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FROM WEIGHT LOSS TO WEIGHT REGAIN WITH TIRZEPATIDE: BODY COMPOSITION AND THE ROLE OF NUTRITIONAL INTERVENTIONS AND EXERCISE DURING AND AFTER TREATMENT

DA PERDA DE PESO AO REGANHO DE PESO COM TIRZEPATIDA: COMPOSIÇÃO CORPORAL E O PAPEL DAS INTERVENÇÕES NUTRICIONAIS E DO EXERCÍCIO DURANTE E APÓS O TRATAMENTO

DE LA PÉRDIDA DE PESO A LA RECUPERACIÓN DEL PESO CON TIRZEPATIDA: COMPOSICIÓN CORPORAL Y EL PAPEL DE LAS INTERVENCIONES NUTRICIONALES Y EL EJERCICIO DURANTE Y DESPUÉS DEL TRATAMIENTO

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ABSTRACT

Dual GIP/GLP-1 receptor agonists promote substantial weight loss, predominantly through reductions in fat mass, but may also reduce lean mass. Following treatment discontinuation, clinical studies indicate progressive weight regain and attenuation of some cardiometabolic benefits. However, the body composition of regained weight remains poorly characterized, and available data do not establish whether the lost body compartments are restored in the same proportions. This review discusses body composition trajectories during weight loss and after withdrawal of tirzepatide, together with the role of nutritional interventions and exercise in preserving lean mass. The literature reviewed highlights the importance of individualized nutritional care, with particular attention to protein adequacy and nutrient density, combined with exercise, especially resistance training. These strategies may support the preservation of muscle mass and function, although evidence specifically addressing their effectiveness in maintaining body composition after tirzepatide withdrawal remains limited. Management should therefore be continuous and multidisciplinary, and further studies are needed to assess weight, body composition and neuromuscular function together throughout treatment and following discontinuation.

KEYWORDS: *Obesity. Gastric inhibitory polypeptide. Glucagon-like peptide 1. Body composition.*

RESUMO

Os agonistas duplos dos receptores GIP/GLP-1 promovem uma perda de peso substancial, predominantemente por meio da redução da massa gorda, mas também podem levar à redução da massa magra. Após a interrupção do tratamento, estudos clínicos indicam um reganho de peso progressivo e a atenuação de alguns benefícios cardiometabólicos. Contudo, a composição corporal do peso recuperado ainda é pouco compreendida, e os dados disponíveis não esclarecem se os compartimentos corporais perdidos são restaurados nas mesmas proporções. Esta revisão discute as trajetórias da composição corporal durante a perda de peso e após a interrupção do uso de tirzepatida, bem como o papel das intervenções nutricionais e do exercício físico na preservação da massa magra.

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A literatura analisada destaca a importância de um acompanhamento nutricional individualizado — com atenção especial à adequação proteica e à densidade de nutrientes — aliado à prática de exercícios, especialmente o treinamento resistido. Tais estratégias podem favorecer a preservação da massa e da função muscular, embora ainda existam poucas evidências específicas sobre a sua eficácia na manutenção da composição corporal após a interrupção da tirzepatida. Portanto, o manejo deve ser contínuo e multidisciplinar; são necessários mais estudos para avaliar, de forma integrada, o peso, a composição corporal e a função neuromuscular, tanto durante o tratamento quanto após a sua interrupção.

PALAVRAS-CHAVE: Obesidade. Polipeptídeo inibidor gástrico. Peptídeo semelhante ao glucagon-1. Composição corporal.

RESUMEN

Los agonistas duales de los receptores GIP/GLP-1 promueven una pérdida de peso sustancial, principalmente mediante la reducción de la masa grasa, aunque también pueden disminuir la masa magra. Tras la interrupción del tratamiento, los estudios clínicos indican una recuperación progresiva del peso y una atenuación de algunos beneficios cardiometabólicos. No obstante, la composición corporal del peso recuperado no está bien caracterizada, y los datos disponibles no permiten determinar si los compartimentos corporales perdidos se recuperan en las mismas proporciones. Esta revisión analiza las trayectorias de la composición corporal durante la pérdida de peso y tras la retirada de la tirzepatida, así como el papel de las intervenciones nutricionales y el ejercicio en la preservación de la masa magra. La literatura revisada subraya la importancia de un abordaje nutricional individualizado —con especial atención a la ingesta adecuada de proteínas y a la densidad de nutrientes—, combinado con la práctica de ejercicio, particularmente el entrenamiento de fuerza. Estas estrategias pueden favorecer la preservación de la masa y la función muscular; sin embargo, la evidencia sobre su eficacia específica para mantener la composición corporal tras la retirada de la tirzepatida sigue siendo limitada. Por tanto, el manejo debe ser continuo y multidisciplinario, y se requieren más estudios que evalúen de forma integral el peso, la composición corporal y la función neuromuscular, tanto durante el tratamiento como tras su interrupción.

***PALABRAS CLAVE**: Obesidad. Polipéptido inhibidor gástrico. Péptido similar al glucagón tipo 1. Composición corporal.*

GRAPHICAL ABSTRACT



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KEY POINTS

1. Weight loss induced by dual GIP/GLP-1 receptor agonists primarily reflects reductions in body fat, but may also involve lean mass loss; its clinical relevance should be assessed alongside muscle strength and physical performance.
2. Discontinuation of pharmacotherapy is associated with progressive weight regain, but evidence concerning the body composition of regained weight remains limited.
3. Follow-up care should integrate individualized nutritional support, adequate protein intake and exercise, with an emphasis on resistance training, while monitoring not only weight but also body composition and muscle function.

1. INTRODUCTION

Obesity is a chronic disease with a multifactorial etiology, and its clinical management has been substantially transformed by the introduction of incretin-based therapies, particularly glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucose-dependent insulinotropic polypeptide/GLP-1 (GIP/GLP-1) receptor agonists. These drug classes act on homeostatic and hedonic circuits in the central nervous system, as well as at peripheral sites, promoting early satiety, delaying gastric emptying and reducing spontaneous energy intake (American Diabetes Association, 2024; Look *et al.*, 2025).

Despite their established therapeutic benefits, the composition of the weight lost has prompted debate regarding patients' functional and nutritional status. Rapid weight loss primarily reflects the mobilization of total and visceral adipose tissue, but is accompanied by reductions in lean mass or fat-free mass (Look *et al.*, 2025; Braga *et al.*, 2026).

Although the relative proportion of lean mass loss is comparable to that observed with energy restriction alone or bariatric surgery, the magnitude of weight reduction may result in substantial absolute losses of lean tissue. This raises clinical concerns in vulnerable subgroups regarding the risk of sarcopenia-related functional impairment and reductions in basal energy expenditure (Mechanick *et al.*, 2025; Santana *et al.*, 2025; Braga *et al.*, 2026).

Furthermore, sustaining clinical outcomes over the long term remains a challenge in incretin-based treatment, as pharmacological discontinuation may lead to the regain of previously lost weight (Aronne *et al.*, 2024; Wu *et al.*, 2025; West *et al.*, 2026). Withdrawal of the pharmacological stimulus triggers counter-regulatory biological adaptations, including increases in orexigenic hormones, suppression of endogenous satiety signals and compensatory reductions

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in resting metabolic rate, thereby favoring weight regain (Jensen *et al.*, 2024; Senatorska *et al.*, 2025; van Baak and Mariman, 2025; Tessele *et al.*, 2026).

