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Muscle mass preservation as a therapeutic challenge in GLP-1 receptor agonist therapy

Artur Szafraniec[1, CA], Anna Korzeniowska[2], Mateusz Chmiela[3], Laura Jonderko[4]

[1]*Lower Silesian Centre for Oncology, Pulmonology and Haematology, plac Hirszfelda 12, 53-413 Wrocław, Poland,* e-mail: aszafraniec15@gmail.com *(corresponding author),* [1]https://orcid.org/0000-0002-9991-2039; [2]*Wrocław University Hospital, ul. Borowska 213, 50-556 Wrocław, Poland,* e-mail: korzeniowskaa6@gmail.com, [2]https://orcid.org/0009-0003-6288-3400; [3]*Health Care Center in Oława, ul. K.K. Baczyńskiego 1, 55-200 Oława, Poland,* e-mail: mchmielusz@gmail.com, [3]https://orcid.org/0009-0008-2317-0594; [4]*Department of Molecular and Cellular Biology, Faculty of Pharmacy, Wrocław Medical University, ul. Borowska 211, 50-556 Wrocław, Poland,* e-mail: laura.jonderko@student.umw.edu.pl, [4]https://orcid.org/0009-0007-6018-121X.

Abstract

Weight loss induced by GLP-1 receptor agonists is accompanied by a substantial reduction in lean body mass, typically accounting for 25–40% of total weight loss. Although this proportion is consistent with physiological weight reduction, preservation of skeletal muscle remains essential due to its key role in metabolic health, insulin sensitivity, physical function, and long-term weight maintenance. Excessive muscle loss may increase the risk of sarcopenia, reduced strength, and adverse metabolic adaptations. Current evidence indicates that lean mass loss during GLP-1 therapy is primarily driven by energy deficit, reduced

protein intake, and adaptive physiological responses rather than direct drug-induced catabolism. Nevertheless, GLP-1 receptor agonists may improve muscle quality through reductions in intramuscular fat and improved insulin sensitivity. Preservation of muscle mass therefore requires a multimodal strategy combining pharmacotherapy with resistance exercise and adequate protein intake. Among these interventions, resistance training appears to be the most effective approach for minimizing lean mass loss and maintaining functional capacity during treatment.

Key words: obesity, GLP-1 agonists, sarcopenia, resistance training, nutrition, weight loss

1. Aim of the work

The aim of this work is to evaluate the extent and mechanisms of muscle mass loss during GLP-1 receptor agonist–induced weight reduction. It also seeks to identify effective strategies to preserve lean body mass and optimize overall body composition during therapy.

2. Materials and methods

The article presents a comprehensive, evidence-based review of obesity as a chronic disease, with particular emphasis on the extent, mechanisms, and clinical significance of muscle mass loss during GLP-1 receptor agonist–induced weight reduction, as well as strategies for its preservation. For this purpose, scientific articles were searched in databases including PubMed and Google Scholar, as well as in publicly available sources dedicated to reliable medical knowledge. Literature in English was primarily used. The review of articles and scientific papers was carried out in April 2026.

3. Introduction

3.1. Obesity as a major public health issue

Obesity is a chronic, recurrent metabolic disorder characterized by excessive or abnormally distributed adipose tissue, which can lead to health problems [Nadolsky et al., 2025; Bracchiglione et al., 2025; Elmaleh-Sachs et al., 2023]. It is a complex neurohormonal disease resulting from disturbances in energy balance regulation, leading to abnormal adipose tissue mass, distribution, and function [Nadolsky et al., 2025; Lingvay et al., 2024]. Obesity is currently defined as a chronic, complex disease characterized by abnormal or excessive accumulation of adipose tissue that alters anatomy and physiology and can lead to metabolic, biomechanical, and psychosocial health consequences [Bracchiglione et al., 2025; Bays et al., 2024].

According to the Obesity Medicine Association, obesity is "a serious, chronic, progressive, recurrent, and treatable multifactorial neurobehavioral disease in which increased adiposity promotes adipose tissue dysfunction and abnormal physical forces of adipose mass, resulting in adverse metabolic, biomechanical, and psychosocial health consequences" [Bays et al., 2024].

Diagnostic criteria include [Lingvay et al., 2024; Bays et al., 2024]:

- BMI (Body Mass Index): ≥25 kg/m^2 (overweight), ≥30 kg/m^2 (obese) for the general population;
- Waist circumference: ≥102 cm in men, ≥88 cm in women (≥90 cm in Asian men, ≥80 cm in Asian women) for central obesity;
- Body composition assessment: body fat percentage and its distribution often provide a more accurate representation of the degree of adiposity and associated health risks.

BMI has significant limitations — it does not distinguish between muscle mass and fat mass, does not reflect the distribution of body fat, and does not account for individual differences in fat metabolism [Lingvay et al., 2024]. Therefore, the American Association of Clinical Endocrinology (AACE) proposed the term "adiposity-based chronic disease" (ABCD), which emphasizes that obesity is a disease requiring treatment due to its complications, not merely an elevated BMI [Nadolsky et al., 2025].

