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About the Author

Michael Tsoukas, MD

Dr. Michael Tsoukas is an Associate Professor of Medicine, Division of Endocrinology of the McGill University Health Centre and Research Investigator of the Research Institute of McGill and Hygea Medical Clinic. He completed his residency in medicine at Tuft's University in Boston and subsequently trained in Endocrinology at McGill University. Upon completion, he pursued a post-graduate research fellowship in diabetes and obesity at Harvard University, with a focus on GLP-1 receptor pharmacotherapy, brain signaling, and enterohormone treatments. Further training involved pathophysiological regulation of GLP-1 receptor agonists important in energy homeostasis, diabetes, and obesity. Currently, Dr. Tsoukas is the Co-Director of the Metabolic Centre of Excellence of the McGill University Health Centre and Director of Endocrinology at the Montreal General Hospital. He continues to conduct clinical interventional studies and has authored over 50 articles in peer-reviewed journals, chapters, and abstracts.

Affiliations:
Associate Professor of Medicine, Division of Endocrinology
Co-Director, Metabolic Centre of Excellence and Metabolic Weight Optimization Clinic McGill University Health Centre, Montreal, QC

Losing Weight, Losing Muscle? Muscle Health During GLP-1-Based Obesity Therapy

Michael Tsoukas, MD

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related nutrient-stimulated hormone (NuSH) therapies have transformed obesity pharmacotherapy, delivering weight loss approaching that seen with bariatric surgery.[1-4] However, concerns have emerged regarding loss of fat-free mass, skeletal muscle mass, and possible sarcopenia. Reductions in lean mass occur during treatment with semaglutide and tirzepatide, but these changes are generally proportional to total weight loss and occur alongside greater reductions in fat mass, visceral adiposity, and ectopic lipid deposition.[1,5,6] The clinical interpretation of lean mass loss is further complicated by limitations of dual-energy X-ray absorptiometry, which cannot distinguish contractile muscle from body water, organs, and connective tissue.[6] Importantly, available data suggest that muscle quality and metabolic function may improve despite reductions in absolute lean mass.[6] Overall, current evidence does not support disproportionate skeletal muscle loss during GLP-1-based obesity therapy. This review summarizes current evidence on GLP-1RA and NuSH-associated changes in muscle mass, discusses mechanisms, identifies populations at risk, and outlines practical strategies to preserve muscle health during treatment.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related nutrient-stimulated hormone (NuSH) therapies have transformed obesity pharmacotherapy, producing weight loss that approaches outcomes historically associated with bariatric surgery.[1-4] The approval of GLP-1RAs, such as semaglutide and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) such as tirzepatide, have changed the therapeutic landscape of obesity management. In the STEP 1 trial, once-weekly semaglutide 2.4 mg produced a mean body-weight reduction of 14.9% at 68 weeks,[1] while in the SURMOUNT-1 trial, tirzepatide produced mean reductions of up to 20.9% at 72 weeks.[3] Current evidence indicates that reductions in lean mass occur during treatment with semaglutide and tirzepatide, but these changes are generally proportional to total weight loss and occur alongside larger reductions in fat mass, visceral adiposity, and ectopic lipid deposition.[1,5,6]

These benefits have raised an important clinical question: does incretin-based pharmacological weight loss compromise skeletal muscle? This question is particularly relevant for those at higher risk for muscle loss, including older adults, patients with sarcopenic obesity, and individuals with low baseline muscle reserve. Skeletal muscle is central to mobility, insulin-stimulated glucose disposal, resting energy expenditure, and healthy aging.[7,8] Loss of muscle mass and strength is associated with frailty, falls, disability, and adverse metabolic outcomes.[9]

However, lean-mass loss during weight reduction is not unique to GLP-1RAs or other NuSH therapies. Across dietary restriction, bariatric surgery, and pharmacotherapy, approximately 20–40% of total weight loss may derive from fat-free mass.[8,10] Therefore, the central clinical issue is not whether lean mass decreases, but whether the magnitude, composition, and functional consequences of this decrease are maladaptive.

