance, and heightened multisystem cardiometabolic risk.[5-8] Thus, preservation of muscle quality and quantity represents a clinically relevant objective in populations already vulnerable to functional decline. Weight reduction and glycemic optimization remain central to the management of obesity, T2DM, and related cardiometabolic disorders, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are now routinely incorporated into clinical practice for these indications.[9] Although GLP-1RA therapy confers meaningful cardiometabolic benefits, body composition sub-studies and real-world imaging studies have consistently demonstrated reductions in absolute lean mass accompanying greater losses in adipose tissue. The magnitude of lean mass decline varies according to agent, dose, treatment duration, baseline phenotype, and measurement modality.[1,10-13] This ob-

servation has attracted increasing clinical attention because additional reductions in lean tissue among individuals with already limited muscle reserve may plausibly exacerbate insulin resistance, frailty, and vulnerability to adverse outcomes, even in the context of an overall weight loss that is metabolically favorable.[1-3]

Body composition and measurement

Fat mass refers to adipose tissue. Lean mass and fat-free mass (FFM) refer to non-fat compartments, but the terms are not interchangeable, and neither should be equated with contractile skeletal muscle mass. Dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) can provide practical estimates of body composition. DXA estimates fat mass and lean mass from X-ray attenuation, with FFM derivable by adding bone mineral content, whereas BIA estimates FFM primarily from total body water using prediction equations. Accordingly, alterations in hydration status may meaningfully affect lean mass estimates obtained by either modality which therefore require cautious interpretation at the individual level, particularly when preservation of skeletal muscle is the primary clinical objective.[14,15] Computed tomography (CT) and magnetic resonance imaging (MRI) provide more anatomical proxies of muscle quantity and assess muscle quality through fat infiltration, which is clinically relevant because myosteatosis is associated with poorer strength and mobility and may change independently of muscle size.[6,7] This framework is relevant for GLP-1RA-associated weight loss because lean mass and FFM are indirect body composition constructs and can be influenced by non-muscle compartments and hydration, whereas strength and performance more directly reflect contractile function and clinical reserve. Accordingly, lean tissue changes are most interpretable when reported alongside the measurement modality and at least one functional or quality-sensitive marker rather than treated as stand-alone evidence of skeletal muscle loss.[2,6,7,10]

Current evidence

A recent network meta-analysis of 22 randomized controlled trials comprising 2,258 participants evaluated the effects of GLP-1 receptor agonists and related incretin-based therapies on body composition. Active treatment was associated with a reduction in total body weight of 3.55 kg, driven by decreases in fat mass (2.95 kg) and lean mass (0.86 kg), indicating that approximately one-quarter of the overall weight loss was attributable to lean tissue. Notably, the percent change in lean mass from baseline did not differ significantly across treatment comparisons.[16] Additionally, liraglutide administered at 1.8 mg or 3.0 mg daily achieved significant weight reduction without a statistically significant lean mass reduction, whereas semaglutide 2.4 mg and tirzepatide 15 mg produced the greatest reduction in body weight and fat mass, but ranked less favorably for lean mass preservation.[16] A 2025 systematic review and meta-analysis encompassing 38 studies and 1735 participants similarly demonstrated modest reductions in lean mass relative to fat mass loss. In a separate meta-analysis focused specifically on populations with T2DM (24 studies; n=850), muscle mass was not significantly reduced (mean change −0.74 kg) despite a concomitant decrease in fat mass of −3.18 kg. In contrast, among participants without T2DM, muscle mass declined by −1.41 kg alongside a fat mass reduction of −6.02 kg. Across populations, lean tissue accounted for less than 20% of total weight loss, underscoring the predominance of adipose reduction in incretin-based therapy-associated weight change.[1] These pooled estimates define average lean change, but clinical meaning remains uncertain because function and muscle quality endpoints are inconsistently reported.[1,16]