Evidence indicates that, following treatment discontinuation, individuals experience progressive weight regain that attenuates previously achieved cardiometabolic benefits, including in settings where standardized behavioral interventions are maintained (Aronne *et al.*, 2024; Wu *et al.*, 2025; West *et al.*, 2026).

During this transition after pharmacotherapy, a knowledge gap emerges concerning the tissue composition of regained weight, with a persisting biological hypothesis that fat mass may be restored disproportionately relative to lean mass. Discussion of the composition of regained weight, and uncertainty regarding the proportion of fat-free mass recovered, draws on reviews and mechanistic studies of metabolic regulation following weight loss (Turicchi *et al.*, 2020; Martins *et al.*, 2023; van Baak and Mariman, 2025).

Nutritional care and structured exercise should be integrated into treatment, although their effectiveness in preventing weight regain and preserving body composition after tirzepatide withdrawal remains insufficiently established. These interventions should be based on nutritional support with individualized protein intake and exercise training, with particular emphasis on resistance training (Jensen *et al.*, 2024; Mozaffarian *et al.*, 2025; Rakhsha *et al.*, 2026).

Against this background, this review aims to discuss body composition trajectories from weight loss to weight regain following discontinuation of tirzepatide, examining the role of nutritional interventions and exercise in preserving lean mass.

2. METHODS

This narrative review focuses on tirzepatide, a dual GIP and GLP-1 receptor agonist, addressing body composition changes during treatment, weight trajectories after treatment withdrawal, and the role of nutrition and exercise. Studies involving other incretin-based therapies, including semaglutide and liraglutide, were considered for comparison or contextualization of the evidence relevant to tirzepatide.

Literature searches were conducted in PubMed, the Cochrane Library, and the CAPES Journals Portal (Portal de Periódicos CAPES). Searches began on October 20, 2026, and were last updated on November 11, 2026. Articles published in English, Portuguese, or Spanish were considered, with no restrictions on publication year.

Search terms were drawn from Medical Subject Headings (MeSH; PubMed) and Health Sciences Descriptors (DeCS; Virtual Health Library), including descriptors and alternative terms

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related to “glucagon-like peptide-1 receptor agonists”, “gastric inhibitory polypeptide receptor”, “weight loss”, “body composition”, “weight gain or regain”, “diet therapy”, “exercise”, “tirzepatide”, “discontinuation”, “weight maintenance”, “fat mass”, “lean mass”, "physical performance", "subcutaneous fat", "liver fat", and "muscle fat infiltration". Synonymous terms within each concept were combined using the Boolean operator OR, and different concepts were combined using AND.

Six search combinations were used: (1) incretin-related terms AND weight loss AND body composition; (2) incretin-related terms AND weight gain or regain AND body composition; (3) incretin-related terms AND weight loss AND body composition AND diet therapy or exercise; (4) incretin-related terms AND weight gain or regain AND body composition AND diet therapy or exercise; (5) tirzepatide AND body composition or adipose tissue distribution, muscle mass, strength, physical performance; and (6) tirzepatide AND terms related to treatment discontinuation, withdrawal, weight regain, or weight maintenance.

Articles were initially selected by screening their titles, abstracts, and keywords, followed by full-text reading to assess their relevance to the review objectives. The narrative synthesis was organized around body composition during active tirzepatide treatment, weight outcomes after tirzepatide withdrawal, and nutritional and exercise-related strategies. Particular attention was given to distinguishing changes in body weight from changes in fat mass, lean mass, fat-free mass, and skeletal muscle mass, as well as from measures of muscle strength and physical performance.

The reference lists of included articles were also manually screened to identify additional publications relevant to the review objectives that might not have been retrieved through the database searches. This supplementary approach aimed to broaden coverage of the relevant literature. Publications identified through reference-list screening were assessed for relevance using the same title, abstract, keyword, and full-text reading process.

3. TIRZEPATIDE AND WEIGHT LOSS

3.1. Mechanisms of Action of GLP-1 and GIP

GLP-1 and GIP are peptide hormones secreted by the gastrointestinal tract in response to nutrient ingestion. GLP-1 is produced by enteroendocrine L cells located predominantly in the ileum and colon, whereas GIP is secreted by K cells in the duodenum and jejunum. Both hormones bind specific G protein-coupled receptors and contribute to the regulation of glucose and energy homeostasis. The clinical efficacy of incretin-based drugs is mediated by a

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combination of central, including hypothalamic, and peripheral mechanisms (Melson *et al.*, 2025; Tessele *et al.*, 2026). The evidence supporting these actions is, however, heterogeneous: some effects have been documented in clinical studies, whereas others derive from experimental models or from indirect inference. For this reason, the mechanisms are presented below according to the level of evidence available.

3.1.1. Effects supported by clinical evidence

Activation of GLP-1 receptors stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner, delays gastric emptying and reduces appetite and energy intake. By slowing the passage of gastric contents into the small intestine, GLP-1 prolongs postprandial satiety, reducing the frequency of hunger, snacking and meal size. Together, these effects contribute to weight loss (Jordan *et al.*, 2024; Moiz *et al.*, 2024; Melson *et al.*, 2025; McGuane *et al.*, 2026; Tessele *et al.*, 2026).

In patients with type 2 diabetes, tirzepatide reduced appetite, energy intake and fat mass (Heise *et al.*, 2023), and a randomized phase 1 trial showed that short-term tirzepatide treatment modified ingestive behavior in adults with overweight or obesity (Martin *et al.*, 2025). GLP-1 also modulates hepatic lipid and glucose metabolism by reducing de novo lipogenesis and stimulating fatty acid oxidation, thereby decreasing hepatic fat accumulation (McGuane *et al.*, 2026). GLP-1 is further associated with reductions in triglyceride and low-density lipoprotein (LDL) cholesterol concentrations (Moiz *et al.*, 2025).

3.1.2. Mechanisms proposed from experimental studies

Central control of food intake has been mapped mainly in animal models. GLP-1 receptors are expressed in the hypothalamus, brainstem and mesolimbic system (Tessele *et al.*, 2026). In the nucleus of the solitary tract, GLP-1 neurons modulate glutamatergic and serotonergic signaling, promoting satiety and reducing the desire to eat (Alhadeff *et al.*, 2012; Moiz *et al.*, 2025).

GLP-1 also modulates dopaminergic circuits involved in food reward, reducing the hedonic value of food and thereby contributing to lower excessive intake and improved energy balance (Tessele *et al.*, 2026). The area postrema in the brainstem lacks a blood–brain barrier and is involved in detecting circulating signals related to hunger and satiety (Rinaman, 2010; Moiz *et al.*, 2025).