Recent expert analyses have challenged the assumption that reductions in lean mass necessarily indicate clinically meaningful muscle loss. Neeland et al. highlighted the substantial variability in reported lean-mass changes across GLP-1-based therapies and emphasized that lean mass should be interpreted in the context of muscle composition, function, metabolic health, and overall weight loss.[11] Likewise, Conte et al. argue that weight-loss–associated reductions in fat-free mass are expected physiological adaptations and should be evaluated according to their effects on strength, mobility, physical function, and long-term health outcomes rather than body-composition measurements alone.[12] Together, these perspectives suggest that the effects of GLP-1-based therapies on skeletal muscle are more complex than changes in lean mass alone and require a broader assessment of muscle health.

Evidence of Body Composition Changes

Body Composition Changes With Liraglutide

Liraglutide was the first GLP-1 receptor agonist approved for obesity treatment, with efficacy established in the SCALE trial program. Although body-composition data are limited, a magnetic resonance imaging (MRI)-based randomized controlled trial involving 128 participants demonstrated a significant reduction in thigh muscle fat infiltration with liraglutide compared with placebo, while muscle volume remained unchanged.[13] These findings suggest that liraglutide may improve muscle quality through reductions in intramuscular fat without adversely affecting muscle mass, a pattern that is consistent with observations reported for newer GLP-1-based therapies. However, functional muscle outcomes were not assessed.

Body Composition Changes With Semaglutide

The STEP 1 body-composition substudy provides the most frequently cited and robust semaglutide data. In adults with overweight or obesity without diabetes, semaglutide 2.4 mg reduced total fat mass by 19.3% and visceral fat mass by 27.4% over 68 weeks.[1] Lean body mass also declined by 9.7%; however, fat mass decreased to a substantially greater extent. Consequently, the proportion of body weight represented by lean mass increased by approximately 3 percentage points, and the lean mass-to-fat mass ratio improved.[1] These findings suggest favourable body-composition remodelling despite reductions in absolute lean mass.

The commonly cited concern is that a sizable fraction of total weight loss observed in the STEP 1 trial reflected lean mass. This finding should be interpreted cautiously. First, dual-energy X-ray absorptiometry (DXA)-derived lean mass includes not only contractile skeletal muscle,

