Review Article *Volume 6, Issue 4*

JCMCRI

Journal of Clinical & Medical Case Reports, Images

Received: August 04, 2026 Published: August 17, 2026

DOI: 10.55920/3064-8025/1234

Loss of Muscle Mass During Treatment with GLP-1 Receptor Agonists and Dual GIP/GLP-1 Receptor Agonists: A Systematic Review of Current Evidence

Almoutaz Alkhier Ahmed*

A/Professor - Family Medicine- MBRU, SSR family medicine -Nad Alhamar Health Center. DAHC

FRCGP [int], MSc Diabetes, MSc endocrinology, Senior fellow of IDF, MPH, FESC, FASLM, Dip IBLM, ELMC, Pg Cer medical education.

Abstract

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonists have transformed the management of obesity and type 2 diabetes mellitus (T2DM) by producing substantial and sustained weight loss. As these therapies become increasingly utilized, concerns have appeared around their potential effects on skeletal muscle and lean body mass, notably in older adults and other populations at increased risk of sarcopenia. Distinguishing physiological reductions in lean tissue that accompany weight loss from clinically significant muscle wasting is necessary for optimizing long-term treatment outcomes.

Objective: To systematically review current evidence regarding changes in skeletal muscle mass and lean body mass during treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonists in individuals with obesity and type 2 diabetes mellitus.

Design: Systematic review of randomized controlled trials, prospective cohort studies, and body-composition sub-studies evaluating changes in lean body mass, skeletal muscle mass, or fat-free mass during treatment with GLP-1 receptor agonists or dual GIP/GLP-1 receptor agonists. Data Sources: We searched several databases, including PubMed, Embase, the Cochrane Library, Scopus, and Web of Science, from their inception to June 2026.

Results: Evidence reliably demonstrates that treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists produces substantial reductions in body weight and adiposity. However, reductions in lean body mass accompany weight loss in most studies. Across body-composition analyses, approximately 20–40% of total weight loss was attributable to lean tissue, while the majority was attributable to fat mass reduction. Semaglutide and liraglutide were associated with modest decreases in lean body mass, whereas tirzepatide demonstrated larger absolute reductions owing to greater overall weight loss. Current evidence suggests that lean tissue losses observed with incretin-based therapies are broadly comparable to those reported with lifestyle intervention and bariatric surgery. Data on muscle strength, physical performance, and long-term risk of sarcopenia remain limited.

Conclusion: Researchers have found that using GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists may result in substantial weight loss, which is also associated with a decrease in lean body mass. However, the current research doesn't show that this causes excessive skeletal muscle wasting, though some people might need special help to maintain their muscle mass. To better understand this, future studies should use standardized methods to measure muscle quantity, quality, and function. This will help us better understand how these treatments affect the body and who might need extra care to stay healthy.

Keywords: GLP-1 receptor agonists; semaglutide; tirzepatide; GIP; obesity; sarcopenia; skeletal muscle mass; body composition.

1.Introduction

Obesity is one of the most pressing public health challenges of the twenty-first century, affecting more than one billion people worldwide and making a significant contribution to the global burden of cardiovascular disease, type 2 diabetes mellitus (T2DM), chronic kidney disease, metabolic dysfunction-associated steatosis liver disease (MASLD), several cancers, and premature mortality [1]. Although sustained weight reduction remains the cornerstone of obesity management, increasing attention has shifted from the magnitude of weight loss alone to the quality and composition of weight loss. Preservation of metabolically active lean tissue, particularly skeletal muscle, is now recognized as an essential determinant of long-term health outcomes [2].

Traditionally, the success of obesity treatment has been evaluated primarily by the percentage of total body weight lost. However, weight reduction consists of varying proportions of adipose tissue and lean body mass, and these components have markedly different physiological consequences. Excessive loss of muscle during weight reduction may contribute to sarcopenia, frailty, impaired physical Skeletal muscle accounts for approximately 40% of total body mass and plays a central role in glucose homeostasis, insulin sensitivity, resting energy expenditure, physical function, and metabolic flexibility performance, reduced quality of life, and an increased risk of hospitalization and mortality, notably in older adults and individuals with chronic disease [3].

New treatments for obesity and type 2 diabetes have changed the manner we approach these conditions [4]. Medicines that mimic the hormone glucagon-like peptide-1, such as liraglutide and semaglutide, have been shown to help people lose weight and improve blood sugar control, while also reducing the risk of heart and kidney prob-

***Corresponding Author:** *Almoutaz Alkhier Ahmed, A/Professor -MBRU, SSR family medicine -Nad Alhamar Health Center. DAHC

Citation: Almoutaz Alkhier Ahmed*, Loss of Muscle Mass During Treatment with GLP-1 Receptor Agonists and Dual GIP/GLP-1 Receptor Agonists: A Systematic Review of Current Evidence. Jour of Clin & Med Case Rep, Imag 2026; 6(4): 1234.

lems [4]. More recently, new medicines that act on two hormones, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, such as tirzepatide, are even more effective, with people losing an average of more than 20% of their body weight in clinical trials [5]. These new treatments are a big step forward in managing obesity and are increasingly recommended in clinical guidelines worldwide [6,7]. They offer new hope for people struggling with their weight and related health issues. By improving blood sugar control and decreasing the risk of heart and kidney problems, these medicines can help people live healthier lives (6-7). While research continues to advance, we can expect to see even more effective treatments for obesity and type 2 diabetes in the future.

When you lose weight, it's normal to lose some muscle too. This happens no matter how you lose weight, whether by changing your lifestyle, eating fewer calories, taking medication, or having weight-loss surgery. Studies have shown that about 20-30% of the weight you lose is muscle, not just fat [8]. There's been some debate about whether certain medicines that help with weight loss, like those that work with incretin, cause more muscle loss than they should for weight you lose. It's still not clear whether this is true.

When you're on GLP-1 receptor agonists, there are a few reasons why your muscle mass might change. For one, these medicines can suppress your appetite, which means you might not be taking in as many calories as you need [9]. This can lead to a negative energy balance, where your body starts to break down both fat and muscle for energy [9]. If you're not eating enough protein because you're feeling full sooner, that can also affect your muscles [10]. Your body needs protein to build and repair muscle tissue, so if you're not getting enough, your muscles might start to weaken [10]. When you lose weight, your muscles don't have to work as hard to support your body, which can lead to muscle loss over time [10]. All these factors together could potentially lead to faster muscle loss if you're not careful to eat enough protein and exercise regularly, especially with weights or other resistance exercises that help build muscle. It's kind of like a balance,if you're not putting in the right ingredients and challenging your muscles, you might start to lose them.