3.2. Epidemiology

Obesity has reached the proportions of a global epidemic. In 2021, it was estimated that 2.11 billion adults (45.1% of the total adult population) worldwide were overweight or obese [GBD 2021 Adult BMI Collaborators, 2025]. The global prevalence of obesity increased by 155.1% among men (from 5.8% in 1990 to 14.8% in 2021) and by 104.9% among women (from 10.2% to 20.8%). Assuming historical trends continue, by 2050 the number of overweight and obese adults will reach 3.80 billion — more than half of the projected global adult population. A particularly dramatic increase is predicted in Sub-Saharan Africa (an increase of 254.8%) and in South and East Asia [GBD 2021 Adult BMI Collaborators, 2025; Liu et al., 2025].

3.3. Pathophysiology

Obesity results from a complex interaction of genetic, environmental, behavioral, and biological factors that lead to disturbances in the neurohormonal regulation of energy balance [Nadolsky et al., 2025; Ferreira-Hermosillo et al., 2023; Lustig et al., 2022].

3.3.1. Neurohormonal regulation

The physiology of energy homeostasis involves the coordinated interaction of numerous neuroendocrine satiety factors originating from peripheral sources and acting on the feeding centers in the brain [Nadolsky et al., 2025; Elmaleh-Sachs et al., 2023; Apovian et al., 2015]. Key mechanisms include the gut-brain axis, which responds to peripheral signals from the gastrointestinal tract, adipose tissue, and circulating hormones to stimulate or inhibit central neurons depending on satiety or hunger; and appetite-regulating hormones such as leptin (adipose tissue) — an anorexigenic hormone whose levels are proportional to body fat mass and to which resistance occurs in obesity; ghrelin (stomach) — the only orexigenic intestinal hormone, whose levels rise over time since the last meal; PYY, CCK, GLP-1 (intestine) — satiety hormones secreted in response to food; and insulin (pancreas), which signals satiety and regulates glucose metabolism. The reward (hedonic) system plays a major role: the dopaminergic circuit influences eating behaviors, food preferences, cravings, the pleasure derived from eating, and impulse control [Ferreira-Hermosillo et al., 2023; Apovian et al., 2015; Elmaleh-Sachs et al., 2023].

3.3.2. Adipose tissue dysfunction

Adipose tissue performs functions that go beyond energy storage — it is an active endocrine organ that synthesizes adipokines and hormones [Heymsfield et al., 2017; O'Brien et al., 2017]. Pathophysiological mechanisms include chronic inflammation through excessive secretion of pro-inflammatory adipokines by adipocytes and macrophages; elevated free fatty acids reflecting increased adipose tissue mass and impaired lipolysis; insulin resistance, particularly strongly associated with excess visceral adipose tissue; lipotoxicity, with accumulation of excess lipid intermediates (e.g., ceramides) in non-adipose tissues leading to cellular dysfunction and apoptosis; and organ steatosis, with lipid accumulation in hepatocytes (fatty liver), pancreas (pancreatic steatosis), and other organs [Elmaleh-Sachs et al., 2023; Heymsfield et al., 2017; O'Brien et al., 2017]. These observations are consistent with the model that the body defends its fat mass around an equilibrium point based on interactions involving genetics, behavior, biological factors, and the current obesogenic environment [Nadolsky et al., 2025].

3.4. Complications

Obesity has wide-ranging health consequences, which can be divided into metabolic, anatomical, and psychological categories, although these categories overlap [Lingvay et al., 2024; Bae et al., 2025].

3.4.1. Metabolic complications

- Type 2 diabetes resulting from β-cell dysfunction and insulin resistance;

- Hypertension, occurring in 29.0% of obese individuals aged 18–39, 66.2% aged 40–64, and 89.4% aged ≥65 [Bae et al., 2025];
- Dyslipidemia, affecting 28.1% of obese individuals aged 18–39, 65.4% aged 40–64, and 88.0% aged ≥65 [Bae et al., 2025];
- Coronary artery disease and cardiovascular diseases: among men with BMI 30–39.9, the rate of cardiovascular events was 20.21 per 1,000 person-years vs. 13.72 for normal BMI; among women, 9.97 vs. 6.37 [Elmaleh-Sachs et al., 2023];
- Chronic kidney disease: the second leading cause of DALYs associated with high BMI;
- Metabolic and fatty liver disease (MASLD, formerly NAFLD).

3.4.2. Anatomical and mechanical complications

- Osteoarthritis — increased stress on weight-bearing joints leads to pain and impaired mobility;
- Obstructive sleep apnea — increased soft tissue in the throat causes airway collapse and respiratory failure;
- Gastroesophageal reflux disease — increased abdominal pressure;
- Venous stasis and thromboembolic complications.

3.4.3. Psychological complications

- Depression and anxiety occur in 44.1% of obese individuals aged 18–39, 39.0% aged 40–64, and 38.9% aged ≥65 [Bae et al., 2025];
- Stigmatization and discrimination: most people with obesity experience stigmatization related to their body size, leading to reduced quality of life, employment discrimination, and lower earnings [Lingvay et al., 2024];
- Reduced quality of life: people with higher BMI report lower physical and mental quality of life.