The nucleus of the solitary tract and area postrema transmit these signals to the arcuate nucleus of the hypothalamus, where GLP-1 signaling increases anorexigenic pro-

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opiomelanocortin neurons and reduces orexigenic neuropeptide Y and agouti-related peptide neurons, resulting in reduced food intake and increased energy expenditure (Geloneze *et al.*, 2017; Moiz *et al.*, 2025). In the paraventricular nucleus, GLP-1 signaling influences the release of corticotropin-releasing hormone, oxytocin and thyrotropin-releasing hormone, all of which reduce food intake. In the lateral hypothalamus, GLP-1 inhibits orexin-producing neurons involved in appetite stimulation (Moiz *et al.*, 2025).

Activation of GLP-1 receptors on enteric neurons, particularly myenteric neurons, initiates neural pathways that promote gastrointestinal smooth muscle relaxation, reduce antral and duodenal contractility and suppress postprandial motility. At the peripheral level, GLP-1 receptors on enteric and vagal afferent neurons engage a vagovagal reflex that reduces antral and duodenal contractility and increases pyloric tone, thereby slowing the passage of gastric contents into the duodenum (Halim *et al.*, 2018; McGuane *et al.*, 2026).

Experimental studies further indicate that GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK signaling in mice (Beiroa *et al.*, 2014), and that GLP-1 signaling reduces nuclear factor kappa B (NF-κB) activation, lowers the production of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β), and may stimulate AMPK and interleukin-10 (IL-10) signaling while reducing reactive oxygen species generation (Geloneze *et al.*, 2017; Alharbi, 2024).

Hepatic effects, including reduced de novo lipogenesis and increased fatty acid oxidation, have likewise been proposed (McGuane *et al.*, 2026). These findings are biologically plausible, but their quantitative contribution to the reduction in energy intake and body weight produced by tirzepatide in humans has not been established. In addition, in the clinical setting it is not possible to separate direct drug effects from those mediated by weight loss and the accompanying metabolic improvement.

3.1.3. Mechanisms whose contribution in humans remains uncertain

Both GLP-1 and GIP stimulate insulin secretion in a glucose-dependent manner. GIP may also reduce glucagon secretion, although this response depends on the prevailing glycemic context, and GIP influences lipid metabolism by increasing lipogenesis and lipid-buffering capacity, potentially resulting in a more favorable lipid profile. Recent studies suggest that GIP receptor agonists may also increase energy expenditure and improve metabolic flexibility, enabling more efficient switching between glucose and fat as energy substrates (Jordan *et al.*, 2024; Melson *et al.*, 2025; Moiz *et al.*, 2025; Tessele *et al.*, 2026).

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GIP receptors are also present in the central nervous system and may integrate peripheral metabolic signals with behavioral responses related to food intake, but their specific role in the effects of tirzepatide has not been defined (Tessele *et al.*, 2026). Another physiological response associated with GLP-1 receptor activation is the modulation of gut hormones such as ghrelin, peptide YY (PYY) and cholecystokinin (CCK). GLP-1 receptor agonists appear to attenuate the hunger-stimulating effects of ghrelin and enhance the release and action of PYY and CCK, thereby amplifying their appetite-suppressing effects (Linnemann *et al.*, 2015; Boland *et al.*, 2022; Moiz *et al.*, 2025; McGuane *et al.*, 2026).

Taken together, the reduction in body weight produced by tirzepatide is well documented clinically and is most parsimoniously explained by reduced energy intake resulting from central appetite control and delayed gastric emptying. Additional mechanisms involving thermogenesis, inflammatory signaling, hepatic lipid metabolism and gut hormone modulation remain plausible but insufficiently established, and should be presented as hypotheses rather than as demonstrated clinical effects.

3.2. Weight Loss and Changes in Body Composition

GIP and GLP-1 receptor agonists have substantial effects on weight reduction and body composition (Locatelli *et al.*, 2024). Individuals with overweight or obesity treated with tirzepatide have shown reductions in body weight, body fat and lean mass. Selected studies addressing body composition during tirzepatide treatment, weight outcomes after withdrawal, and comparative or contextual evidence from other incretin-based therapies are summarized in Table 1.

In a phase 3 double-blind, randomized, controlled trial involving 2539 adults with overweight or obesity, Jastreboff *et al.* (2022) showed that weight reduction at 72 weeks was greater with tirzepatide than with placebo across the doses studied (-15.0% with 5-mg weekly doses, -19.5% with 10-mg doses, -20.9% with 15-mg doses and -3.1% with placebo). Improvements in cardiometabolic measures were observed with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation.

An integrative review of clinical trials and systematic reviews published between 2021 and 2026 found that tirzepatide produces significant weight loss, with greater metabolic effects than GLP-1 receptor agonists alone, together with substantial reductions in visceral fat. However, body composition analyses indicated that weight loss also involved reductions in fat-free mass (Braga *et al.*, 2026).

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The proportion of fat-free mass lost varies according to dose, treatment duration and participants' clinical characteristics (Braga *et al.*, 2026). Nevertheless, studies have reported that approximately 74% of total weight loss was attributable to reductions in fat mass and 26% to lean mass loss, a proportion similar to that reported for weight loss induced by lifestyle modification and bariatric surgery (Pownall *et al.*, 2016; Jabbour and Salman, 2021; Look *et al.*, 2025).

In the SURMOUNT-1 body composition substudy, tirzepatide was associated with reductions in body weight, fat mass and lean mass after 72 weeks. Although the reduction occurred predominantly in the adipose compartment, absolute lean tissue loss was also observed (Look *et al.*, 2025). In SURMOUNT-2, which enrolled 938 adults with obesity and type 2 diabetes, tirzepatide 10 and 15 mg reduced body weight by 12.8% and 14.7%, respectively, at 72 weeks, compared with 3.2% with placebo (Garvey *et al.*, 2023). In SURMOUNT-CN, a 52-week trial in 210 Chinese adults without diabetes, weight reductions were 13.6% and 17.5% with tirzepatide 10 and 15 mg versus 2.3% with placebo, accompanied by a marked reduction in waist circumference (Zhao *et al.*, 2024). A systematic review of randomized trials also confirmed a dose-dependent weight-lowering effect of tirzepatide, with gastrointestinal events as the most frequent adverse effects (Lin *et al.*, 2023), and a recent systematic review has extended these findings to longer-term and real-world settings (Olaniyi *et al.*, 2026).

A retrospective study showed that tirzepatide therapy resulted in significant reductions in body weight (-31.1 kg; -27.8%), BMI (-10.4 kg/m²; -27.8%), body fat percentage (-16.2%; -37.6%), fat mass (-26.4 kg; -54.2%), fat-free mass (-4.5 kg; -7.3%), skeletal muscle mass (-2.8 kg; -8.3%), and total body water (-3.5 kg; -7.7%). Weight loss was predominantly attributable to fat mass, comprising 85.7% of total weight loss, with smaller contributions from fat-free and skeletal muscle mass. Reductions in extracellular (-2.6 kg; -9.5%) and intracellular water (-1.3 kg; -7.4%) were observed (Corso *et al.*, 2026).

An observational study involving individuals with obesity and type 1 diabetes mellitus treated with GLP-1 receptor agonists, either alone or in combination with GIP receptor agonism, reported clinically significant weight loss. This was accompanied by improvements in glycemic control and favorable reductions in total fat mass and changes in regional body fat distribution, despite a reduction in lean mass (Al Ozairi *et al.*, 2026).