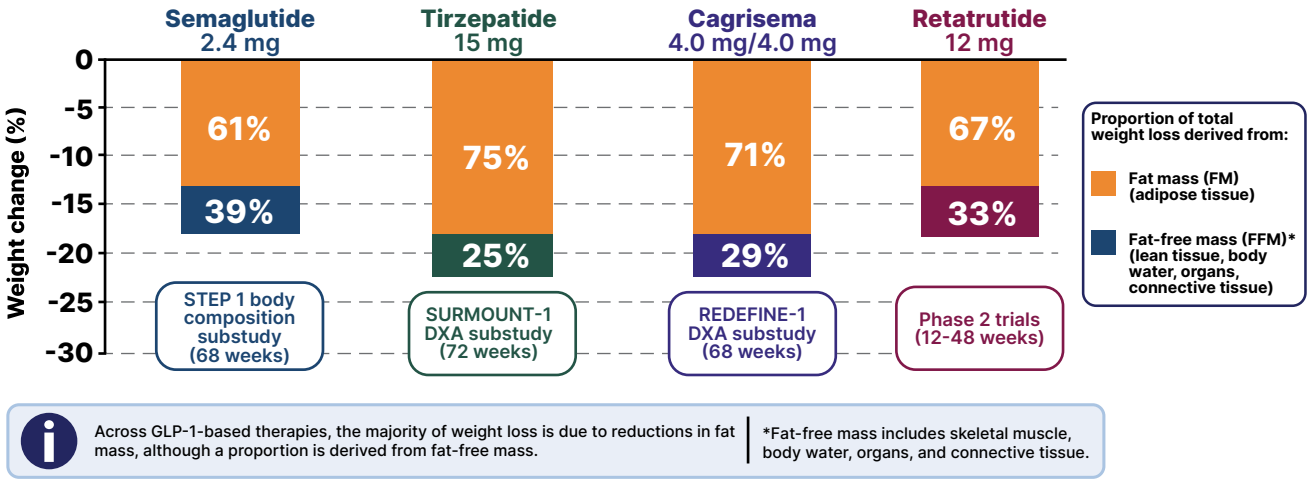

Figure 1. Composition of Weight Loss During GLP-1-Based and NuSH-Based Obesity Pharmacotherapy; *adpted from Rubino D et al. Diabetes Care. 2021;44:1988-1996 (STEP 1 body composition substudy); Look AHEAD et al. JAMA. 2022;327:1389-1400 (SURMOUNT-1 DXA substudy); Aronne LJ et al. Obesity (Silver Spring). 2024;32:2326-2334 (REDEFINE-1 DXA substudy); Rosenstock J et al. N Engl J Med. 2023;389:514-526 (retatrutide phase 2 body composition analysis).*

Note: Percentages may not sum to 100% due to rounding.

Abbreviations: DXA: dual-energy X-ray absorptiometry; **GLP-1RA:** glucagon-like peptide-1 receptor agonists

but also water, organs, connective tissue, and other non-fat compartments. Second, loss of lean tissue is expected when total body weight and mechanical loading decrease. Third, the direction of overall body-composition change was favourable, with greater reductions in adiposity than lean mass, and a relative increase in lean mass.[1,6]

Longer-term semaglutide data from the STEP 5 trial demonstrated sustained body-weight reduction over 104 weeks, although detailed muscle-function outcomes were limited.[2] Taken together, findings from the STEP program support the interpretation that semaglutide produces substantial fat loss accompanied by expected reductions in lean mass, rather than selective muscle wasting.[1,2]

Body Composition Changes With Tirzepatide

Tirzepatide produces greater mean weight loss than semaglutide in placebo-controlled obesity trials. In the SURMOUNT-1 trial, adults with obesity or overweight without diabetes treated with tirzepatide lost up to 20.9% of body weight at 72 weeks.[3]

The SURMOUNT-1 DXA substudy reported that tirzepatide reduced body weight by 21.3%, fat mass by 33.9%, and lean mass by 10.9% at week 72.5 Approximately 75% of weight lost was fat mass and 25% was lean mass, a distribution consistent with many intensive weight-loss interventions.[5] These findings are clinically reassuring because they suggest preferential reduction in adiposity rather than disproportionate depletion of lean tissue.

Direct comparisons between semaglutide and tirzepatide body-composition studies is limited by differences in trial design, populations, and methodology. Nevertheless, both agents appear to produce favourable remodelling of body composition, with fat mass accounting for the majority of total weight lost.[1,5]

Emerging New Treatments

Amylin-based therapies may represent an important development in obesity pharmacotherapy. Cagrilintide, a long-acting amylin analog, is being evaluated both as monotherapy and in fixed-dose combination with semaglutide (CagriSema). In the REDEFINE-1 trial, CagriSema produced mean weight reductions of up to 22.7% at 68 weeks. In a prespecified DXA substudy, fat mass decreased by 35.7% while lean soft-tissue mass decreased by 14.4%, with approximately two-thirds of total weight loss