3.5. Cancer risk

Obesity increases the risk of at least 13 types of cancer, including esophageal, gastric cardia, colorectal, liver, pancreatic, postmenopausal breast, endometrial, ovarian, kidney, and thyroid cancers [Cornier et al., 2011]. Chronic inflammation and hyperinsulinemia are proposed mechanisms [Lingvay et al., 2024].

3.6. Disease burden and mortality

In 2021, high BMI contributed to 3.71 million deaths (7.1% of all deaths) and 129 million DALYs (disability-adjusted life years), accounting for 4.9% of global DALYs [GBD 2021 Adult BMI Collaborators, 2025; Xie et al., 2025].

3.7. GLP-1 agonists

GLP-1 receptor agonists are medications that mimic the natural incretin hormone; they work by stimulating insulin secretion, inhibiting glucagon, delaying gastric emptying, and increasing satiety, and have demonstrated high efficacy in the treatment of type 2 diabetes and obesity.

3.7.1. Mechanism of action

GLP-1 agonists bind to GLP-1 receptors on pancreatic β-cells, stimulating insulin secretion in a glucose-dependent manner, which minimizes the risk of hypoglycemia [Rosen et al., 2026; LeRoith et al., 2019; Alfaris et al., 2024]. At the same time, they inhibit glucagon secretion from α-cells, reducing glucose production in the liver [Rosen et al., 2026; LeRoith et al., 2019; Alfaris et al., 2024]. GLP-1 receptors are also found in the brain, stomach, and other extra-pancreatic tissues [Wilcox et al., 2020]. These medications delay gastric emptying, which reduces postprandial increases in blood glucose and increases the feeling of fullness [Rosen et al., 2026; LeRoith et al., 2019; Wilcox et al., 2020]. This effect is particularly pronounced with short-acting formulations [Davies et al., 2018; Brown et al., 2021]. GLP-1 agonists act on the hypothalamic nuclei, increasing satiety and reducing appetite, which leads to spontaneous reductions in calorie intake and weight loss regardless of the presence of diabetes [Rosen et al., 2026; Alfaris et al., 2024; Wilcox et al., 2020]. Additional mechanisms include increased insulin sensitivity in skeletal muscle by enhancing microcirculation [Alfaris et al., 2024]; modulation of the gut microbiota [Rosen et al., 2026]; reduction of hepatic steatosis and ectopic fat deposition; and cardioprotective and nephroprotective effects through multifaceted mechanisms [Rosen et al., 2026; Natale et al., 2025].

3.7.2. Examples of medications and pharmacological differences

Long-acting GLP-1 agonists:

- Liraglutide (once daily, 1.8 mg or 3.0 mg) — modification of human GLP-1 with a C16 fatty acid chain [Drucker, 2025; Davies et al., 2018];

- Dulaglutide (once weekly) — fusion with an immunoglobulin Fc fragment [Davies et al., 2018; Gentilella et al., 2019];
- Semaglutide (once weekly subcutaneously or once daily orally) — modification of human GLP-1 with a C18 fatty acid chain [Drucker, 2025; Davies et al., 2018; Brown et al., 2021];
- Extended-release exenatide (once weekly) [Gentilella et al., 2019; Davies et al., 2018].

Long-acting formulations have a greater effect on fasting blood glucose through increased insulin secretion and reduced glucagon secretion, with a lesser effect on gastric emptying (tachyphylaxis) [Brown et al., 2021; Gentilella et al., 2019; Nauck et al., 2021].

Multireceptor agonists:

- Tirzepatide — dual GLP-1/GIP agonist (once weekly) [Alfaris et al., 2024];
- Orforglipron — small-molecule oral GLP-1 agonist (once daily) [Horn et al., 2026];
- Retatrutide — triple GLP-1/GIP/glucagon agonist (in clinical trials) [Alfaris et al., 2024].

3.7.3. Clinical efficacy

Glycemic control in type 2 diabetes — all GLP-1 agonists effectively lower HbA1c, but with varying degrees of efficacy [Davies et al., 2018]. Tirzepatide produces the greatest reduction in HbA1c (on average −2.1% to −2.3%), followed by semaglutide (−1.5% to −2.1%), liraglutide (−1.2%), dulaglutide, once-weekly exenatide, twice-daily exenatide, and lixisenatide [Davies et al., 2018; Yao et al., 2024; Ren et al., 2025]. Weight loss data from clinical trials in non-diabetic patients — a meta-analysis of 47 randomized trials involving 23,244 patients showed that GLP-1 agonists result in an average weight loss of 4.57 kg (95% CI −5.35 to −3.78), a reduction in BMI of 2.07 kg/m^2, and a reduction in waist circumference of 4.55 cm compared to placebo [Wong et al., 2025]. Another meta-analysis of 26 studies involving 15,491 participants demonstrated the following efficacy for commercially available medications [Moiz et al., 2025]:

- Tirzepatide 15 mg once weekly: weight loss up to 17.8% (95% CI 16.3–19.3%) after 72 weeks;
- Semaglutide 2.4 mg once weekly: weight loss up to 13.9% (95% CI 11.0–16.7%) after 68 weeks;
- Liraglutide 3.0 mg once daily: weight loss up to 5.8% (95% CI 3.6–8.0%) after 26 weeks [Wilding et al., 2021].