Conversely, accumulating experimental and clinical evidence suggests that incretin-based therapies may exert direct or indirect beneficial effects on skeletal muscle. GLP-1 signalling has been associated with improved insulin sensitivity, enhanced mitochondrial function, increased skeletal muscle perfusion, reduced oxidative stress, and attenuation of chronic low-grade inflammation [11,12]. Weight loss may also improve mobility, cardiorespiratory fitness, and participation in physical activity, therewith promoting muscle function despite reductions in lean mass. Consequently, changes in muscle quantity may not necessarily reflect deterioration in muscle quality or functional capacity [13]. Methodological distinctions in body composition assessment add to the complexity of interpretation of the current evidence. Many clinical studies quantify lean body mass using dual-energy X-ray absorptiometry (DXA), which measures all non-fat tissues, including organs, extracellular fluid, connective tissue, and bone-free lean tissue, rather than skeletal muscle alone [14]. Consequently, reductions in DXA-derived lean mass may overestimate true losses of contractile muscle tissue [15]. Imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT), together with emerging techniques including ultrasound and assessments of muscle strength and physical performance, provide more extensive evaluation of skeletal muscle quantity, quality, and function [16].

An additional limitation of the current literature is the considerable heterogeneity in study populations, treatment duration, concomitant lifestyle interventions, nutritional intake, and methods for assessing body composition. Most randomized controlled trials were designed primarily to evaluate weight loss and metabolic outcomes rather than muscle preservation, resulting in limited reporting of functional outcomes, muscle strength, protein intake, or exercise participation. Consequently, if observed reductions in lean mass represent clinically meaningful muscle wasting or expected physiological adaptation remains unclear.

To get the best results from obesity treatments, such as GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists, we need to understand how they affect our muscles. This is important because it will help us figure out who is most at risk of losing muscle, and how we can prevent it. We can use this information to provide tailored advice on diet and exercise and to closely monitor patients during treatment. By doing so, we can create strategies that help people lose fat without losing too much muscle. This way, we can ensure these treatments are as effective as possible while keeping patients safe and healthy. The objective of this systematic review is to carefully analyse the current evidence regarding changes in lean body mass and skeletal muscle during treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists. Specifically, we examine the magnitude of lean tissue loss reported across clinical studies, compare outcomes among incretin-based therapies, assess the influence of body composition measurement techniques, identify methodological weaknesses in the existing literature, and highlight priorities to guide future research aimed at preserving skeletal muscle during pharmacological weight management.

2.Methods Study Design

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [17]. The method used for this review was carefully planned before it started to ensure everything was clear, could be repeated, and was done in a very thorough and detailed way. This planning was done for all parts of the review, including choosing which studies to include, extracting the relevant information from those studies, and assessing the quality of the studies.

2.1. Eligibility Criteria

Studies were considered eligible if they met the following inclusion criteria:

The study focused on adults who were 18 years or older and had certain health issues, such as being overweight or obese, or having type 2 diabetes. Evaluated treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists. Reported quantitative assessments of body composition. Included at least one outcome related to lean body mass, fat-free mass, skeletal muscle mass, or appendicular skeletal muscle mass. Studies that were published as full-text articles in peer-reviewed journals were considered; these included randomized controlled trials, prospective cohort studies, and noninterventional studies. Some studies weren't included in this research. These were studies that only looked at animals or were done in a lab; reports of individual cases; general reviews; editorials; or conference presentations that didn't have a full paper published. Also, any study that didn't provide information on body composition, specifically lean tissue or skeletal muscle, was excluded.

2.2. Search Strategy

A comprehensive literature search was performed using the electronic databases PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus. The search strategy combined controlled vo-

cabulary (Medical Subject Headings [MeSH] where applicable) with free-text keywords related to GLP-1-based therapies and body composition.

The principal search terms included:
"GLP-1 receptor agonist" "semaglutide" "liraglutide" "tirzepatide" "GIP" "body composition" "lean mass" "fat-free mass" "skeletal muscle" "muscle mass" "appendicular muscle" "sarcopenia" "obesity"
To improve our search, we used special expressions like "AND" and "OR". We also reviewed lists of references from reputable studies and important articles to identify any other publications we might have missed in our online database searches.

2.3. Study Selection

To start with, the principal investigator assessed the titles and summaries of the studies to determine whether they met the criteria. Then they got the full articles of the studies that appeared relevant and checked them against the rules that had set for what to include and what to leave out.

2.4. Data Extraction

Data were independently extracted using a standardized data collection form. The following information was collected from each included study:
Study characteristics (author, publication year, country, and study design) Participant characteristics (sample size, age, sex, body mass index, and clinical population) Type and dosage of GLP-1 receptor agonist or dual GIP/GLP-1 receptor agonist Duration of treatment and follow-up Changes in body weight Changes in fat mass and lean body mass Skeletal muscle-related outcomes Methods used to assess body composition, including dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT), or bioelectrical impedance measurement (BIA) Quality Assessment.

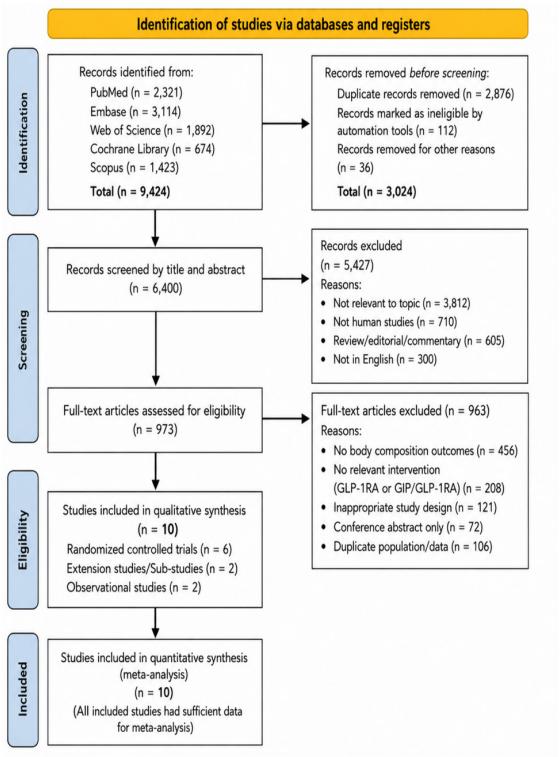

Figure 1

3.Results

3.1. Study Selection: This research looked at studies on how certain medications, like GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists, affect body composition in adults who are obese, overweight, or have type 2 diabetes. The researcher searched through many records, removed duplicates, and carefully read the titles, abstracts, and full texts of the studies that appeared relevant. The studies included in the analysis were randomized, controlled, and met certain criteria (Table 1).