Study/Source	Population	Intervention	Duration	Body-composition Findings	Clinical Interpretation
Pandey et al.[13]	Adults with overweight or obesity (n=128)	Liraglutide 3.0 mg vs placebo	36 weeks	Significant reduction in thigh muscle fat infiltration on MRI; muscle volume unchanged	Suggests improved muscle quality without adverse effects on muscle volume
STEP 1 body-composition substudy[1]	DXA substudy of STEP 1	Semaglutide 2.4 mg vs placebo	68 weeks	Fat mass—19.3%, visceral fat mass—27.4%, lean body mass—9.7%; relative lean mass proportion increased by 3.0 percentage points	Favourable body-composition remodelling despite absolute lean-mass reduction
SURMOUNT-1 DXA substudy[5]	DXA substudy (n=160)	Tirzepatide vs placebo	72 weeks	Body weight—21.3%, fat mass—33.9%, lean mass—10.9%; approximately 75% of weight lost was fat mass and 25% was lean mass	Lean-mass reduction appears proportional and not excessive relative to fat loss
REDEFINE-1 DXA substudy[14]	Adults with overweight or obesity (DXA subgroup, n=252)	CagriSema (cagrilintide + semaglutide) vs placebo	68 weeks	Fat mass—35.7%, lean soft-tissue mass—14.4%; approximately 67% of total weight loss attributable to fat mass	Suggests favourable body-composition remodelling with preferential fat-mass reduction despite absolute lean-mass loss
Linge et al.[6]	Narrative review/primer	GLP-1RA and dual incretin therapy	—	Emphasized muscle quantity, composition, and function	Argues many observed muscle changes may be adaptive rather than maladaptive

Table 1. Evidence Summary Table, Summarizing Body Composition Findings; *courtesy of Michael Tsoukas, MD.*

Abbreviations: DXA: dual-energy X-ray absorptiometry; **GLP-1RA:** glucagon-like peptide-1 receptor agonists; **MRI:** magnetic resonance imaging

attributable to fat mass and one-third attributable to lean soft tissue.[14] These findings suggest favourable body-composition remodelling similar to that observed with semaglutide and tirzepatide. The RASMUS study, which is currently ongoing, is specifically designed to evaluate the effects of CagriSema on skeletal muscle insulin sensitivity, composition, and function. However, dedicated studies evaluating skeletal muscle quality, myosteatosis, strength, and long-term functional outcomes remain limited.

NuSH triple agonists may further reshape the field of obesity treatment. Retatrutide, a GLP-1/GIP/glucagon receptor agonist, has demonstrated weight reductions approaching 24–28% in studies, approaching outcomes observed after bariatric surgery.[15] Glucagon receptor activation may enhance energy expenditure, lipid oxidation, and reductions in adiposity, but human evidence regarding its independent effects on body composition, particularly lean mass and skeletal muscle, is currently limited. Ongoing TRIUMPH trials

may provide important insights regarding body composition, muscle quality, and functional outcomes during large-magnitude pharmacologically induced weight loss.

Oral incretin therapies may further expand access to obesity treatment. Orforglipron, a non-peptide oral GLP-1 receptor agonist, has demonstrated clinically meaningful weight loss in phase 3 obesity trials, although detailed body-composition and muscle-function data remain limited.[16] Future studies are needed to determine whether oral GLP-1 therapies produce muscle and body-composition effects comparable to injectable incretin-based treatments.

Mechanistic Considerations

Several mechanisms may explain the observed changes in body composition.

First, GLP-1RAs reduce energy intake through appetite suppression, delayed gastric emptying, and central satiety signalling.[1,3] The resulting reduced caloric intake inevitably creates a catabolic state in which both fat and lean tissues may decrease. If protein intake is insufficient, muscle protein synthesis may be impaired, especially in older adults with anabolic resistance.[9,11]

Second, GLP-1RA and NuSH therapies improve insulin sensitivity and reduce visceral and ectopic fat.[1,3] Skeletal muscle is the major site of insulin-stimulated glucose disposal. Improved insulin action may enhance muscle metabolic function even when absolute lean mass decreases.[8]

Furthermore, reductions in myosteatosis may improve muscle quality. Intramuscular lipid accumulation has been associated with impaired strength, poor physical performance, and metabolic dysfunction.[6,12] Reducing ectopic lipid within and around muscle may therefore improve the functional capacity of remaining muscle tissue.