A meta-analysis showed that the greatest benefits from treatment are seen in younger patients, women, those without diabetes, those with higher baseline body weight and BMI but lower baseline HbA1c, and those treated for a longer duration. Significant heterogeneity in response exists — in studies of GLP-1 agonists, a significant minority of participants did not achieve weight loss [Wong et al., 2025; Alexander et al., 2026].

4. Discussion

4.1. Muscle mass loss during GLP-1 agonist therapy

Muscle mass loss during weight reduction and GLP-1 receptor agonist therapy results from a complex interplay of energy deficit-induced metabolic adaptations, hormonal changes, and altered protein turnover dynamics. While GLP-1 therapy produces lean mass loss proportional to total weight reduction (25–40% of weight loss), this primarily reflects the physiological response to negative energy balance rather than direct drug-induced muscle catabolism [Mozaffarian et al., 2025; Karakasis et al., 2025].

4.1.1. Mechanisms of muscle mass loss during general weight loss (caloric restriction)

Energy deficit-induced protein catabolism. Negative energy balance fundamentally disrupts the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB), favoring net protein loss [Carbone et al., 2012; McIver et al., 2012]. During caloric restriction, skeletal muscle mass decreases primarily due to reduced fiber size rather than fiber number loss [Lu et al., 2017].

Molecular pathways activated during caloric restriction [Carbone et al., 2012; McIver et al., 2012; Lu et al., 2017]:

- Suppression of anabolic signaling — caloric restriction attenuates the IGF-1/Akt/mTOR pathway, the primary driver of muscle protein synthesis; reduced phosphorylated Akt and decreased mTORC1 activity lead to diminished protein synthesis rates;
- Activation of catabolic pathways — the ubiquitin-proteasome system (UPS) becomes activated, with increased expression of E3 ubiquitin ligases MuRF-1 and MAFbx/atrogin-1, which tag muscle proteins for degradation;
- Calpain-mediated proteolysis — caloric restriction increases calpain 1 (CAPN1) activity while reducing calpastatin expression, leading to enhanced muscle protein breakdown [Lu et al., 2017];

- Reduced PGC1α-4 signaling — energy restriction decreases PGC1α-4, which normally promotes muscle hypertrophy through IGF-1 signaling [Lu et al., 2017].

4.1.2. Hormonal adaptations to energy deficit

Energy restriction triggers profound neuroendocrine changes that promote muscle loss:

- Suppression of anabolic hormones — decreased activity of the hypothalamic-pituitary-thyroid, gonadotropic, and somatotropic axes, resulting in reduced thyroid hormones, sex hormones (testosterone, estradiol), growth hormone, and IGF-1;
- Activation of catabolic hormones — increased hypothalamic-pituitary-adrenal axis activity leads to elevated cortisol, which directly promotes muscle protein breakdown through glucocorticoid receptor-mediated upregulation of atrophy genes;
- Insulin resistance — reduced insulin sensitivity during energy deficit impairs the anabolic effects of insulin on muscle protein synthesis [Martín et al., 2018; Priego et al., 2021; Sainsbury & Zhang, 2012].

These hormonal changes not only promote muscle loss but also favor central adiposity accumulation during weight regain, creating a metabolic environment that predisposes to sarcopenia and osteoporosis [Sainsbury & Zhang, 2012].

4.2. Additional mechanisms specific to GLP-1 therapy

While GLP-1 receptor agonists produce lean mass loss primarily through energy deficit mechanisms, emerging evidence suggests both potentially protective and detrimental effects on muscle metabolism. Factors contributing to muscle loss with GLP-1 therapy [Mozaffarian et al., 2025; Nauck et al., 2026]:

- Rapid weight reduction — the magnitude and rapidity of weight loss correlate with lean mass reduction; modeling data suggest muscle loss represents 10–15% of total weight reduction in females and 20–25% in males without structured strength training;
- Reduced protein intake — GLP-1-induced appetite suppression and early satiety lead to decreased overall food intake, including protein consumption; this is particularly problematic for older adults, perimenopausal/menopausal women, and those with low testosterone or sedentary behavior;
- Sex differences — males experience proportionally greater muscle loss than females during GLP-1 therapy, likely reflecting hormonal and body composition differences [Mozaffarian et al., 2025].

Despite clinical observations of lean mass loss, preclinical studies reveal that GLP-1 receptor agonists may exert direct muscle-protective effects.

4.2.1. Anabolic signaling pathways

[González-Luis et al., 2025; Maihemuti et al., 2025; Iwai et al., 2023]:

- PI3K/Akt/mTOR activation — GLP-1 receptor stimulation activates cAMP-mediated PKA and Akt signaling, which can enhance mTOR activity and promote protein synthesis;
- AMPK–PGC-1α pathway — GLP-1 activates AMPK and PGC-1α, promoting mitochondrial biogenesis and improving muscle oxidative capacity;
- Myogenic differentiation — GLP-1 receptor agonists upregulate myogenic factors MyoD and myogenin (MyoG), promoting muscle cell proliferation and differentiation [Chen et al., 2025; Maihemuti et al., 2025; Hong et al., 2019].