A randomized, double-blind study evaluating the effects of tirzepatide 15 mg, semaglutide 1 mg, and placebo on body weight and composition in people with type 2 diabetes was conducted by Heise *et al.* (2023). Tirzepatide treatment demonstrated significant reductions in body weight compared with placebo and semaglutide, resulting in greater fat mass reduction.

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Yao *et al.* (2026) conducted an observational study involving Chinese adults with obesity without diabetes. Tirzepatide was associated with greater reductions in body weight and a higher proportion of patients achieving more than 10% weight loss than semaglutide. Moreover, tirzepatide demonstrated superior efficacy in reducing total fat mass and visceral adiposity, achieving greater total weight loss and excess weight loss percentages, and ameliorating insulin resistance. By contrast, the effects on food cravings and appetite regulation were comparable between the two medications.

A systematic review and network meta-analysis comparing the effects of major antidiabetic drugs on key body composition parameters found that tirzepatide was the most effective of the drugs assessed in inducing body fat loss, but also produced the greatest reduction in lean mass. Combining pharmacological treatment with exercise favored lean mass preservation (Rakhsha *et al.*, 2026). In a systematic review of randomized, controlled studies, tirzepatide showed a superior decrease in body fat compartments (i.e., total fat mass, visceral adipose tissue and waist circumference) compared to other anti-obesity medications (e.g., dulaglutide and semaglutide) taken over the same duration (Rochira *et al.*, 2024).

Tirzepatide treatment favors reductions in ectopic lipid deposition within skeletal muscle, a feature of altered fat distribution in individuals with obesity. This dual GIP/GLP-1 receptor agonist may therefore improve muscle quality, metabolic flexibility and local insulin sensitivity, potentially attenuating some of the functional risks associated with reductions in lean body mass (Yen and Li, 2026).

In a post hoc magnetic resonance imaging analysis of SURPASS-3, involving adults with type 2 diabetes, tirzepatide reduced thigh muscle fat infiltration and thigh muscle volume over 52 weeks, whereas insulin degludec modestly increased muscle volume without improving fat infiltration. Notably, the reduction in muscle volume with tirzepatide was in line with what would be expected for the magnitude of weight loss. As discussed in the accompanying editorial, these data suggest a qualitative improvement in muscle composition, although muscle strength and function were not assessed (Sattar *et al.*, 2025; Stefan, 2025).

An integrative review evaluating the effects of GLP-1 and dual GIP/GLP-1 receptor agonists on body composition found that, irrespective of the drug used, these agents promoted significant weight loss, predominantly through reductions in total and visceral fat, with relative preservation of lean mass. These findings were consistent across the clinical trials reviewed, regardless of the study population, treatment duration or method used to assess body composition. However, only two of the six studies included in the review assessed functional

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outcomes, such as muscle strength or physical performance, limiting the clinical interpretation of the findings (Santana *et al.*, 2025).

Regarding body fat distribution pattern, Cariou *et al.* (2024) evaluated the effects of tirzepatide in people with type 2 diabetes. They found that tirzepatide-treated participants had significant decreases in visceral adipose tissue and liver fat but increased abdominal subcutaneous adipose tissue, suggesting a possible treatment-related alteration in the fat distribution pattern.

Another relevant consideration is that reduced protein intake has been observed in patients treated with tirzepatide, alongside reductions in fat-free mass. This effect was greater than that induced by liraglutide, a GLP-1 receptor agonist. Treatment with these agents may therefore compromise muscle protein synthesis, further challenging lean mass preservation. Dietary changes in these patients also include reduced vitamin and mineral intake, increasing their susceptibility to other diseases (Martin *et al.*, 2025; Prokopidis *et al.*, 2026; Sorić *et al.*, 2026).

Several factors have been associated with muscle loss during GLP-1 and GIP receptor agonist therapy, including energy restriction, inadequate protein intake, reduced appetite, food aversion, gastrointestinal effects, comorbidities, a history of weight regain, pre-existing low muscle mass or malnutrition, aging and physical inactivity (Mechanick *et al.*, 2025).

Insufficient weight loss or weight regain after metabolic bariatric surgery represents another challenge in obesity management. Stoll *et al.* (2025) retrospectively assessed the effects of adjunctive tirzepatide therapy over six months following sleeve gastrectomy or Roux-en-Y gastric bypass. Treatment significantly enhanced weight loss, reduced body mass index (BMI), waist circumference and body fat percentage, and improved metabolic health in patients who had undergone bariatric surgery, irrespective of surgery type or sex. Tirzepatide has also produced substantial weight loss in a prospective real-world cohort of patients with recurrent weight gain after bariatric surgery or endoscopic bariatric therapy (mean total body weight loss of 18.1% at 24 weeks), although this study was small (n = 34) and uncontrolled (Vinciguerra *et al.*, 2026).

A case series described three patients, two women and one man, with BMIs ranging from 32.9 to 51.9 kg/m², who prioritized strategies to preserve lean tissue during semaglutide or tirzepatide treatment. They undertook purposeful exercise or structured physical activity on 4-7 days per week, including resistance training on 3-5 days per week, and consumed protein intakes ranging from 0.7 to 1.7 g/kg/day relative to body weight and from 1.6 to 2.3 g/kg/day relative to fat-free mass. All three individuals lost weight and fat mass; in one patient, lean tissue accounted for 8.7% of the weight lost, whereas the other two experienced increases in lean tissue. These findings highlight the possibility that some individuals may preserve or even increase lean tissue

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during tirzepatide treatment when pharmacotherapy is combined with lifestyle strategies (Tinsley and Nadolsky, 2025).

An important consideration regarding the consequences of potential fat-free mass reductions during GLP-1 and GIP receptor agonist treatment is that these medications improve insulin sensitivity and reduce muscle fat infiltration, contributing to an adaptive process associated with improved muscle quality (Neeland *et al.*, 2024).

Angelopoulos *et al.* (2026) evaluated short-term changes in body composition in 51 adults with obesity treated with tirzepatide for 12 weeks, using bioelectrical impedance analysis. Body weight decreased by 8.75 kg (-8.18%), primarily driven by fat mass reduction (-6.87 kg), with a smaller decrease in soft lean mass (-1.73 kg). Despite this, the relative proportion of lean mass increased, indicating preferential fat loss. Approximately 78% of total weight loss was attributable to fat mass.

Efficacy and safety of tirzepatide were evaluated through a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial involving Japanese adults with obesity disease. At week 72, a higher proportion of participants achieved at least 5% bodyweight reduction with tirzepatide 10 mg and 15 mg compared with placebo. Cardiometabolic and body composition indices were also improved with tirzepatide. However, participants treated with tirzepatide experienced treatment-emergent adverse events more frequently than those who received placebo, most commonly gastrointestinal symptoms (Kadowaki *et al.*, 2025).

Taken together, the studies discussed indicate that weight loss during these therapies predominantly reflects reduced adiposity, but may also involve lean tissue loss. The relevance of this loss cannot be determined solely by its proportion of total weight lost, as it depends on the compartment assessed, the measurement method and the functional consequences. Conclusions regarding muscle safety or the risk of functional impairment therefore require the integration of body composition, strength and physical performance assessments, rather than lean mass quantification alone.