Most of the available evidence originated from studies evaluating liraglutide, semaglutide, and tirzepatide. Assessment of body composition was predominantly performed using dual-energy X-ray absorptiometry (DXA). At the same time, several studies additionally employed magnetic resonance imaging (MRI), computed tomography (CT), or bioelectrical impedance measurement (BIA) to quantify changes in adipose tissue and lean mass.

3.2. Characteristics of Included Studies

The studies looked at adults who were obese, overweight without risks, or had type 2 diabetes. The treatment lasted anywhere from 12 weeks to almost 2 years, but the number of people in each study and how they were treated varied widely. Also, the way the results were reported was different from one study to another (Table 2).

The results showed that, overall, the most common outcomes found in the studies that were looked at were: Total body weight reduction, Changes in total fat mass, Changes in lean body mass, Relative contributions of fat mass and lean mass to overall weight loss (Table3).

On the other hand, not many studies have looked at the results that are directly related to the health of our skeletal muscles, such as: Appendicular skeletal muscle mass, muscle strength, physical performance, functional measures of sarcopenia

3.3. Effects of GLP-1 Receptor Agonists on Body Composition: Liraglutide

When you lose weight with liraglutide, you're mainly losing fat, not muscle. This is a good thing, because when you're trying to get healthier, you want to keep your muscle and lose the extra fat. The studies [21,22-26ư showed that about 65-80% of the weight people lost was fat, and only 20-35% was muscle. This means the muscle loss was proportional to the weight loss, and the treatment didn't seem to degrade muscle tissue too much. For people with obesity and type 2 diabetes, liraglutide also helped with blood sugar control and other health issues related to the heart. Even though they lost a bit of muscle, it didn't seem to hurt the overall benefits of the treatment. So, liraglutide appears to be a helpful treatment for weight loss and boosting health, especially for people with type 2 diabetes. It's worth noting that when you're losing weight, it's normal to lose some muscle along with the fat. But in this case, the amount of muscle lost was relatively small compared to the amount of fat lost. This suggests that liraglutide is a relatively safe and effective treatment for weight loss and can be a useful tool for people trying to get healthier. Overall, the studies [21-22,26] showed that liraglutide is a beneficial treatment for weight loss and boosting health, and it's worth considering for people who are struggling with obesity and type 2 diabetes. By helping people lose fat and improve their blood sugar control, liraglutide can be an important component of a comprehensive treatment plan. And because it doesn't seem to cause excessive muscle loss, it's a relatively safe and effective option for people trying to get healthier.

Table 1: *Key Clinical Studies Evaluating Body Composition Changes During GLP-1RA and Dual GIP/GLP-1RA Therapy.*

Study	Population	Intervention	Duration	Body Composition Method	Main Findings
STEP 1 Sub-study (18)	Obesity without diabetes	Semaglutide 2.4 mg weekly	68 weeks	DXA	Significant reductions in total fat mass and lean body mass; fat mass accounted for majority of weight loss
STEP 2 (19)	T2DM with obesity	Semaglutide 2.4 mg weekly	68 weeks	DXA	Greater reduction in fat mass than lean mass
STEP 3 (20)	Obesity	Semaglutide + intensive behavioural therapy	68 weeks	DXA	Improved body composition despite lean mass reduction
SCALE Obesity and Prediabetes (21)	Obesity	Liraglutide 3.0 mg daily	56 weeks	DXA	Weight loss predominantly attributable to fat mass reduction
SCALE Diabetes (22)	T2DM	Liraglutide 3.0 mg daily	56 weeks	DXA	Significant fat mass reduction with modest lean mass loss
SURMOUNT-1 Body Composition Sub-study (23)	Obesity	Tirzepatide	72 weeks	DXA	Approximately 75% of weight loss attributable to fat mass
SURPASS Program (24)	T2DM	Tirzepatide	40–104 weeks	DXA/BIA	Improved body composition and metabolic markers
SUSTAIN Program (25)	T2DM	Semaglutide	Variable	DXA/BIA	Consistent preferential reduction in adiposity
LEAD-2 Body Composition Substudy (26)	Adults with type 2 diabetes mellitus inadequately controlled with metformin; overweight or obese	Liraglutide 1.2 mg or 1.8 mg once daily added to metformin	26 weeks	Dual-energy X-ray absorptiometry (DXA)	Liraglutide produced significant weight loss, with the majority attributable to fat mass reduction. Lean body mass decreased modestly, resulting in a relative preservation of lean tissue compared with fat loss.
AWARD Program (27)	T2DM	Dulaglutide	Variable	BIA	Reduced fat mass with modest lean tissue decline

Table 2: *Characteristics of Included Studies.*

Study	Country / Study Design	Participant Characteristics	Fat Mass and Lean Body Mass Changes	Skeletal Muscle-related Outcomes
STEP 1 Sub-study	Multicentre international RCT; obesity without diabetes	n≈140 in DXA sub-study; mean age ~47 years; ~70% female; BMI ~38 kg/m²; adults with obesity without T2DM	Total fat mass reduced substantially (~19%); lean body mass also decreased (~9%); proportion of weight loss mainly from fat mass (~60–70%)	Reduction in appendicular lean mass; no evidence of disproportionate muscle loss; physical function maintained
STEP 2	International multicentre RCT; T2DM with obesity	n=1,210 participants; mean age ~55 years; ~49% female; BMI ~35–36 kg/m²; T2DM with obesity	Greater reduction in fat mass compared with lean mass; preferential adipose tissue loss	Lean mass decreased proportionally less than total weight loss; no clinically meaningful deterioration in physical function reported
STEP 3	International RCT; obesity with intensive behavioural therapy	n≈611; mean age ~46 years; majority female; BMI ~38 kg/m²	Significant reduction in total fat mass; lean mass decreased but represented smaller proportion of total weight loss	Skeletal muscle quantity reduced with weight loss; functional outcomes improved with lifestyle intervention
SCALE Obesity and Prediabetes	International multicentre RCT	n=3,731; mean age ~45 years; ~79% female; BMI ≥30 kg/m² or ≥27 kg/m² with comorbidity	Majority of weight reduction derived from fat mass; modest reduction in lean tissue	Preservation of relative lean mass; no evidence of excessive muscle loss
SCALE Diabetes	International RCT; T2DM and obesity	n=846; mean age ~54 years; ~48% female; BMI ~34 kg/m²	Significant reduction in fat mass with smaller decrease in lean mass	Skeletal muscle outcomes not directly measured; lean tissue reduction consistent with weight loss
SURMOUNT-1 Body Composition Sub-study	International phase 3 RCT; obesity without diabetes	n≈160 DXA substudy; mean age ~45 years; ~70% female; BMI ~38 kg/m²	Approximately 75% of weight loss attributed to fat mass reduction; lean mass accounted for ~25%	Reduction in appendicular lean mass occurred but preservation of muscle proportion relative to body weight
SURPASS Program	International phase 3 RCT programme; T2DM	Combined population >6,000; mean age ~57 years; BMI ~32–34 kg/m²; mixed sex distribution	Reductions in fat mass greater than reductions in lean mass	Limited direct skeletal muscle assessment; improvements in metabolic health and physical parameters reported
SUSTAIN Program	International RCTs and prospective analyses	Adults with T2DM; mean age ~55–65 years; BMI ~30–35 kg/m²	Preferential reduction in fat mass; modest lean mass decline	No significant evidence of clinically important muscle deterioration
LEAD Program	International, multicentre, randomized controlled Phase III trial (LEAD-2 DXA substudy). Countries included Europe, North America, South America, and Asia.	Adults with type 2 diabetes mellitus inadequately controlled on metformin; overweight or obese. DXA substudy included approximately 160 participants. Mean age ≈55 years; BMI ≈33 kg/m²; both sexes.	Mean body weight decreased by 2.0–2.5 kg. Approximately 70–75% of weight loss was attributable to fat mass reduction, while lean body mass decreased modestly, preserving the relative proportion of lean tissue.	Skeletal muscle mass was **not measured directly**. DXA assessed total lean body mass only; no muscle strength or physical performance outcomes were reported.
AWARD Program	International RCT programme; T2DM	Adults with T2DM; BMI ~30–35 kg/m²; mean age ~55–65 years	Reduction in fat mass with small reductions in lean tissue	Skeletal muscle mass not directly assessed; BIA-derived lean mass changes minimal