Newer studies sharpen clinical interpretation by adding imaging granularity and functional readouts. In a recent cohort study by Wang *et al.,* which compared bariatric surgery (n=1257) with GLP-1 receptor agonist therapy (n=1809) over 24 months, GLP-1RA treatment was associated with substantial reductions in fat mass and relatively modest declines in fat-free mass of approximately 2% to 3%.[17] In a CT-based, within-person imaging study by Nelson *et al*. (2024), initiation of semaglutide was associated with reductions in skeletal muscle cross-sectional area and muscle attenuation on follow-up imaging. These findings suggest that tissue-level changes in muscle quantity and quality may be detectable by advanced imaging modalities, even when conventional clinical endpoints, such as total body weight or glycemic control demonstrate apparent improvement.[13] In contrast, in the prospective DXA-based SEMALEAN study (semaglutide 2.4 mg), weight reduced by 13% at 12 months, while fat mass decreased by 19%. Lean mass declined initially by 5% and then remained stable through 12 months, handgrip strength improved, and the prevalence of sarcopenic obesity decreased from 49% to 33% at 12 months.[18] A similar conclusion is supported by the post-hoc analysis of the SURPASS-3 trial, which observed reduced muscle adiposity with a modest loss in muscle volume.[5] Taken together, these studies suggest that fat loss generally exceeds lean loss during GLP-1-based weight reduction. Lean-preservation strategies are now being evaluated in registry-posted and ongoing studies, and trials pairing GLP-1 therapy with resistance training and protein optimization (LEAN-PREP, NCT06885736; BICEP, NCT07226947), as well as add-on approaches that target DXA-measured lean mass and functional endpoints (PROACT, NCT07101939) (Table 1).

Function-focussed interpretation and practical framework for care

Lean mass is a body composition construct, not a clinical endpoint. Interpretation should be anchored to muscle function and quality, consistent with sarcopenia frameworks that prioritize low strength and use muscle quantity or quality as confirmatory domains.[2,3] Vulnerability concentrates in patients who start GLP-1-based therapy with a limited reserve or high consequence from small functional losses. This included older

patients with co-morbidities such as CKD, lung disease and heart failure. A function-focused framework for interpreting lean mass changes during GLP-1RA therapy is shown in Figure 1.

From a clinical perspective, lean mass changes during GLP-1RA therapy are best interpreted in relation to muscle function, with assessment beginning before dose escalation. First, define baseline reserve and risk using measures that can be implemented in routine care. Document recent unintentional weight loss, dietary intake risk, and activity limitation, and capture at least one functional marker such as handgrip strength, repeated chair raises, or gait speed when feasible.[2,3] Second, match monitoring intensity to phenotype. In lower-risk obesity treatment, weight trajectory and symptoms may be sufficient, with selective DXA or BIA to contextualize body composition change. In higher-risk phenotypes, add serial functional assessments and, when available via clinical imaging, incorporate quantitative and qualitative muscle information from CT or MRI to contextualize lean

Table 1. Effects of glucagon-like peptide-1-based therapies on body composition and muscle: published evidence, completed registry results, and ongoing trials.

Study and status	Population and design	Intervention and comparator	Follow-up	Body composition methods	Change in body weight	Change in fat mass	Change in lean mass/FFM
Randomized controlled trials							
McCrimmon *et al.* 2020	Randomized substudy; T2DM; DXA subset n=178	Semaglutide 1.0 mg weekly *vs* canagliflozin 300 mg daily	52 weeks	DXA (total mass, FM, LM)	-5.7 *vs* -4.1 kg	-3.0 *vs* -2.3 kg (total FM)	-2.3 *vs* -1.5 kg (total LM)
Wilding *et al.* 2021	RCT body-composition subset; overweight/obesity (no diabetes) n=140	Semaglutide 2.4 mg weekly *vs* placebo (both + lifestyle)	68 weeks	DXA	-15.0% *vs* -3.6%	Total FM -19.3%; visceral FM -27.4% (semaglutide)	Lean body mass -9.7% (semaglutide)
NCT05616013	Phase 2; overweight/obesity; enrollment 507; completed	Bimagrumab (IV; dose arms) + semaglutide (1.0 or 2.4 mg) *vs* placebo + semaglutide	48 weeks (core); includes week-72 follow-up endpoints	DXA + BIA	NR	BIA: Delta body fat mass at week 48: -5.64 kg (bimagrumab+ sema 2.4) *vs* -2.78 kg (placebo+ sema 2.4)	DXA: Delta lean mass at week 48: +0.5 kg (bimagrumab+ sema 2.4) *vs* -0.5 kg (placebo+ sema 2.4)
SURPASS-3 MRI	Post hoc imaging substudy of RCT; T2DM; MRI cohort n=396	Tirzepatide 5/10/15 mg weekly *vs* insulin degludec	52 weeks	MRI thigh	Pooled tirzepatide -10.1% (95% CI -11.2 to -9.0)	NR	Muscle volume -0.64 L (95% CI -0.77 to -0.51); muscle fat infiltration -0.36 percentage points (95% CI -0.65 to -0.08)
Observational study							
Nelson *et al.* 2024	Retrospective clinical cohort; semaglutide initiators n=241; weight-loss subgroup n=67	Semaglutide in routine care (no control)	Mean post-treatment CT ~263 days (subgroup)	CT abdomen (L3)	-10.8 kg (subgroup)	SAT area -9.6%; VAT area -9.3% (subgroup)	Skeletal muscle area -7.1% (subgroup)
Alissou *et al.* 2026	Prospective real-world study; obesity; enrolled n=115; completed n=106	Semaglutide 2.4 mg weekly (no control)	12 months (M7 and M12)	DXA + function tests	-9.8% (M7); -12.7% (M12)	-14.3% (M7); -18.9% (M12)	Lean mass -3.0 kg by M7; stable to M12
Wang *et al.* 2026	Retrospective cohort; obesity; GLP-1RA n=1809; surgery n=1257	Semaglutide or tirzepatide *vs* bariatric surgery	Up to 24 months	BIA	NR	GLP-1RA: FM -10.3% (6 mo), -17.3% (12 mo), -18.0% (24 mo)	GLP-1RA: FFM -1.8% (6 mo), -3.0% (12 mo), -3.3% (24 mo)
NCT05302596	Single-center, prospective, randomized, open-label; age >=65; obesity; n=16	Semaglutide 0.25->1.0 mg weekly + lifestyle *vs* lifestyle (SOC)	16 weeks	DXA	107.8->99.7 kg (Delta -8.1) *vs* 100.0->97.1 kg	(Delta -2.9) 52.1->46.8 kg (Delta -5.3) *vs* 47.8->46.3 kg (Delta -1.5)	51.0->49.5 kg (Delta -1.5) *vs* 47.8->47.0 kg (Delta -0.8)