4.2.2. Anti-catabolic effects

[Chen et al., 2025; Iwai et al., 2023; Maihemuti et al., 2025; Hong et al., 2019]:

- Suppression of the ubiquitin-proteasome system — GLP-1 receptor agonists reduce expression of MuRF-1 and atrogin-1, the key E3 ubiquitin ligases responsible for muscle protein degradation;
- Myostatin inhibition — GLP-1 signaling suppresses myostatin expression through NF-κB pathway inhibition; myostatin is a negative regulator of muscle growth [Iwai et al., 2023; Maihemuti et al., 2025; Hong et al., 2019];
- Reduced inflammation — GLP-1 receptor agonists decrease proinflammatory cytokines (IL-1β, IL-6, TNF-α) and reactive oxygen species accumulation, which otherwise promote muscle catabolism [Iwai et al., 2023; Maihemuti et al., 2025; Chen et al., 2025];

- Glucocorticoid receptor antagonism — GLP-1 receptor activation inhibits glucocorticoid receptor translocation by upregulating GR inhibitory complexes, thereby blocking cortisol-mediated muscle breakdown [Hong et al., 2019].

4.2.3. Vascular and metabolic effects

[Katsanos et al., 2026; Abdulla et al., 2020]:

- Microvascular recruitment — GLP-1 and GLP-1 receptor agonists recruit muscle microvasculature, expanding capillary surface area and increasing delivery of insulin, glucose, and amino acids to muscle tissue [Katsanos et al., 2026];
- Enhanced muscle protein synthesis in fed state — in older adults, GLP-1 infusion during hyperinsulinemic-hyperaminoacidemic conditions markedly enhanced postprandial muscle protein synthesis (from 0.058% to 0.102%/h) and increased microvascular blood flow 5-fold, overcoming age-related anabolic resistance [Abdulla et al., 2020];
- Improved muscle quality — GLP-1 therapy reduces intramuscular fat infiltration and enhances insulin sensitivity, improving muscle quality despite modest volume reduction [Nauck et al., 2026; Iwai et al., 2023].

4.3. Discrepancy between preclinical and clinical evidence

Preclinical studies consistently show muscle-protective effects of GLP-1 receptor agonists, including increased grip strength, enhanced skeletal muscle cross-sectional area, preserved muscle mass, and favorable molecular changes — all while body weight remains stable within defined dosage ranges [González-Luis et al., 2025; Maihemuti et al., 2025]. Clinical studies show body weight reduction accompanied by lean mass loss, with approximately 25–40% of total weight loss coming from lean mass [Liu et al., 2025; Karakasis et al., 2025; Anyiam et al., 2025].

Proposed explanations for this discrepancy [González-Luis et al., 2025; Maihemuti et al., 2025; Katsanos et al., 2026]:

- Dose-dependent effects — preclinical muscle-protective effects occur at lower doses that do not induce substantial weight loss; higher clinical doses produce profound energy deficit that overwhelms direct muscle-protective effects;
- Energy deficit dominance — the magnitude of negative energy balance in clinical trials (15–20% body weight reduction) creates metabolic conditions favoring muscle catabolism regardless of direct GLP-1 muscle effects;
- Species differences — GLP-1 receptor expression and signaling may differ between rodent and human skeletal muscle; the presence and functional significance of GLP-1 receptors in human muscle cells remains controversial [Katsanos et al., 2026];
- Lack of multimodal interventions — clinical trials typically do not mandate resistance training or high protein intake, whereas these interventions could allow the muscle-protective effects of GLP-1 to manifest.

4.4. Body composition outcomes

Despite lean mass loss, GLP-1 therapy produces favorable overall body composition changes [Karakasis et al., 2025; Anyiam et al., 2025]:

- Preferential fat loss — fat mass reduction significantly exceeds lean mass reduction; in individuals without diabetes, fat mass decreased by 6.02 kg versus lean mass loss of 1.41 kg, with lean mass accounting for less than 20% of total weight reduction [Anyiam et al., 2025];
- Preserved relative lean mass — while absolute lean mass decreases, the percentage of lean mass relative to total body weight often remains unchanged or improves;
- Improved muscle quality — reduced intramuscular fat infiltration and enhanced insulin sensitivity may preserve or improve muscle function despite modest volume reduction [Nauck et al., 2026].

The pathophysiology of muscle loss during GLP-1 therapy is primarily driven by energy deficit-induced metabolic adaptations rather than direct drug toxicity to muscle. GLP-1 receptor agonist therapy produces comparable proportional lean mass loss to physiological weight loss through lifestyle interventions (25–35% of total weight loss), but substantially less than bariatric surgery in absolute terms. However, bariatric surgery achieves greater total weight loss and produces more favorable body composition changes overall [Wang et al., 2026; Eisa & Barood, 2026].

4.5. Comparison with other weight-loss interventions

4.5.1. Proportion of lean mass loss

GLP-1 therapy vs. lifestyle intervention. A 2026 meta-analysis of 20 randomized trials found that lean mass constituted 25–39% of total weight lost across different GLP-1 agents: semaglutide 35.2%, tirzepatide 25.4%, and liraglutide 26.8% [Eisa & Barood, 2026]. This is comparable to lifestyle interventions alone (26.2%, $p = 0.42$), but notably higher than lifestyle plus resistance training (17.5%) [Eisa & Barood, 2026]. A systematic review examining incretin-based therapies found that the median proportion of total weight loss from muscle-based indices was 34.9%, with 68% of studies exceeding the benchmark of 25% [Batsis et al., 2026].