Table 3: *Body weight change and quality assessment.*

Study	Body Weight Change	Body Composition Assessment	Quality Assessment
STEP 1 Sub-study	Mean weight reduction ~15% with semaglutide vs ~2.4% placebo	DXA	Low risk of bias (randomised, double-blind, placebo-controlled; objective body composition assessment)
STEP 2	Weight loss ~9.6% with semaglutide 2.4 mg	DXA	Low risk of bias (large RCT, validated measurement method)
STEP 3	Mean weight reduction ~16%	DXA	Low risk of bias
SCALE Obesity and Prediabetes	Mean weight loss ~8%	DXA	Low risk of bias (large placebo-controlled RCT)
SCALE Diabetes	Weight reduction ~6%	DXA	Low risk of bias
SURMOUNT-1 Body Composition Sub-study	Mean weight reduction ~15–21% depending on dose	DXA	Low risk of bias (randomised controlled trial with objective assessment)
SURPASS Program	Weight reduction approximately 7–13 kg depending on dose	DXA and BIA in substudies	Low-to-moderate risk of bias (high-quality RCTs; body composition data limited to substudy populations)
SUSTAIN Program	Weight loss generally 3–6 kg	DXA/BIA	Moderate quality (heterogeneous studies; some post hoc analyses)
LEAD -2	Mean weight loss of approximately 2.8 kg with liraglutide 1.2 mg and 3.0 kg with liraglutide 1.8 mg after 26 weeks.	DXA	Low risk of bias
AWARD Program	Weight loss modest (~2–5 kg)	BIA	Moderate quality (body composition outcomes generally secondary endpoints)

3.4. Effects of GLP-1 Receptor Agonists on Body Composition: Semaglutide

Semaglutide has displayed superior weight-loss efficacy compared with earlier GLP-1 receptor agonists and has generated the most comprehensive body-composition data to date through the STEP clinical trial program [18-20]. In the body-composition sub-study of STEP 1 [18], semaglutide treatment resulted in substantial reductions in total fat mass, visceral adipose tissue, and lean body mass. However, fat mass constituted most of the total weight loss. Although absolute lean mass declined, the relative proportion of lean tissue increased because adipose tissue was reduced to a greater extent, indicating an overall improvement in body composition. Furthermore, magnetic resonance imaging (MRI)-based analyses demonstrated preferential reductions in ectopic fat depots, including visceral and hepatic fat, both of which are closely associated with insulin resistance and increased cardiometabolic risk. This evidence indicates that semaglutide preferentially improves metabolically detrimental fat distribution while preserving lean tissue in proportion to overall weight reduction [18-20,25].

3.5. Other GLP-1 Receptor Agonists: Dulaglutide

Research on exenatide and dulaglutide [27] has shown that these therapies can lead to changes in body composition. These changes are like those seen with liraglutide and semaglutide. When people take these medications, they tend to lose more fat than muscle. This suggests that the weight loss associated with these medications is primarily fat loss. Overall, the evidence does not indicate that these medications cause people to lose muscle mass at a rate greater than would be expected when someone is trying to lose weight on purpose [27]. In fact, the reduction in fat mass is much more significant than the reduction in lean body mass, which includes muscle [27]. This is a positive finding, as it means that these medicines can help people lose weight without inducing excessive muscle loss.

3.6. Effects of Dual GIP/GLP-1 Receptor Agonists Tirzepatide

Tirzepatide is a revolution for treating obesity and being overweight. It's the first drug of its kind to target two important hormones in the body, GIP and GLP-1 [28]. This medicine has shown amazing results in helping people lose weight. In a big clinical trial program called SURMOUNT [23], researchers found out what happens to the body when people take tirzepatide. The people in the study who got tirzepatide lost a lot of weight ,almost as much as people who have certain types of weight-loss surgery. When the researchers looked more closely, they saw that tirzepatide didn't just help people lose weight; it also changed how their bodies stored fat. It reduced body fat, especially in areas that can be harmful to health, such as around organs and in the liver. This is a big deal because it shows that tirzepatide can have a powerful effect on the body's fat stores.

When you lose weight, you don't just lose fat; you also lose some muscle (Table 4). But with tirzepatide, about 75% of the weight you lose is fat, and only about 25% is muscle [23,24]. This is like what happens when people make big changes to their lifestyles or have weight-loss surgery. So, it seems like tirzepatide doesn't cause you to lose too much muscle, which is a good thing. This is important because when you're losing weight, you want to make sure you're not losing too much muscle, which helps you stay strong and healthy.