4. DISCONTINUATION OF PHARMACOTHERAPY AND WEIGHT REGAIN

Studies have shown that, following discontinuation of GLP-1 and GIP receptor agonists, the loss of pharmacologically mediated appetite suppression favors weight regain, although behavioral changes may partially attenuate this effect (Jensen *et al.*, 2024; Tessele *et al.*, 2026). In individuals with obesity or overweight, discontinuing tirzepatide treatment favors substantial regain of previously lost weight, whereas continued treatment maintains and extends the initial weight reduction (Aronne *et al.*, 2024). Similarly, follow-up studies from the SURMOUNT program

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demonstrate progressive weight regain after tirzepatide withdrawal, suggesting that continued pharmacological action plays a central role in sustaining the benefits (Aronne *et al.*, 2024; Wu *et al.*, 2025).

More recently, a randomized maintenance trial showed that, after an open-label weight-loss period with tirzepatide, continuing the maximum tolerated dose or reducing it to 5 mg preserved weight loss and cardiometabolic benefits over 52 weeks compared with switching to placebo. These findings suggest that lower-dose maintenance may be a viable alternative to abrupt discontinuation, although the long-term effects of this strategy on body composition remain to be established (Horn *et al.*, 2026).

A real-world, observational 26-week follow-up study included participants who completed 52 weeks' study treatment during SURMOUNT-CN, and the authors observed reductions in weight and waist circumference from trial baseline to week 52, and then there was an increase in these anthropometric parameters up to week 78; however, the weight loss was greater than the subsequent weight regain (Chen *et al.*, 2025).

A retrospective cohort study evaluated patients with obesity who discontinued tirzepatide treatment, classifying the discontinuation as early (i.e., within 3 months of index date) or late (i.e., within 3-12 months). Mean weight reduction at 1 year was 12.4%; however, weight loss was greater among patients who did not discontinue obesity pharmacotherapy at year 1 compared with the other two groups. Furthermore, those who discontinued treatment later showed greater mean percentage reduction in weight than the group that discontinued treatment earlier (Gasoyan *et al.*, 2025).

In a systematic review and meta-analysis of 37 studies, West *et al.* (2026) estimated greater mean weight regain after discontinuation of newer, more effective incretin-based medications, including tirzepatide. A return to baseline weight was projected within approximately 1.7 years across all medications and 1.5 years for the subgroup that included tirzepatide. These findings represent average estimates, and projections for the newer medications extended beyond the available follow-up period; they should therefore be interpreted cautiously.

In assessing weight trajectories after discontinuation of anti-obesity medications, Wu *et al.* (2025) found that body weight in previously treated patients continued to decline during the first four weeks after treatment cessation, followed by a trend towards gradual increases after eight weeks. However, at four weeks after discontinuation, there was no statistically significant difference in weight change between the previously treated groups and controls. After 26 weeks, the weight regain trajectory stabilized, suggesting that substantial weight regain may occur within the first six months after drug withdrawal.

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Importantly, weight regain does not necessarily imply restoration of the lost body compartments in the same proportions. Characterizing the quality of regained weight requires serial assessments of fat mass and non-adipose components, ideally accompanied by measures of strength and physical performance. Weight outcomes from the STEP 1 extension and SURMOUNT-4 alone do not establish the proportions of fat and lean tissue recovered after withdrawal (Look *et al.*, 2025). The body composition changes observed during treatment and the uncertainty surrounding the tissue composition of weight regain after treatment withdrawal are summarized in Figure 1.

Research has investigated potential factors associated with weight regain after weight loss induced by different approaches, including energy restriction, pharmacotherapy and bariatric surgery. These factors include adipose tissue immune cell profiles, the gut microbiome, fat-free mass loss during weight reduction and appetite regulation (van Baak and Mariman, 2019; Hafida and Apovian, 2022; Flanagan *et al.*, 2023; van Baak and Mariman, 2025).

Discontinuation of GIP and GLP-1 receptor agonist treatment leads to reactivation of homeostatic neurohormonal systems that favor weight regain, including increased ghrelin release and reduced leptin and PYY levels, reflecting the physiological drive to restore energy balance (Senatorska *et al.*, 2025; van Baak and Mariman, 2025). Another factor potentially associated with weight regain is fat-free mass loss, which occurs during GIP and GLP-1 receptor agonist treatment and may contribute to reduced energy expenditure and increased appetite, thereby promoting weight recovery. Nevertheless, evidence linking fat-free mass loss to weight regain remains inconsistent. Greater increases in ghrelin secretion have been observed under ketogenic conditions, suggesting a relationship between fat-free mass and appetite regulation (Turicchi *et al.*, 2020; Martins *et al.*, 2023; Spranger *et al.*, 2023).

Adipose tissue in individuals with obesity is characterized by increased numbers of pro-inflammatory immune cells, resulting in low-grade inflammation within the tissue. Animal research has shown that some of these adipose tissue immune alterations persist after weight loss induced by energy restriction. It has therefore been proposed that immune cells retained in adipose tissue after weight loss act as an immunological “memory of obesity” that may increase the risk of weight regain (Cottam *et al.*, 2022; van Baak and Mariman, 2025).

Obesity is also associated with alterations in the gut microbiota that relate to processes involved in weight regulation, including energy provision to the host, energy absorption, appetite control, fat storage, chronic inflammation and circadian rhythms (Liu *et al.*, 2021). A study of women with severe obesity assessed five years after Roux-en-Y gastric bypass found significant differences in the gut microbiome between those who regained weight and those who maintained

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their weight loss (Faria *et al.*, 2020). However, further studies are required to clarify the relationship between the gut microbiota and weight regain.

Interpreting the mechanisms of weight regain therefore requires distinguishing the loss of pharmacological effects from adaptations induced by weight loss itself. Changes in appetite, energy expenditure and body composition may contribute in an integrated manner, whereas mechanisms involving immunological memory and the microbiota remain supported partly by experimental models or populations exposed to other interventions. Their specific contribution to weight regain following withdrawal of GIP and GLP-1 receptor agonists should therefore be interpreted cautiously (van Baak and Mariman, 2019; Hafida and Apovian, 2022; Flanagan *et al.*, 2023).

5. LIFESTYLE INTERVENTIONS DURING ACTIVE TREATMENT, TRANSITION OFF PHARMACOTHERAPY AND SUBSEQUENT MAINTENANCE: STRATEGIES TO PRESERVE BODY COMPOSITION

Sustained lifestyle modifications are indispensable components of successful obesity treatment with incretin-based therapies. Weight maintenance is a primary objective, allowing health benefits to be preserved for as long as possible. Favorable long-term outcomes are achieved when pharmacotherapy is integrated into an interdisciplinary approach (American Diabetes Association, 2024; Senatorska *et al.*, 2025).

Clinical data support the importance of combining pharmacotherapy with behavioral therapy to improve treatment efficacy. Combining GIP/GLP-1 receptor agonists with intensive behavioral interventions produces greater and more sustained weight loss than either treatment alone. Ongoing monitoring of adherence and engagement enables early intervention in patients who do not respond to treatment and reduces dropout rates (Tronieri *et al.*, 2020; American Diabetes Association, 2024; Senatorska *et al.*, 2025).