Finally, GLP-1 signalling exerts anti-inflammatory and mitochondrial effects. Obesity is characterized by chronic low-grade inflammation, oxidative stress, and impaired mitochondrial function, all of which may contribute to muscle dysfunction.[6,13] Whether GLP-1RAs directly protect skeletal muscle independent of weight loss remains uncertain and requires further study.

Muscle Mass Versus Muscle Function

A major limitation of current evidence is that most trials assess body composition rather than muscle function. Sarcopenia is not defined by low muscle mass alone; contemporary consensus definitions emphasize low muscle strength as the primary parameter, with low muscle quantity or quality used to confirm the diagnosis.[9]

Therefore, a reduction in DXA-derived lean mass should not automatically be interpreted as sarcopenia. Measures of muscle quality, strength, gait speed, chair-rise performance, and patient-reported function are clinically more relevant than lean mass alone.[9] Available reviews conclude that GLP-1RA-associated reductions in lean mass may often represent adaptive remodelling during weight loss rather than pathological muscle wasting.[6]

However, the absence of robust long-term functional data is an important evidence gap. Few GLP-1RA obesity trials have systematically measured grip strength, walking speed, falls, frailty, or physical-performance batteries. This limits confidence when extrapolating trial results to frail older adults or patients with established-sarcopenia.

Muscle Quality: The Emerging Paradigm

One of the most important developments in obesity medicine is the distinction between muscle quantity and muscle quality. Traditional body-composition techniques such as DXA provide estimates of lean mass but offer limited information regarding muscle composition, strength, mitochondrial function, or intramuscular lipid accumulation. Consequently, reductions in lean mass may not accurately reflect a deterioration in skeletal muscle health.

Neeland et al. reviewed body-composition outcomes across multiple GLP-1-based clinical trials and demonstrated substantial heterogeneity in reported changes in lean mass.[11] The authors noted that lean-mass changes are influenced by baseline adiposity, diabetes status, age, imaging methodology, and magnitude of weight loss. Importantly, improvements in insulin sensitivity and reductions in ectopic fat may improve muscle quality despite reductions in absolute lean tissue.

Similarly, Conte et al. questioned whether weight-loss–induced reductions in muscle mass are clinically relevant in the absence of impaired physical function.[12] Successful weight-loss interventions, including caloric restriction, bariatric surgery, and pharmacotherapy, consistently reduce both fat mass and fat-free mass. However, available evidence does not demonstrate that these reductions necessarily translate into weakness, disability, or adverse functional outcomes.[20] Rather, improvements in mobility, cardiometabolic health, and physical performance frequently accompany substantial weight reduction.

These observations support a shift toward multidimensional assessment of muscle health incorporating muscle composition, strength, function, mobility, and physical performance rather than relying on lean-mass measurements alone.[6,9,12,19] Future obesity trials should therefore prioritize clinically meaningful measures of muscle function alongside body-composition assessments.

High-Risk Populations

Older adults deserve particular attention. Aging is associated with progressive loss of muscle mass, impaired muscle protein synthesis, reduced neuromuscular function, and lower levels of physical activity.[9] Patients with sarcopenic obesity may have high adiposity but low muscle reserve, making them vulnerable to functional decline during rapid weight loss.

Other high-risk groups include patients with chronic inflammatory disease, advanced heart failure, chronic kidney disease, cancer survivorship, prolonged immobility, very low protein intake, or prior bariatric surgery. In such patients, GLP-1RA therapy should not necessarily be avoided, but it should be paired with proactive nutritional and exercise strategies.

Clinical Strategies to Preserve Muscle

The most important clinical approach is to treat incretin-based obesity pharmacotherapy as part of a comprehensive lifestyle and nutrition program rather than as stand-alone drug therapy.