Table 4: *Clinical Interpretation of Lean Mass Changes During Weight-Loss Interventions.*

Intervention	Typical Weight Loss	Lean Mass Contribution	Fat Mass Contribution
Caloric restriction	5–10%	20–35%	65–80%
Intensive lifestyle intervention	7–15%	20–30%	70–80%
Bariatric surgery	20–35%	20–30%	70–80%
Liraglutide	5–10%	20–35%	65–80%
Semaglutide	10–15%	25–35%	65–75%
Tirzepatide	15–25%	20–30%	70–80%

3.7. Comparison Between Tirzepatide and GLP-1 Receptor Agonists

Direct comparative studies [23,24] indicate that tirzepatide produces greater absolute reductions in lean body mass than liraglutide or semaglutide. Nevertheless, these data primarily reflect the substantially greater overall weight loss achieved with tirzepatide rather than a preferential catabolic effect on skeletal muscle. When lean tissue loss is considered relative to total body weight reduction, preservation of lean mass appears broadly comparable between tirzepatide

and conventional GLP-1 receptor agonists. Current evidence therefore does not support the hypothesis that dual GIP/GLP-1 receptor agonism confers an increased risk of disproportionate skeletal muscle wasting compared with GLP-1 receptor agonist monotherapy.

3.8. Muscle Quality Versus Muscle Quantity

An important limitation of the current literature is the predominant emphasis on changes in lean body mass rather than the assessment of skeletal muscle quality and function [18]. Although lean mass is frequently used as a surrogate marker of muscle preservation, it does not fully reflect functional muscle health (29). Muscle quality encompasses multiple biological characteristics, including muscle strength, contractile performance, intramuscular fat infiltration, mitochondrial function, and overall physical performance [30]. Consequently, reductions in lean mass alone should not be interpreted as evidence of impaired muscle function.

New research shows that when people lose a lot of weight with certain medications, such as GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists, their muscle quality improves [31]. This is true even if they don't have as much muscle as they used to. When there's less fat inside the muscles, they work better, and the body is more sensitive to insulin (table). This means the body can use energy more efficiently. Also, when there's less inflammation in the body, blood sugar levels are more stable, heart health improves, and muscles work better (table). So, when doctors assess how well weight-loss treatments work, they should consider more than just how much weight someone loses (table). They should also assess the person's muscle strength, mobility, and ability to perform physical tasks. This will help doctors understand if the weight loss is really making a difference in the person's overall health.

3.9. Older Adults and Risk of Sarcopenia

Older adults represent a population in whom preservation of skeletal muscle is of clinical importance [32]. Age-related sarcopenia is characterized by progressive declines in skeletal muscle mass, strength, and physical performance, causing frailty, falls, disability, and increased mortality [33]. Given that GLP-1 receptor agonists promote weight loss primarily through appetite suppression and reduced energy intake, concerns have been raised about the potential for inadequate protein intake and accelerated loss of lean tissue in older individuals.

When elderly use certain medications for weight loss, there's limited research on how these medications affect their body composition. The available studies show that these adults tend to lose both fat and muscle mass, like younger people, and there's no clear evidence that the medication causes greater muscle loss than usual [18]. However, since elderly already have a harder time maintaining their physical strength and are more prone to muscle loss, doctors should keep a close eye on them when they're using these medications to lose weight [34]. This is important because elderly have less of a buffer to fall back on if they start to lose too much muscle, rendering them more vulnerable to health problems. As a result, careful monitoring is necessary to ensure that any weight loss is healthy and sustainable. Routine assessment should include measures of muscle strength, physical function, dietary protein and energy intake, and habitual physical activity. Incorporating resistance exercise and individualized nutritional counselling into treatment plans may help mitigate age-related declines in muscle mass and optimize functional outcomes in this high-risk population.

3.10. Overall conclusion

All included GLP-1RA and dual GIP/GLP-1RA studies consistently indicate that most of the weight loss results from reductions in fat mass rather than in lean body mass. Tirzepatide (SURMOUNT-1) showed the greatest preferential fat-mass reduction, with approximately 75% of total weight loss attributable to fat mass. In comparison, trials of semaglutide and liraglutide generally reported 60–70% weight loss attributable to fat mass. Across studies, reductions in lean mass were modest and proportional to total weight loss, with no convincing evidence of clinically significant skeletal muscle deterioration or impaired physical function.

4. Discussion

This systematic review demonstrates that treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists is consistently associated with significant reductions in body weight and adiposity, accompanied by measurable decreases in lean body mass. Across the included studies [18-27], lean tissue accounted for approximately 20–40% of total weight loss, whereas most weight reduction was attributable to decreases in fat mass. These data are consistent with the bodily adaptations usually observed during intentional weight loss and do not support selective or excessive skeletal muscle wasting attributable to incretin-based therapy. Research has demonstrated that these treatments produce significant changes in body composition, with major reductions in body fat, especially around organs and in muscle [21,23,24]. This type of fat is closely linked to problems like insulin resistance, inflammation, and heart disease [35]. As a result, the positive changes in body composition are likely to have a significant role in the treatments' ability to improve heart health, control blood sugar levels, and reduce obesity-related complications [35], this is especially important for people at risk of heart disease, diabetes, and other conditions linked to obesity, as it can help them manage their conditions more effectively and reduce their risk of long-term complications.

Comparison with Lifestyle-Induced Weight Loss: When you lose weight with medicines like GLP-1 receptor agonists, you also lose lean tissue, which is like what happens when you try to lose weight by changing your diet and exercise routine. Usually, when you cut calories, about 20-30% of the weight you lose is from muscle and other lean tissue, not just fat [36]. Even when you make big changes to your diet to lose weight, you might still lose some muscle mass, even though you're getting healthier and losing fat [36]. This data shows that when people lose lean tissue while on incretin-based therapy, it's mostly due to weight loss and their bodies adjusting to having less energy. It's not necessarily a bad side effect of the drug. So, when we're worried about losing lean mass, we should think about it in terms of how our body works when we lose weight.

Comparison with Bariatric Surgery: For people who are severely obese, having bariatric surgery is still the best way to lose a lot of weight and keep it off [37]. But after the surgery, people often lose muscle mass too [38]. Studies have shown that about a quarter of the weight people lose after bariatric surgery is muscle, not just fat [36,39]. This is like what happens when people take certain medications, like semaglutide and tirzepatide, to lose weight. It's worth noting that these medications may also produce significant muscle loss, which is why it's critical to monitor and maintain muscle health during weight loss. By doing so, people can ensure they lose weight in a healthy, sustainable way.

When you're trying to lose weight, it's common to lose some muscle mass too. This doesn't just happen with certain medications but with many weight-loss methods. So, it's a good idea to include strategies to preserve muscle in all weight-loss plans, no matter what method you're using (table). This way, you can make sure you're losing fat,

not muscle.

Critical Appraisal of Evidence on Lean Body Mass Changes with GLP-1-Based Therapies

The current evidence evaluating changes in lean body mass during treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonists is derived predominantly from randomized controlled trials (RCTs originally designed to assess weight reduction and glycaemic efficacy rather than body composition outcomes. Consequently, although these trials provide high-quality evidence regarding treatment success and safety, their ability to determine the impact of incretin-based therapies on skeletal muscle preservation remains limited.