Nutritional counseling, with or without incretin-based therapies, has been associated with lower muscle mass loss, suggesting that nutritional counseling may attenuate lean mass loss during treatment. Nutritional counseling has also been associated with greater mean visceral fat loss and, when combined with GLP-1-based treatment, greater mean fat mass loss (Hoffman *et al.*, 2026).

Pharmacological effects of GIP and GLP-1 receptor agonists also create challenges for nutritional management. These medications reduce appetite and the amount of food that can be consumed at meals, alter food preferences and cause gastrointestinal symptoms, potentially

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resulting in inadequate intakes of protein, fluids, fiber and micronutrients in susceptible patients (Zambrano-Villacres *et al.*, 2026).

Several factors are associated with weight maintenance: eating at regular times each day; regularly consuming breakfast; increasing the consumption of minimally processed foods; avoiding sugar-sweetened beverages, highly processed foods and snack foods; and allowing flexibility in food choices and occasional treats in controlled portions rather than imposing severe restrictions (National Weight Control Registry, 2026). The main nutritional priorities for individuals receiving these incretin-based therapies therefore include structuring meals around protein provision, ensuring nutrient density and gradually increasing fiber intake to support gastrointestinal function (Zambrano-Villacres *et al.*, 2026).

Individualized nutritional interventions are recommended to support weight management and lean mass maintenance during and after GLP-1 and GIP receptor agonist treatment. Protein intake should be carefully monitored to ensure that individual requirements are met. High-quality protein sources that provide essential amino acids should be prioritized to support protein synthesis (Mechanick *et al.*, 2025; Mollero *et al.*, 2026). This is essential for preserving lean mass during GIP and GLP-1 receptor agonist treatment. Proposed targets include 1.2-1.6 g of protein/kg body weight/day, 25-35 g of fiber/day, and 30–35 mL of fluids/kg body weight/day. Achieving protein intake targets is nevertheless challenging because early satiety, delayed gastric emptying and gastrointestinal adverse effects may reduce spontaneous food intake (Mozaffarian *et al.*, 2025; Mollero *et al.*, 2026; Zambrano-Villacres *et al.*, 2026).

Several dietary strategies may help maintain adequate nutrient intake despite early satiety and delayed gastric emptying. These include consuming smaller, more frequent meals, modifying food texture, individualizing meal schedules and prioritizing protein-rich foods over other meal components (Mollero *et al.*, 2026).

Adequate vitamin and mineral intake is also important because these nutrients have essential roles in macronutrient metabolism. Some micronutrients are particularly relevant to lean mass preservation, including calcium, which stimulates myogenic gene expression, and vitamin D, which regulates intracellular calcium concentrations, potentiates the effects of leucine and stimulates angiogenic and promyogenic growth factors. Both are therefore associated with increased muscle protein synthesis, which is relevant to lean mass preservation. Dietary adequacy and correction of deficiencies in these micronutrients should consequently be prioritized (Owens *et al.*, 2015; Tu *et al.*, 2016).

Nutritional supplementation may also support the maintenance of body composition, particularly lean mass, in individuals who have discontinued GIP and GLP-1 receptor agonist

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treatment, especially when combined with exercise. Examples include creatine and whey protein, the latter being rich in branched-chain amino acids; these supplements support muscle protein synthesis, lean mass and muscle strength. However, the studies demonstrating these effects of creatine and whey protein were not conducted in patients treated with GIP and GLP-1 receptor agonists (Sepandi *et al.*, 2022; Desai *et al.*, 2024).

The literature therefore indicates that nutritional care should be integrated across the main phases of incretin-based therapy, from pretreatment assessment through dose titration and active weight loss to long-term weight maintenance. Before treatment, the main dietary strategy is to establish a structured meal pattern featuring protein-rich foods and a gradual increase in fiber intake, while ensuring adequate hydration. During adaptation to medication and dose titration, smaller meals, slow chewing and a consistent fluid intake routine are important. During active weight loss, a nutrient-dense diet should be provided alongside protein-rich meals to reduce lean mass loss. During weight maintenance, the established dietary structure should be sustained, with continued emphasis on protein-rich foods (Mozaffarian *et al.*, 2025; Zambrano-Villacres *et al.*, 2026).

During tirzepatide treatment, the Mediterranean diet may act synergistically with this incretin-based agent. Paternò *et al.* (2026) showed the efficacy of tirzepatide on adiposity and metabolic markers and provided exploratory evidence that adherence to a Mediterranean diet enhances its impact on visceral adiposity. After three months, patients showed significant reductions in weight, BMI, waist circumference, WHtR, body roundness index, and visceral adiposity index (VAI). Higher adherence to the Mediterranean diet was associated with lower insulin levels, improved HOMA index, and greater reductions in VAI, even after adjusting for age, gender, and BMI.

In a prospective real-world study of 115 adults with a body mass index ≥27 kg/m² treated with low-dose tirzepatide (2.5–5 mg) alongside Mediterranean diet counseling and daily walking, reductions in body weight, waist circumference, and fat mass were observed after a median of 30 days, with minimal changes in fat-free mass and total body water (Adamidis *et al.*, 2025).

Another lifestyle intervention that could improve outcomes with tirzepatide is a standardized low-carbohydrate diet combined with tailored physical activity. A 24-week retrospective observational analysis included adults with overweight or obesity, and without diabetes, in whom tirzepatide was initiated at a dose of 2.5 mg once weekly and increased to 5 mg after 4 weeks. In comparison to baseline, reductions in body weight, BMI, waist circumference, waist-to-height ratio, and fat mass were observed after 24 weeks. However, fat-free mass slightly decreased by 5% (Brancato *et al.*, 2026).

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Incorporating resistance training and body composition monitoring into treatment programs may support the preservation of muscle mass. Other strategies associated with weight maintenance include regular physical activity (≥60 min/day), self-monitoring of body weight, dietary intake and physical activity, limiting screen time (<10 h/week), and using coping strategies such as social support, advance planning and problem-solving skills (Eisa and Barood, 2026; Rakhsha *et al.*, 2026).

Although both aerobic and anaerobic exercise are important in the treatment of individuals with obesity, resistance training is particularly valuable during and after weight-loss pharmacotherapy for helping maintain muscle mass and function. Resistance exercise programs should be individualized, taking into account age, baseline fitness, nutritional status, pre-existing cardiovascular disease or risk factors, joint health and overall mobility, respiratory health, other comorbidities, patient motivation and psychological factors (Mechanick *et al.*, 2025).

GIP and GLP-1 receptor agonists should therefore be prescribed alongside a structured exercise program incorporating regular strength training at least three times per week and a minimum of 150 minutes per week of moderate-intensity aerobic exercise, to support muscle health and weight management. These programs should be tailored to each individual's fitness level and physical capacity to support adherence and effectiveness (Cava *et al.*, 2017; Sardeli *et al.*, 2018; Jakicic *et al.*, 2024; Locatelli *et al.*, 2024).