Resistance training should be recommended at least two to three times weekly, targeting major muscle groups. Resistance exercise is the most effective intervention for preserving or increasing muscle strength during weight loss.[10,17] Aerobic exercise remains valuable for cardiometabolic health but is less potent than progressive resistance training for preserving lean mass.

Emerging evidence suggests that structured exercise may be particularly important when combined with GLP-1-based pharmacotherapy. Lundgren et al. demonstrated that the combination of supervised exercise and GLP-1 receptor agonist therapy resulted in more favourable long-term body-composition outcomes compared with pharmacotherapy alone.[19] Participants receiving combined treatment maintained greater reductions in body-fat percentage and were more likely to sustain clinically significant weight loss after treatment discontinuation.[20] These findings support the concept that exercise should not be viewed merely as an adjunct to pharmacological therapy but rather as an integral component of obesity treatment aimed at preserving lean tissue, maintaining physical function, and improving long-term weight-loss maintenance. Furthermore, resistance exercise may partially offset lean-mass reductions associated with rapid pharmacologically induced weight loss while simultaneously improving muscle strength and functional capacity.[14,20]

Protein intake should be explicitly assessed. A practical target for many adults undergoing weight loss is approximately 1.0–1.5 g/kg/day of protein, individualized by renal function, age, comorbidities, and obesity severity.[17] Older adults and patients with sarcopenic obesity may require higher protein density because total caloric intake often falls substantially during GLP-1RA therapy.

Clinicians should monitor more than body weight. Waist circumference, dietary intake, resistance-training adherence, symptoms of weakness, functional capacity, and, when feasible, grip strength or chair-rise performance may provide clinically meaningful information. DXA, computed tomography (CT), MRI, or bioimpedance can be considered in selected high-risk patients, but results should be interpreted in context.

Future Directions

Future trials should include standardized measures of muscle strength and physical performance, rather than relying soley on DXA-derived lean mass. MRI and CT may better

distinguish skeletal muscle from non-contractile lean tissue and quantify myosteatosis. Studies are also needed in older adults, frail patients, and those with sarcopenic obesity, because these groups are underrepresented in pivotal obesity trials.

Another emerging strategy is the combination of incretin-based therapies with muscle-preserving agents. Bimagrumab, an activin type II receptor antagonist, has been shown to reduce fat mass while increasing lean body mass in individuals with obesity and type 2 diabetes.[20] Although still investigational, therapies targeting the myostatin/activin pathway may help mitigate lean-mass loss during pharmacological weight reduction and represent a promising future approach to optimizing body composition.

Randomized trials combining GLP-1RA therapy with structured resistance training, protein supplementation, or anabolic-preserving interventions would help determine optimal clinical protocols. Long-term follow-up is also needed to assess whether lean-mass reductions translate into meaningful differences in disability, falls, resting energy expenditure, or weight regain.

Conclusion

GLP-1RAs and related incretin-based therapies produce substantial and clinically meaningful weight loss. Although reductions in lean mass are observed, current evidence suggests that these changes are generally proportional to total weight loss and occur alongside larger reductions in fat mass and visceral adiposity. Semaglutide and tirzepatide appear to improve overall body composition rather than selectively deplete skeletal muscle. Emerging evidence further suggests that improvements in insulin sensitivity, reductions in myosteatosis, and enhanced muscle quality may offset reductions in absolute lean mass.[12,19] Nevertheless, caution is warranted in older adults and patients with low baseline muscle reserve. Muscle-preserving care should include resistance exercise, adequate protein intake, and functional monitoring. Future research should prioritize muscle strength, physical performance, muscle composition, and muscle quality rather than lean mass alone when evaluating the effects of GLP-1-based therapies on skeletal muscle health.

Correspondence

Michael Tsoukas, MD
Email: michael.tsoukas@mcgill.ca

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