Neeland et al. [18] provided a comprehensive review of the available evidence on changes in lean body mass associated with GLP-1-based therapies. They considered potential mitigation approaches, including strength exercise and adequate protein intake. The review provides important mechanistic insight into the physiological basis of lean mass reduction during pharmacological weight loss and highlights the need to preserve muscle during obesity treatment. However, as a narrative review, it is subject to potential selection bias, lacks quantitative synthesis, and relies on the methodological quality of the underlying studies. Therefore, although valuable for clinical interpretation, it represents a lower level of evidence compared with systematic reviews and meta-analyses.

The STEP clinical trial program provided some of the strongest evidence on semaglutide-associated changes in body composition. In STEP 2, Davies et al. [19] conducted a large, multicentre, randomized, double-blind, placebo-controlled phase 3 trial evaluating semaglutide 2.4 mg weekly in adults with overweight or obesity and type 2 diabetes mellitus. The study demonstrated substantial weight reduction accompanied by improvements in glycaemic and cardiometabolic parameters. However, body composition assessment was performed only in a subgroup, and lean mass was not a primary endpoint. Additionally, the study did not evaluate muscle strength or physical function, limiting interpretation of whether the observed reductions in lean mass represented clinically significant muscle loss. Despite these limitations, the randomized design, large sample size, and prolonged follow-up provide robust evidence regarding treatment efficacy.

Similarly, the STEP 3 trial by Wadden et al. [20] revealed considerable weight loss with semaglutide combined with intensive behavioural therapy. The trial benefited from rigorous randomization, standardized lifestyle intervention, and high-quality outcome assessment. However, interpretation of changes in lean mass is limited because body composition was not comprehensively assessed across the entire cohort. Furthermore, the contribution of intensive behavioural therapy to changes in dietary intake and physical activity may have influenced body composition outcomes independently of pharmacological treatment.

Earlier liraglutide studies, including the SCALE Obesity [21] and SCALE Diabetes trials [22], provided important evidence regarding weight reduction with GLP-1 receptor agonism. Pi-Sunyer et al. [21] demonstrated clinically meaningful weight loss with liraglutide 3.0 mg in adults with obesity, while Davies et al. [19] confirmed similar benefits among individuals with type 2 diabetes. However, these studies primarily focused on weight and metabolic outcomes, and detailed assessments of fat mass and lean mass were not included as major endpoints. Therefore, conclusions regarding muscle preservation are indirect and largely based on assumptions regarding the proportional composition of weight loss.

The emerging evidence from dual GIP/GLP-1 receptor agonists provides additional insight into changes in body composition. The SURMOUNT-1 body composition sub-study by Look et al. [23] is among the most extensive analyses of tirzepatide-associated changes in fat and lean mass. The study used dual-energy X-ray absorptiometry (DXA) to directly assess body composition. It demonstrated substantial reductions in total body weight, predominantly driven by decreases in fat mass, accompanied by decreases in lean mass. A major strength of this study was the prespecified evaluation of body composition. However, DXA cannot differentiate skeletal muscle tissue from other lean compartments, including organs, connective tissue, and changes in extracellular water. In addition, muscle strength and physical performance outcomes were not assessed, limiting conclusions regarding sarcopenia risk.

The SURPASS-2 trial by Frías et al. [24] evaluated tirzepatide versus semaglutide in individuals with type 2 diabetes and displayed superior reductions in glycated haemoglobin and body weight with tirzepatide. However, the open-label design brings potential performance bias, and body composition outcomes were not included. Consequently, although the trial provides important comparative efficacy data, it contributes limited evidence regarding preservation of lean body mass.

Other landmark GLP-1RA cardiovascular and diabetes efficacy trials, including SUSTAIN 2 (semaglutide versus sitagliptin) [25], LEAD-2 (26), and AWARD-3 (dulaglutide versus metformin) [27], demonstrated favourable effects on glycaemic control and modest weight reduction. However, these studies did not incorporate direct measurements of body composition. The absence of DXA, bioelectrical impedance measurement, magnetic resonance imaging, or functional muscle assessments limits the contribution of these assessments to understanding the effects of GLP-1-based therapies on muscle health.

Overall, the available evidence demonstrates that GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists produce considerable weight loss mainly through reductions in adipose tissue, with smaller reductions in lean body mass. Nevertheless, several important methodological restrictions remain. First, most clinical trials were not designed with body composition as a primary outcome. Second, available assessments have relied primarily on DXA, which estimates lean tissue but does not directly quantify skeletal muscle mass or quality. Third, few studies have incorporated clinically meaningful measures of muscle strength, physical performance, frailty, or sarcopenia. Finally, older adults and people at high risk of sarcopenia remain underrepresented.

Potential Mechanisms Underlying Lean Mass Reduction:

Several physiological mechanisms may contribute to the reduction in lean body mass observed during incretin-based therapy (Table 5). The main mechanism is reduced energy intake due to appetite suppression and delayed gastric emptying, which together create a sustained negative energy balance. Although adipose tissue serves as the principal source of mobilized energy, some degree of lean tissue catabolism is an inevitable component of weight loss. When you don't eat enough, you might not get the protein your body needs. This can hurt your muscles and make it harder for them to grow and repair themselves. For older people or those who already have muscle problems, not getting enough protein can worsen symptoms and bring about muscle loss. Weight loss also reduces mechanical loading of skeletal muscle. Decreased mechanical stress may attenuate anabolic signalling pathways that normally maintain muscle hypertrophy

and maintenance, particularly in sedentary individuals.

When you lose weight, your body goes through some big changes. Your hormones, such as insulin, leptin, and growth hormone, start working differently. This can affect how your body builds and breaks down muscle. As a result, you might see changes in your lean body mass, which is the parts of your body that aren't fat, like your muscles. Testosterone, cortisol, and other hormones also have a role in this process. All such hormonal changes can be complex, but they're an important part of what happens when you're trying to lose weight.

Table 5: *Potential Mechanisms Contributing to Lean Mass Loss During GLP-1RA and Dual GIP/GLP1 agonist Therapy.*

Mechanism	Proposed Effect
Reduced energy intake	Negative energy balance promotes catabolism
Appetite suppression	Reduced overall nutrient intake
Reduced protein consumption	Impaired muscle protein synthesis
Decreased mechanical loading	Lower anabolic stimulation
Weight-loss-associated hormonal adaptation	Altered muscle protein turnover
Rapid weight reduction	Accelerated lean tissue mobilisation

Potential Protective Effects of GLP-1 Signalling: When you lose weight, you also tend to lose some muscle mass, but recent research suggests that GLP-1 signalling might help protect your muscles. Studies have shown that GLP-1 can improve how well your muscles use insulin, help them take up more glucose, reduce oxidative stress-related damage, and even make your mitochondria work better. It can also reduce chronic inflammation, which is a major contributor to muscle damage. All these effects combined might help keep your muscles healthy and strong, even if you're losing some overall muscle mass. This is important because it means that even if you're not building new muscle, you can still maintain the quality of the muscle you have, which is important for overall health and mobility.