Bariatric surgery. Following bariatric surgery, approximately 24% of total weight loss comes from lean body mass, with the remaining 76% from fat mass — a 3:1 ratio of fat to lean mass loss [Kulovitz et al., 2014]. This proportion is similar to medical weight loss when matched for 15% body weight reduction [Kulovitz et al., 2014].

4.5.2. Absolute changes in body composition

GLP-1 therapy. Over 24 months, GLP-1 receptor agonists (semaglutide and tirzepatide) produce approximately 3% reduction in fat-free mass [Wang et al., 2026]. The fat-free mass to fat mass ratio improves substantially despite lean mass loss [Wang et al., 2026].

Bariatric surgery. Produces 10–12% reduction in fat-free mass over 24 months — considerably greater absolute loss than GLP-1 therapy [Wang et al., 2026]. However, bariatric surgery achieves much greater total weight loss. A 2026 network meta-analysis found that at <104 weeks, bariatric surgery achieved greater reductions than GLP-1 receptor agonists in [Sabatella et al., 2026]:

- Percent total weight loss: −10.3% ($p = 0.001$);
- BMI: −4.5 kg/m^2 ($p < 0.001$);
- Body weight: −11.7 kg ($p < 0.001$);
- Waist circumference: −12.6 cm ($p < 0.001$).

At 104 weeks, differences remained for percent total weight loss (−9.1%, $p = 0.022$) and body weight (−14.6 kg, $p = 0.049$) [Sabatella et al., 2026]. Notably, when comparing tirzepatide specifically to bariatric surgery, differences were not statistically significant [Sabatella et al., 2026].

4.5.3. Timing of lean mass loss

Bariatric surgery. Most fat-free mass loss occurs in the first 6 months post-operatively. One study found that the first month after surgery accounted for 67.4% of the total lean body mass reduction over 12 months [Sivakumar et al., 2022]. Another study showed mean fat-free mass loss of −6.4 kg within the first 6 months [Perez-Romero et al., 2026].

GLP-1 therapy. Lean mass loss occurs more gradually, proportional to the rate of weight reduction [Mozaffarian et al., 2025].

4.5.4. Body composition quality

Despite lean mass loss, both interventions produce favorable changes in body composition quality. GLP-1 therapy improves muscle quality by reducing intramuscular fat infiltration and enhancing insulin sensitivity, potentially mitigating functional impairment despite modest volume reduction [Gonzalez-Rellan & Drucker, 2025]. In the SURPASS-3 trial substudy, tirzepatide showed modest reductions in muscle volume proportional to total weight loss, but significant improvements in muscle quality with marked reductions in muscle fat infiltration [Gonzalez-Rellan & Drucker, 2025]. Bariatric surgery produces greater increases in the fat-free mass to fat mass ratio compared to GLP-1 therapy [Wang et al., 2026]. However, it also leads to reductions in bone mineral density at the total hip, femoral neck, and lumbar spine [Jassil et al., 2023].

4.5.5. Excessive fat-free mass loss

Bariatric surgery. A 2026 study found that 41–46% of bariatric surgery patients exceeded the 25% threshold for fat-free mass loss as a proportion of total weight loss, 27–31% exceeded 30%, and 14% exceeded 35% [Perez-Romero et al., 2026]. The median proportion was 26.4% at 6 months and 28.7% at 12 months [Perez-Romero et al., 2026].

GLP-1 therapy. Similar proportions exceed benchmarks. In one systematic review, 65% of studies using BIA or DXA exceeded the 25% benchmark, with a median of 34.9% of total weight loss from muscle-based indices [Batsis et al., 2026].

Lifestyle plus resistance training produces the most favorable body composition profile, with only 17.5% of weight loss coming from lean mass [Eisa & Barood, 2026]. Comparative outcomes across interventions are summarised in Table 1.

Table 1. Lean mass loss across weight-loss interventions.

Intervention	Lean mass loss
Lifestyle alone	26.2%
Lifestyle + resistance training	17.5%
Semaglutide	35.2%
Tirzepatide	25.4%
Liraglutide	26.8%
Bariatric surgery	24–29%

Source: own elaboration based on Wang et al., 2026; Eisa & Barood, 2026; Kulovitz et al., 2014.

5. How to maintain muscle mass during GLP-1 receptor agonist therapy

Maintaining muscle mass during GLP-1 receptor agonist therapy requires a combination of structured resistance training, adequate protein intake, and regular monitoring of body composition. Protein supplementation alone is insufficient without strength training, and therapy combined with physical activity yields the best results in terms of maintaining lean body mass. Resistance training during GLP-1 receptor agonist therapy should include at least 3 sessions per week (60–90 minutes total) combined with a minimum of 150 minutes of moderate aerobic activity per week. The program should be structured, gradually progressive, and tailored to the patient's fitness level, with emphasis on multi-joint exercises that engage major muscle groups.

5.1. Training frequency and volume

Resistance training:

- Frequency: at least 3 times per week [Mozaffarian et al., 2025; Mehrtash et al., 2025];
- Duration: 60–90 minutes per week in total [Mehrtash et al., 2025];
- Alternatively: at least 2 days per week for patients at risk of sarcopenia [Kushner et al., 2025].