Direct evidence for tirzepatide now comes from a randomized controlled trial in 120 adults with overweight or obesity, in which a 40-week supervised resistance exercise program was added to tirzepatide. Fat mass reductions were similar with tirzepatide alone and with tirzepatide plus resistance exercise, but resistance exercise attenuated the loss of total lean soft tissue mass and appendicular lean soft tissue mass. Moreover, upper- and lower-body muscle strength decreased with tirzepatide alone but increased when resistance exercise was added. These results support the integration of structured resistance training into tirzepatide-based treatment to preserve lean tissue and muscle function (Green *et al.*, 2026). The proposed framework for integrating nutritional care, exercise and monitoring across these treatment phases is presented in Figure 2.

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Table 1. Selected evidence on body composition during tirzepatide treatment and weight outcomes after withdrawal, with comparative and contextual findings from other incretin-based therapies.

Study	Study design and population	Intervention and follow-up	Main findings	Interpretation and limitations
Group 1. Tirzepatide during active treatment: Body composition and lifestyle-related findings				
Look *et al.* (2025)	Body composition substudy of a randomized controlled trial; 160 adults with obesity or overweight without type 2 diabetes included in the efficacy analysis	Tirzepatide 5, 10, or 15 mg, pooled, versus placebo; 72 weeks	With tirzepatide, body weight decreased by 21.3%, fat mass by 33.9%, and lean mass by 10.9%. Approximately 74% of weight reduction was attributable to fat mass and 26% to lean mass.	DXA-derived lean mass is not equivalent to skeletal muscle mass. The substudy did not establish the functional consequences of lean tissue loss or characterize body composition after withdrawal.
Cariou *et al.* (2024)	Exploratory analysis of fat distribution in people with type 2 diabetes, using sex- and BMI-matched virtual reference groups	Tirzepatide versus insulin degludec; 52 weeks	Visceral adipose tissue and liver fat z-scores decreased, whereas the abdominal subcutaneous adipose tissue z-score increased towards the reference mean.	The increase in the subcutaneous fat z-score represents a relative distributional change, not an absolute gain in subcutaneous fat. Findings concern active treatment rather than withdrawal.
Paternò *et al.* (2026)	Prospective observational study; 53 adults with overweight or obesity	Tirzepatide with personalized Mediterranean dietary recommendations; approximately three months	Higher Mediterranean diet adherence was associated with greater reductions in the visceral adiposity index and more favorable metabolic measures.	The visceral adiposity index is a composite surrogate, not a direct imaging measure of visceral fat. The absence of a randomized dietary comparator precludes conclusions about an independent or synergistic dietary effect.

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Brancato *et al.* (2026)	Retrospective observational study; 122 adults with overweight or obesity without diabetes	Tirzepatide with a standardized low-carbohydrate diet and tailored physical activity; 24 weeks	Fat mass decreased by approximately 35% and fat-free mass by approximately 5%. Estimated skeletal muscle mass did not change significantly.	Body composition was assessed by bioelectrical impedance analysis. The design did not isolate the effects of diet or physical activity. A nonsignificant change does not establish equivalence or definitive muscle preservation.
Sattar *et al.* (2025)	Post hoc analysis of open-label phase 3 RCT; adults with T2D, BMI ≥25 kg/m², fatty liver index ≥60	Tirzepatide 5/10/15 mg vs. insulin degludec; 52 weeks	Thigh muscle fat infiltration −0.36 pp; muscle volume −0.64 L, consistent with population estimates for the weight lost; degludec increased muscle volume without changing fat infiltration	MRI of thigh only; no strength or function data; post hoc
Adamidis *et al.* (2025)	Prospective observational; n = 115, BMI ≥27 kg/m², 67.5% women	Tirzepatide 2.5–5 mg + Mediterranean diet and walking; median 30 days	Weight −4.0 kg, waist −5.0 cm, fat mass −3.6 kg; minimal change in fat-free mass	BIA; very short follow-up; no control group
Green *et al.* (2026)	RCT; n = 120 adults with overweight/obesity	Tirzepatide vs. tirzepatide + supervised resistance exercise; 40 weeks	Similar fat loss (−17.19 vs. −17.98 kg); exercise attenuated lean soft tissue loss (difference 1.09 kg); strength ↑ with exercise, ↓ with tirzepatide alone	DXA.
Group 2. Tirzepatide withdrawal: Weight regain and maintenance outcomes				
Aronne *et al.* (2024)	Randomized withdrawal trial; 670 adults with obesity or overweight without diabetes randomized after an initial tirzepatide treatment period	Tirzepatide at the maximum tolerated dose of 10 or 15 mg for 36 weeks, followed by continued tirzepatide or a switch to placebo for 52 weeks	Mean weight reduction during the initial treatment period was 20.9%. From week 36 to week 88, weight decreased by a further 5.5% with continued tirzepatide but increased by 14.0% after switching to placebo. Overall weight reductions from baseline were 25.3% and 9.9%, respectively.	Provides randomized evidence that withdrawal leads to substantial weight regain despite continued lifestyle intervention. Weight outcomes do not establish the proportions of fat and lean tissue regained. Randomization after the initial treatment period

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				limits generalization to all treatment initiators.
Chen *et al.* (2025)	Observational post-trial follow-up; 152 participants who completed the preceding trial treatment	Twenty-six weeks after cessation of 52 weeks of tirzepatide 10 or 15 mg or placebo	From treatment cessation to follow-up, weight increased by 9.1% and 12.3% in the previous tirzepatide 10- and 15-mg groups, respectively. Net weight changes from trial baseline remained −8.7% and −10.6%. Waist circumference also increased after cessation.	Percentage changes from treatment cessation and trial baseline use different reference points. Weight and waist circumference measurements do not characterize the fat and lean composition of regained weight.
Horn *et al.* (2026)	Randomized withdrawal/maintenance trial after open-label tirzepatide lead-in	Maximum tolerated dose vs. 5 mg vs. placebo; 52-week maintenance	Both active maintenance strategies preserved weight loss and cardiometabolic benefits vs. placebo	Body composition not reported.
Group 3. Comparative and contextual evidence involving other incretin-based therapies				
Heise *et al.* (2023)	Randomized, double-blind study in people with type 2 diabetes	Tirzepatide 15 mg versus semaglutide 1 mg and placebo during active treatment	Tirzepatide produced greater reductions in body weight and fat mass than semaglutide and placebo.	Provides direct comparative evidence during treatment, not after withdrawal. Semaglutide 1 mg should not be treated as equivalent to the 2.4-mg regimen used for obesity treatment.
Yao *et al.* (2026)	Single-center retrospective observational study; 183 Chinese adults with obesity without diabetes	Semaglutide up to 1.7 mg/week versus tirzepatide up to 5 mg/week; three months	Mean weight reductions were 8.15 kg with semaglutide and 11.02 kg with tirzepatide, corresponding to a between-group difference of 2.87 kg. Greater reductions in total and visceral adiposity were also reported with tirzepatide.	Nonrandomized treatment allocation, short follow-up, and specific dosing regimens limit causal inference and generalization. No withdrawal outcomes were assessed.
Gasoyan *et al.* (2025)	Retrospective clinical cohort; 7,881 adults with overweight or obesity without type 2 diabetes	Semaglutide or tirzepatide; one-year outcomes according to pharmacotherapy	Across the cohort, mean weight reductions were 3.6% with early discontinuation, 6.8% with later discontinuation, and 11.9% without discontinuation. In the tirzepatide	Results associate treatment persistence with greater net weight reduction. Differences in treatment exposure and the