When you lose weight, you're more likely to be able to move around and exercise, which can help keep your muscles strong. This is important because even if you lose some muscle mass, you might still be able to do everyday tasks and physical activities. So, it's not only about how much muscle you have, but also how well it works.

Table 6: *Potential Mechanisms Protecting Skeletal Muscle During Incretin Therapy.*

Mechanism	Potential Benefit
Improved insulin sensitivity	Enhanced muscle glucose uptake
Reduced systemic inflammation	Improved muscle metabolism
Improved mitochondrial function	Enhanced muscle efficiency
Reduced ectopic fat deposition	Better muscle quality
Increased mobility following weight loss	Preservation of physical function
Improved cardiometabolic health	Enhanced exercise capacity

Clinical Implications: The findings of this review have several important consequences for clinical practice. First, clinicians should anticipate modest reductions in lean body mass during treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists as part of the expected physical response to weight loss. Second, current evidence indicates that these reductions are generally proportional to total weight loss and should not be interpreted as evidence of pathological skeletal muscle wasting.

It's important to keep your muscles healthy and strong, especially as you get older or if you have certain health problems. When trying to manage your weight, it's not only about losing fat, and about keeping your muscles from wasting away. This is why it's a good idea to combine medicine with other proven methods that help preserve muscle mass. Progressive resistance exercise remains the most effective intervention for minimizing loss of lean body mass and improving muscle strength during weight reduction. Adequate dietary protein intake, generally in the range of 1.2–1.6 g/kg/day depending on age, renal function, and comorbidities, should be encouraged to maintain muscle protein synthesis. Regular participation in both aerobic and resistance exercise improves muscle quality, physical performance, and long-term maintenance of weight loss. Finally, patients at increased risk of sarcopenia should undergo periodic nutritional assessment and individualized dietary counselling, ideally under the guidance of a registered dietitian, to ensure adequate energy and protein intake throughout treatment.

5. Conclusion

Current evidence indicates that GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists produce considerable weight loss accompanied by modest reductions in lean body mass. Approximately one-fifth to two-fifths of total weight loss may be attributable to lean tissue, while the majority results from reductions in adipose tissue. Available data do not support disproportionate skeletal muscle wasting associated with these therapies. Nevertheless, preservation of muscle mass and function remains an important clinical consideration, particularly among older adults and individuals at risk of sarcopenia. Combining incretin-based pharmacotherapy with resistance exercise, adequate protein intake, and ongoing nutritional monitoring may optimize body composition and long-term health outcomes.

Clinical Recommendations

Based on the current body of evidence, preservation of skeletal muscle should be considered an integral component of obesity management during treatment with GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists. The following evidence-informed recommendations may help minimize lean mass loss while improving clinical outcomes (Table 7).

Exercise recommendation

When it comes to helping patients taking incretin-based therapies, doctors should always recommend exercises that engage their muscles. This type of exercise, called progressive resistance training, is very effective at maintaining muscle mass and strength and augmenting overall function, even when people are trying to lose weight. There are many ways to do resistance training, such as using free weights or machines at the gym, using resistance bands, or even just your own body weight to strengthen your muscles. The key is to choose exercises that are right for your age, your physical ability, and any other health issues you might have. If possible, it's also a good idea to combine resistance training with regular aerobic exercise, like walking or jogging, to get the most benefits for your heart and overall health. By doing both types of exercise, you can significantly increase the benefits for your body and its overall function.

Protein Intake recommendation

When you're trying to lose weight, especially if you're taking medication to help, getting enough protein from your food is important. This helps your body build and repair muscle and reduces the risk of muscle loss. Most adults trying to lose weight should aim to eat

about 1.0 to 1.2 grams of protein per kilogram of body weight per day. Older adults might need a bit more protein, around 1.2 to 1.5 grams per kilogram of body weight per day, because as we age, our bodies get a bit worse at using protein to build muscle. People at risk of losing a lot of muscle mass might need up to 1.6 grams of protein per kilogram of body weight per day, as long as their kidneys are functioning well and they're otherwise healthy. It's a good idea to talk to a dietitian who can help you figure out the best eating plan for your needs, especially if you don't have much of an appetite or aren't eating enough. They can give you customized advice on how to get the right amount of protein and other nutrients to support your weight loss and overall health.

Monitoring recommendation

Some people are more likely to lose muscle, like older adults or those who are frail. If you have low muscle mass to start with, or if you're losing weight fast, you should get checked by a doctor regularly. The doctor will want to keep an eye on your weight, how much muscle and fat you have, and how strong your muscles are. They'll also want to see how well you can move around and if you're eating well. By checking all these things regularly, the doctor can catch any significant muscle loss early and help you start exercises and meal plans that are just right for you. This can help you stay healthy and strong.

Table 7: *Key messages*

What is already known on this topic?
• GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists produce substantial weight loss in obesity and type 2 diabetes.
• Reductions in lean body mass commonly accompany weight loss.
• Concerns have appeared around potential muscle wasting and sarcopenia during treatment.
What this review adds?
• Current evidence suggests that approximately 20–40% of weight loss during incretin-based therapy may be attributable to lean tissue.
• Most of the weight loss consists of reductions in adipose tissue.
• Lean mass losses appear comparable to those observed with lifestyle intervention and bariatric surgery.
How might this affect clinical practice?
• Clinicians should monitor body composition in at-risk populations.
• Resistance exercise and adequate protein intake should accompany pharmacological weight-loss therapy.
• Future studies ought to prioritize assessment of muscle strength and functional outcomes rather than lean mass alone.