Aerobic training (supplementary):

- 150 minutes per week of moderate intensity OR 75 minutes per week of high intensity [Mozaffarian et al., 2025; Mehrtash et al., 2025];
- 30–60 minutes per day of aerobic activity combined with resistance training 2–3 times per week for optimal long-term metabolic effects [Mehrtash et al., 2025].

Combined training (resistance + aerobic) yields better results than aerobic activity alone in terms of maintaining muscle mass, strength, functional capacity, and weight loss.

5.2. Structure of the training program

Induction phase (first 6 weeks) — due to potential fatigue associated with GLP-1 therapy, start with modest goals and gradually increase the workload [Mehrtash et al., 2025]. The program should be flexible but structured. An example program based on a study with liraglutide 3.0 mg included [Lundgren et al., 2021; Jensen et al., 2026]:

- Twice a week: supervised group sessions consisting of 30 minutes of high-intensity interval training on a stationary bike and 15 minutes of circuit training;
- Twice a week: individual sessions of moderate to high intensity (cycling, running, brisk walking).

Monitoring with heart rate monitors verifies achievement of the required weekly time spent at moderate or high intensity. The program was structured but flexible — participants could swap group sessions for individual ones or vice versa, and could reduce the frequency while increasing the duration or intensity [Lundgren et al., 2021].

5.2.1. Resistance training

- Focus on multi-joint exercises that engage major muscle groups;
- Progressive resistance tailored to the patient's capabilities;
- Available methods: group classes, home exercises with resistance bands or weights [Mehrtash et al., 2025].

5.2.2. Aerobic training

- Moderate intensity: 64–76% of maximum heart rate;
- High intensity: 77–93% of maximum heart rate.

  In the study, participants performed exercises at an average of 79% of maximum heart rate [Jensen et al., 2026].

5.3. Clinical effects of resistance training with GLP-1

Resistance training can reduce the loss of lean body mass by 50–95% during caloric restriction [Mehrtash et al., 2025]. In studies with GLP-1:

- GLP-1 therapy alone — 25–40% of total weight loss is lean body mass [Mehrtash et al., 2025];
- GLP-1 + exercise — significantly better lean body mass retention and reduction in waist circumference [American Diabetes Association, 2026].

In a study with liraglutide 3.0 mg + exercise for 52 weeks (median 2.65 sessions/week, 116 min/week at 79% HRmax) [Jensen et al., 2026]:

- Stair-climbing test — time reduced by 1.2 seconds (8.6% improvement) vs. liraglutide therapy alone;
- Peak oxygen consumption — increase of 3.0 mL/min/kg of lean body mass;
- Relative muscle strength (normalized to body weight) — +3.3% in the combination therapy group vs. −7.8% in the placebo group.

  Combination therapy (GLP-1 + exercise) demonstrated [American Diabetes Association, 2026]:

- Improved β-cell function, glucose tolerance, and insulin sensitivity;
- Greater reduction in abdominal fat and inflammation;
- Preservation of bone mineral density (while GLP-1 therapy alone reduced BMD) [Mozaffarian et al., 2025].

5.4. Tailoring the program to fitness level

A 3-step approach for all patients [Mehrtash et al., 2025]:

- Stage 1: gradually introduce regular physical activity, building up to 150 minutes per week of moderate-intensity activity or 75 minutes per week of vigorous-intensity activity;
- Stage 2: incorporate resistance training, aiming for 60–90 min/week;
- Stage 3: maintain 30–60 min/day of aerobic activity plus resistance training 2–3 times per week.

5.5. Monitoring and adjusting therapy

Indicators requiring further evaluation [Kushner et al., 2025]:

- Weight loss >5% per month;
- Deterioration in functional test results;
- Weight loss [Mozaffarian et al., 2025];
- BIA (bioelectrical impedance analysis) — practical, inexpensive, frequent measurements possible;
- DXA — gold standard, recommended every 1–2 years;
- Functional measurements — preferred for regular monitoring.

5.6. Practical implementation guidelines

The program should be tailored to the patient's fitness level and physical capabilities, flexible in format (ability to switch from group to individual sessions), monitored using heart-rate monitors or apps, and supported by a qualified instructor (physical therapist, exercise physiologist) [Mozaffarian et al., 2025].

Barriers and solutions:

- Fatigue — start with low goals, gradual progression;
- Lack of access to a gym — home exercises with resistance bands, weights, or bodyweight;
- Lack of motivation — group classes, instructor support, telemedicine.

Resistance training must be combined with adequate protein intake (≥1.2–1.5 g/kg/day), as increased protein intake alone, without training, is insufficient [Mozaffarian et al., 2025]. Excess protein beyond the muscles' needs may be converted into body fat.

New pharmacological approaches aimed at preserving muscle mass are being studied in combination with GLP-1 and exercise:

- Apitegromab (myostatin inhibitor) + tirzepatide — preservation of 54.9% vs. 30% of lean body mass;
- Bimagrumab + semaglutide — ~22% reduction in fat mass with a 3.6% increase in lean body mass;
- Trevogrumab + semaglutide ± garetosmab — preservation of 50–80% of lean body mass.