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changes and myosteatosis.[6,7,13] Third, prescribe muscle protection alongside the drug rather than after a decline is detected. Encourage progressive resistance training early and support adequate protein intake, with escalation of support in older adults and in CKD or MASLD, where anabolic responsiveness may be reduced. This aligns with global implementation guidance in obesity care that emphasizes integrated lifestyle and pharmacotherapy strategies and reinforces resistance training to preserve lean mass during weight loss.[19] Fourth, establish clear clinical triggers for reassessment. New or progressive weakness, slower chair-rise performance, reduced walking tolerance, or declining grip strength during active weight loss should prompt evaluation for inadequate energy or protein intake, acute medical events, reduced physical activity, or excessive treatment intensity. In such cases, management should prioritize individualized adjustment of nutrition and appropriately scaled physical activity interventions rather than reflex discontinuation of otherwise effective therapy. Heart failure, especially with preserved ejection fraction (HFpEF) and associated obesity exemplifies the existing implementation gap for people who benefit from weight loss but are at high risk for muscle loss and dysfunction.[20-22]

Future directions

The next phase of evidence should define clinical meaning by quantifying the average change in lean mass. Studies should pre-specify functional endpoints as primary or co-primary outcomes, including strength, chair rise performance, gait speed, walking tolerance, and patient-reported physical function. These outcomes should be interpreted in light of the body composition modality used (*e.g.*, DXA, BIA, CT, or MRI) and reported with sufficient context to avoid misinterpretation. Combination strategies are the logical frontier. Trials should evaluate GLP-1-based therapy paired with structured resistance training and protein adequacy, and test adjunctive ap-

Table 1. Continued from previous page.

Study and status	Population and design	Intervention and comparator	Follow-up	Body composition methods	Change in body weight	Change in fat mass	Change in lean mass/FFM
Ongoing studies							
NCT06732245	Interventional; adults 18-80; BMI >=30 or >=27 plus	NA-931 oral (with placebo control) and/or comorbidity tirzepatide (per arms)	48 weeks (planned)	DXA + BIA (planned)	NR (ongoing)	NR (ongoing)	Planned: lean body mass and fat mass outcomes (DXA/BIA)
NCT06885736	Randomized, 4-arm; obesity; target n=232	Control *vs* resistance exercise *vs* protein (goal 1.6 g/kg/day incl leucine) *vs* combined; all on sema/tirzepatide	6 months	DXA + thigh MRI (quadriceps CSA)	NR (ongoing)	NR (ongoing)	Primary: Delta lean mass (DXA); secondary: quadriceps CSA (MRI)
NCT07091500	Interventional; obesity; target ~40	GLP-1RA therapy with exercise t raining intervention	26 weeks	DXA + D3-creatine + thigh MRI + function tests	NR (ongoing)	NR (ongoing)	Secondary: muscle mass (D3-creatine), muscle volume (MRI), DXA composition
NCT07101939 - PROACT	Interventional; obesity during/post semaglutide therapy	(S)-Pindolol benzoate (ACM-001.1) *vs* placebo (arms per protocol)	20 weeks (per endpoints)	Body composition endpoints include regional lean body mass	NR (ongoing)	NR (ongoing)	Includes Delta lean body mass endpoint
NCT07115069 - REFORM	Randomized; obesity; target n~72	Tirzepatide *vs* semaglutide *vs* lifestyle	24 weeks	DXA	NR (ongoing)	Primary: change in body fat percent (DXA)	Lean tracked (ongoing)
NCT07226947 - BICEP	Randomized; obesity starting GLP-1 agonist; target n~30	Exercise *vs* control during GLP-1 therapy	24 weeks	DXA + activity monitoring + strength tests	NR (ongoing)	NR (ongoing)	Secondary: lean mass and fat mass by DXA
NCT07272837 - GLIMMER:	Observational; semaglutide users; planned n~300	Semaglutide exposure (observational)	12 months	DXA + cardiac imaging (per record)	NR (ongoing)	NR (ongoing)	Primary: change in skeletal muscle mass and cardiac muscle mass (ongoing)