References

1. Blüher M (2019) Obesity: global epidemiology and pathogenesis. Nature reviews endocrinology. 15(5): 288-298.
2. Cava E, Yeat NC, Mittendorfer B (2017) Preserving healthy muscle during weight loss. Advances in nutrition. 8(3): 511-519.
3. Frontera WR, Ochala J (2015) Skeletal muscle: a brief review of structure and function. Calcified tissue international 96(3): 183-195.
4. Papamargaritis D, le Roux CW, Holst JJ, Davies MJ (2023) New therapies for obesity. Cardiovascular Research 119(18): 2825-2842.
5. de Mesquita YL, Pera Calvi I, Reis Marques I, Almeida Cruz S, Padrao EM, (2023) Efficacy and safety of the dual GIP and GLP-1 receptor agonist tirzepatide for weight loss: a meta-analysis of randomized controlled trials: Clinical Research. International Journal of Obesity 47(10): 883-892.
6. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, et al. (2015) European guidelines for obesity management in adults. Obesity facts 8(6): 402-424.
7. Markovic TP, Proietto J, Dixon JB, Rigas G, Deed G, et al. (2022) The Australian obesity management algorithm: a simple tool to guide the management of obesity in primary care. Obesity Research & Clinical Practice 16(5): 353-363.
8. Dubin RL, Heymsfield SB, Ravussin E, Greenway FL (2024) Glucagon-like peptide-1 receptor agonist-based agents and weight loss composition: filling the gaps. Diabetes, Obesity and Metabolism 26(12): 5503-5518.
9. Liu QK (2024) Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Frontiers in endocrinology 15: 1431292.
10. Rossi G, Bucciarelli L, Mananguite CL, Giovarelli M, Fiorina P (2026) Muscle loss and GLP-1R agonists use. Acta diabetologic 63(2): 333-342.
11. Ros-Madrid I, Cano-Mármol RP, Ferrer-Gomez M, Ramos-Molina B (2025) Anti-inflammatory properties of GLP-1 receptor agonists and other ancillary benefits from a pharmacological perspective. Canadian Journal of Physiology and Pharmacology 103(12): 369-377.
12. González-Luis A, Llinares-Arvelo V, Martínez-Alberto CE, Hernández-Carballo C, Mora-Fernández C, et al. (2025) Glucagon-like peptide-1 receptor agonists and muscle health: potential role in sarcopenia prevention and treatment. European Journal of Endocrinology 193(5): R31-44.
13. Neeland IJ, Linge J, Birkenfeld AL (2024) Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. Diabetes, Obesity and Metabolism 26: 16-27.
14. Prado CM, Gonzalez MC, Norman K, Barazzoni R, Cederholm T, et al. (2025) Methodological standards for body composition-an expert-endorsed guide for research and clinical applications: levels, models, and terminology. The American journal of clinical nutrition.
15. Baglietto N, Vaquero-Cristóbal R, Albaladejo-Saura M, Mecherques-Carini M, Esparza-Ros F (2024) Assessing skeletal muscle mass and lean body mass: an analysis of the agreement among dual X-ray absorptiometry, anthropometry, and bioelectrical impedance. Frontiers in nutrition 11: 1445892.
16. Rodriguez C, Mota JD, Palmer TB, Heymsfield SB, Tinsley GM (2024) Skeletal muscle estimation: a review of techniques and their applications. Clinical Physiology and Functional Imaging 44(4): 261-284.
17. Helbach J, Hoffmann F, Pieper D, Allers K (2023) Reporting according to the preferred reporting items for systematic reviews and meta-analyses for abstracts (PRISMA-A) depends on abstract length. Journal of Clinical Epidemiology 154: 167-177.
18. Neeland IJ, Linge J, Birkenfeld AL (2024) Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. Diabetes, Obesity and Metabolism 26: 16-27.
19. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, et al. (2021) Semaglutide 2· 4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. The Lancet 397(10278): 971-984.
20. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, et al. (2021) Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. Jama 325(14): 1403-1413.
21. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, et al. (2015) A randomized, controlled trial of 3.0 mg of liraglutide in weight management. New England Journal of Medicine 373(1): 11-22.
22. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, et al. (2015) Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. Jama 314(7): 687-699.

23. Look M, Dunn JP, Kushner RF, Cao D, Harris C, et al. (2025) Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. Diabetes, Obesity and Metabolism 27(5): 2720-2729.
24. Frías JP, Davies MJ, Rosenstock J, Manghi FC, Landó LF, et al. (2021) Ti2rzepatide versus semaglutide once weekly in patients with type 2 diabetes.
25. Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, et al. (2017) Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. The lancet Diabetes & endocrinology 5(5): 341-354.
26. Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, et al. (2009) LEAD-2 and LEAD-3 Study Groups. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes, Obesity and Metabolism 11(12): 1163-1172.
27. Umpierrez G. TOFÉ POVEDANO S, PÉREZ MANGHI F, SHURZINSKE L, PECHTNER V (2014) Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care 37(8): 2168-2176.
28. Liu QK (2024) Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. Frontiers in endocrinology 15: 1431292.
29. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J (2015) Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. Proceedings of the Nutrition Society 74(4): 355-366.
30. Wang K, Wang X, Wang Y (2024) Factors, mechanisms and improvement methods of muscle strength loss. Frontiers in Cell and Developmental Biology 12: 1509519.
31. Pantazopoulos D, Gouveri E, Papazoglou D, Papanas N (2025) GLP-1 receptor agonists and sarcopenia: Weight loss at a cost? A brief narrative review. Diabetes Research and Clinical Practice pp. 112924.
32. McLeod M, Breen L, Hamilton DL, Philp A (2016) Live strong and prosper: the importance of skeletal muscle strength for healthy ageing. Biogerontology 17(3): 497-510.
33. Larsson L, Degens H, Li M, Salviati L, Lee YI, et al. (2019) Sarcopenia: aging-related loss of muscle mass and function. Physiological reviews 99(1): 427-511.
34. Langer HT, Joshi AS, Müller-Werdan U, Norman K (2026) Causes of sarcopenia and frailty in people taking GLP1RAs. Nature Reviews Endocrinology 14: 1-2.
35. Luo J, Wang Y, Mao J, Yuan Y, Luo P, et al. (2025) Features, functions, and associated diseases of visceral and ectopic fat: a comprehensive review. Obesity 33(5): 825-838.
36. Chaston TB, Dixon JB, O'Brien PE (2007) Changes in fat-free mass during significant weight loss: a systematic review. International journal of obesity 31(5): 743-750.
37. Brolin RE (2002) Bariatric surgery and long-term control of morbid obesity. Jama 288(22): 2793-2796.
38. Nuijten MA, Eijsvogels TM, Monpellier VM, Janssen IM, Hazebroek EJ, et al. (2022) The magnitude and progress of lean body mass, fat-free mass, and skeletal muscle mass loss following bariatric surgery: a systematic review and meta-analysis. Obesity reviews 23(1): e13370.
39. Nuijten MA, Eijsvogels TM, Monpellier VM, Janssen IM, Hazebroek EJ, et al. (2022) The magnitude and progress of lean body mass, fat-free mass, and skeletal muscle mass loss following bariatric surgery: a systematic review and meta-analysis. Obesity reviews 23(1): e13370.