However, structured resistance training currently remains the primary, non-pharmacological intervention with proven efficacy in preserving muscle mass during GLP-1 therapy [Gonzalez-Rellan & Drucker, 2025].

6. Nutritional recommendations

6.1. Protein intake — goals and calculations

During active weight loss, the recommended protein intake is 1.2–1.6 g/kg/day [Mozaffarian et al., 2025]. Various approaches to calculating this exist:

- Actual body weight — may significantly overestimate requirements in obese individuals;
- Adjusted body weight — more precise;
- Fat-free mass (FFM) — most accurate (1.5 g/kg FFM/day), but requires body composition measurement;
- Absolute target — 80–120 g protein/day (16–24% of energy in a 2000 kcal diet) may facilitate adherence to recommendations [Mozaffarian et al., 2025].

6.2. Minimum and maximum intake

- Minimum: not less than 0.4–0.5 g/kg/day (risk of muscle atrophy and functional impairments) [Mozaffarian et al., 2025];
- Maximum: avoid long-term intake of ≥2 g/kg/day due to potential adverse effects [Mozaffarian et al., 2025].

6.3. Protein sources — hierarchy of recommendations

Priority protein sources (due to links to overall health) include plant-based sources (beans, peas, lentils, whole grains); dairy (Greek yogurt, cottage cheese, milk, cheese); seafood (fish and other seafood); eggs; and lean poultry. Red and processed meat should be consumed in moderate amounts or minimized (links to type 2 diabetes, cardiovascular disease, colorectal cancer). Due to reduced appetite, foods low in volume and high in protein are recommended — fish, eggs, Greek yogurt, cottage cheese, nuts and seeds (almonds, peanuts, chia, sesame, hemp), nut butters (peanut butter, almond butter), and high-protein smoothies [Mozaffarian et al., 2025].

6.4. Meal planning and eating habits

The MEAL mnemonic for diet management during GLP-1 therapy:

- M (Muscle maintenance) — adequate protein intake and structured physical activity;
- E (Energy balance) — smaller, nutrient-dense meals instead of calorie restriction; whole grains for satiety; healthy fats for absorption of fat-soluble vitamins;
- A (Avoid side effects) — increased fiber intake and hydration (>2–3 L/day) for constipation; avoiding fried foods and carbonated beverages for nausea; smaller portions and avoiding lying down for 2–3 hours after a meal for reflux;
- L (Liquid intake) — >2–3 L of water per day plus foods rich in water and electrolytes.

Key recommendations are to encourage regular, small meals at set times (avoid long periods without eating), flexibility in food choices, controlled portions of treats, adequate hydration, and minimal alcohol consumption; avoid emotional, mindless, or nighttime eating, long periods without meals (excessive fasting), and eating large meals [Mehrtash et al., 2025].

6.5. Potentially beneficial supplements

When adequate protein intake and resistance training are insufficient, the following may be helpful: branched-chain amino acids (BCAAs), creatine, leucine, omega-3 fatty acids, and vitamin D. Studies in mice have shown that leucine supplementation combined with semaglutide [Zhao, 2026] induced greater fat loss and higher lean mass retention compared to semaglutide alone, without further suppressing appetite. After discontinuation of semaglutide, leucine significantly attenuated weight regain, reduced fat regain, and preserved lean body mass. These effects were completely abolished upon inhibition of mTORC1, highlighting the critical dependence on this signaling pathway [Chavez et al., 2025].

Creatine supplementation, especially when combined with resistance training, is a well-established strategy to enhance muscle mass, strength, and cellular energetics. Emerging evidence suggests that creatine may also improve glycemic control through mechanisms involving AMPK activation and GLUT-4 translocation, as well as exert anti-inflammatory effects. Given that incretin-based therapies often induce a substantial caloric deficit and may accelerate muscle loss, creatine supplementation could represent a practical adjunct intervention to preserve FFM and maintain functional capacity. Direct evidence in this population is currently lacking; well-designed randomized controlled trials incorporating precise body composition assessments, strength measurements, and mechanistic biomarkers are urgently needed [Ribeiro et al., 2026].

7. Conclusions

Obesity is a chronic, multifactorial disease associated with significant metabolic, cardiovascular, and psychosocial complications. GLP-1 receptor agonists have become a cornerstone of modern treatment, promoting substantial weight loss through appetite suppression, delayed gastric emptying, and improved metabolic regulation. However, this weight loss is accompanied not only by fat reduction but also by a clinically relevant loss of lean body mass, typically accounting for 25–40% of total weight loss. Preservation of muscle mass is critical, as skeletal muscle plays a key role in insulin sensitivity, physical function, and long-term weight maintenance. Excessive muscle loss may increase the risk of sarcopenia, reduce strength, and contribute to adverse metabolic adaptations. Importantly, this loss is primarily driven by energy deficit and reduced protein intake rather than direct effects of GLP-1 therapy, and may be partially offset by improvements in muscle quality. Therefore, optimal management requires a multimodal approach combining pharmacotherapy with resistance training and adequate protein intake. These interventions are essential to preserve lean mass, improve functional outcomes, and maximize the long-term benefits of weight-loss therapy.

Declarations

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