DXA, dual-energy X-ray absorptiometry; T2DM, type 2 diabetes mellitus; BIA, bioelectrical impedance analysis; FM, fat mass; FFM, fat-free mass; LM, lean mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; CSA, cross-sectional area; L3, third lumbar vertebra CT level; 6MWD, 6-minute walk distance; NR, not reported.

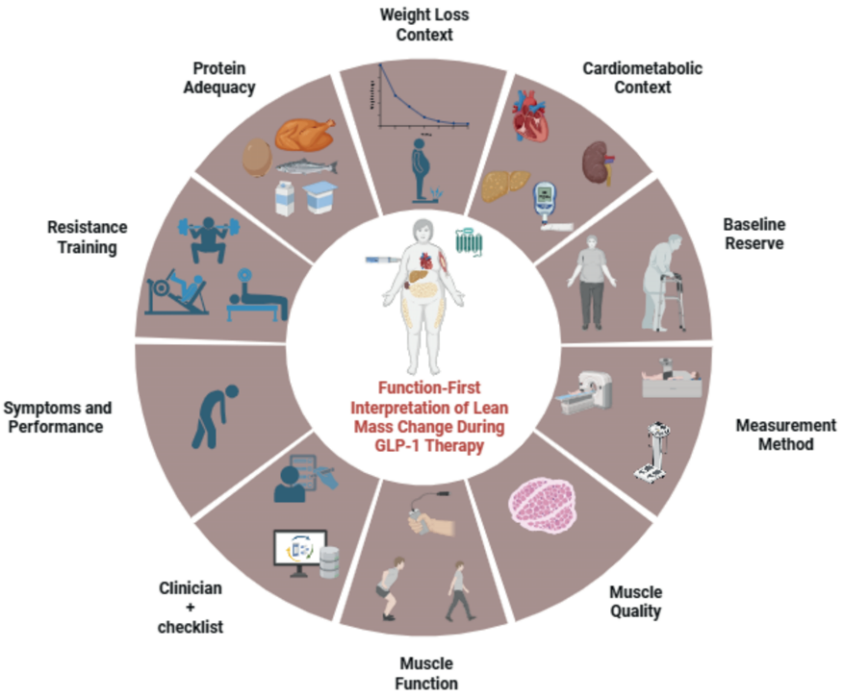

Figure 1. Function-focused framework for interpreting lean mass changes during glucagon-like peptide-1 (GLP-1) receptor agonist therapy. At the center, lean mass change is anchored to muscle function as the primary determinant of clinical relevance. Interpretation is modified by the weight-loss context, including the magnitude and trajectory of weight reduction, and by the cardiometabolic context, reflecting underlying conditions such as obesity, type 2 diabetes mellitus, and related metabolic disease. Baseline muscle reserve denotes pre-treatment muscle mass and functional capacity, which shapes

proaches intended to preserve FFM while maintaining cardiometabolic benefit. Lean mass decline can accompany effective GLP-1-based weight loss, but the actionable signal is deterioration in strength, mobility, or exercise capacity. When function is stable or improving, modest reductions in DXA or BIA lean mass should rarely prompt discontinuation of therapy that is improving cardiometabolic risk. Instead, clinicians should treat muscle preservation as a co-therapy from the start. Identify baseline vulnerability, monitor at least one simple functional marker over time, and intensify resistance training and nutrition support if functional decline emerges. This approach helps patients retain physical reserve while capturing the metabolic and cardiovascular gains that motivated treatment.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no potential conflict of interest.

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