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		discontinuation status	subgroup, mean weight reduction was 12.4% overall and 15.3% among those who did not discontinue pharmacotherapy.	observational design prevent interpretation as an isolated causal effect of withdrawal or a direct estimate of weight regained.
West *et al.* (2026)	Systematic review and meta-analysis of 37 studies	Weight trajectories after cessation of weight-management medications	Estimated average weight regain was 0.4 kg/month across medications and 0.8 kg/month for newer, more effective incretin-based medications, including tirzepatide.	The 0.8-kg/month estimate is not specific to tirzepatide. Pooled estimates describe average trajectories, and projections for newer agents extended beyond observed follow-up. The analysis did not determine the composition of regained weight.
Rochira *et al.* (2024)	Systematic review of 6 randomized controlled trials involving adults with overweight or obesity, with or without type 2 diabetes.	Tirzepatide compared with placebo or other treatments; intervention duration varied across studies, with follow-up of up to 72 weeks.	Tirzepatide reduced total fat mass, visceral adipose tissue and waist circumference. Some trials reported greater fat mass reductions with tirzepatide than with dulaglutide or semaglutide. Reductions in fat-free mass were reported, but the magnitude and comparative effects remained inconclusive.	No meta-analysis because of differences in assessment methods and outcome reporting. Only 3 trials assessed fat-free mass. The review does not establish the composition of weight regained after tirzepatide withdrawal.

Legend: Studies are organized into three groups: (1) body composition and lifestyle-related findings during active tirzepatide treatment; (2) weight regain and maintenance outcomes following tirzepatide withdrawal; and (3) comparative and contextual evidence involving other incretin-based therapies. Findings should be interpreted according to study design, population, treatment exposure, follow-up duration, and assessment method. Lean mass, fat-free mass, lean soft tissue, and skeletal muscle mass represent distinct outcomes and should not be used interchangeably. Changes in body weight or waist circumference alone do not establish the fat and lean composition of regained weight, and reductions in lean tissue do not, by themselves, demonstrate functional impairment. Evidence from other medications or from active-treatment interventions does not directly establish effectiveness after tirzepatide withdrawal. Percentage changes refer to the reference time point specified for each study; pp denotes absolute differences in percentage points. Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MRI, magnetic resonance imaging; pp, percentage points; RCT, randomized controlled trial; T2D, type 2 diabetes.

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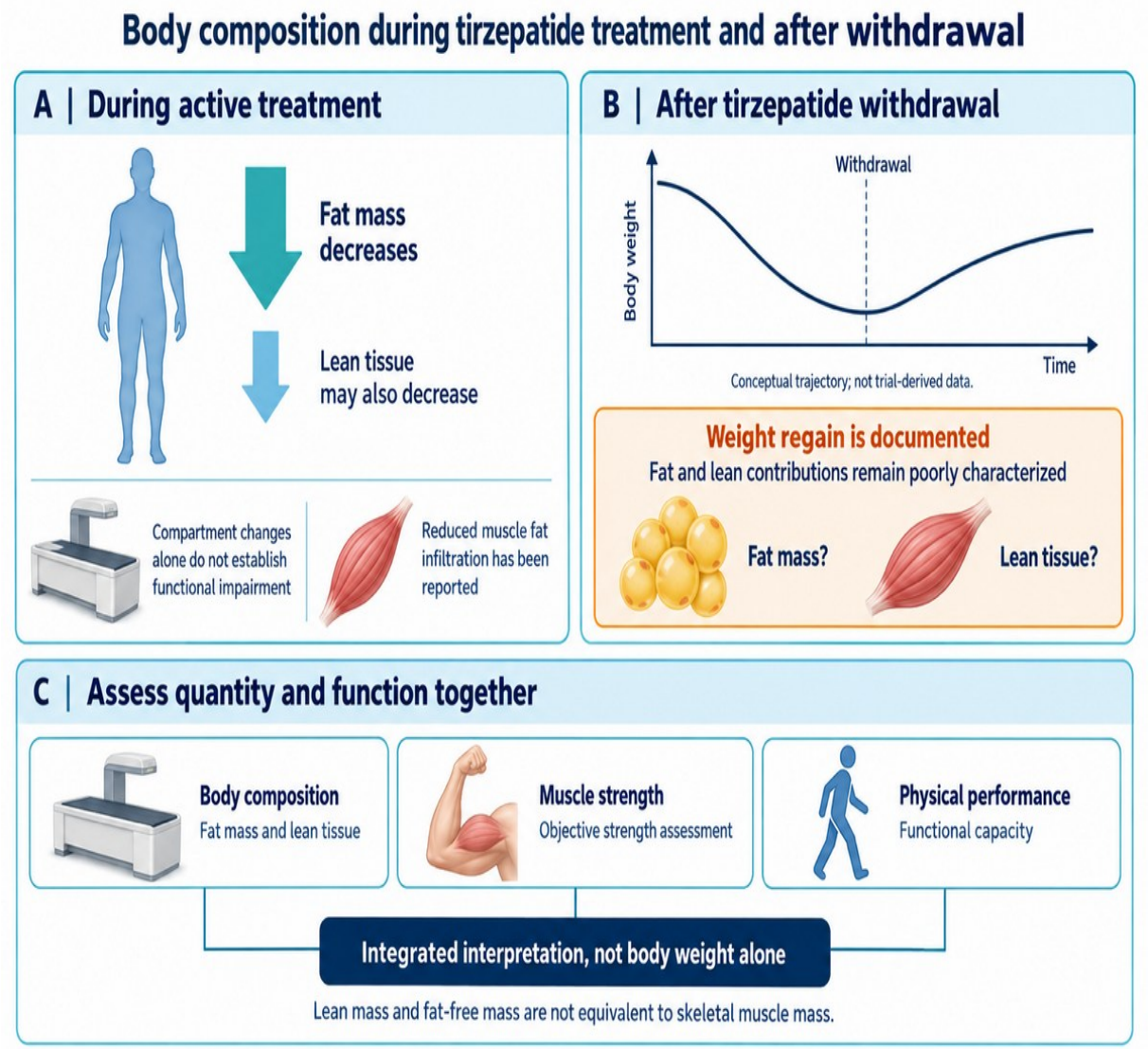
Figure 1. Body composition during tirzepatide treatment and after withdrawal.



Legend: (A) During active treatment, weight loss occurs predominantly through reductions in fat mass, although lean tissue may also decrease. Changes in body compartments alone do not establish functional impairment. Reduced muscle fat infiltration has been reported in people with type 2 diabetes treated with tirzepatide. (B) After treatment withdrawal, progressive weight regain has been documented, but the relative contributions of fat and lean tissue to regained weight remain poorly characterized. The weight trajectory is conceptual and does not represent empirical trial data. (C) Clinical interpretation should integrate body composition with objective assessments of muscle strength and physical performance. Lean mass and fat-free mass are not equivalent to skeletal muscle mass. Sources: Look *et al.*, 2025; Mechanick *et al.*, 2025; Aronne *et al.*, 2024; Sattar *et al.*, 2025; Neeland *et al.*, 2024.

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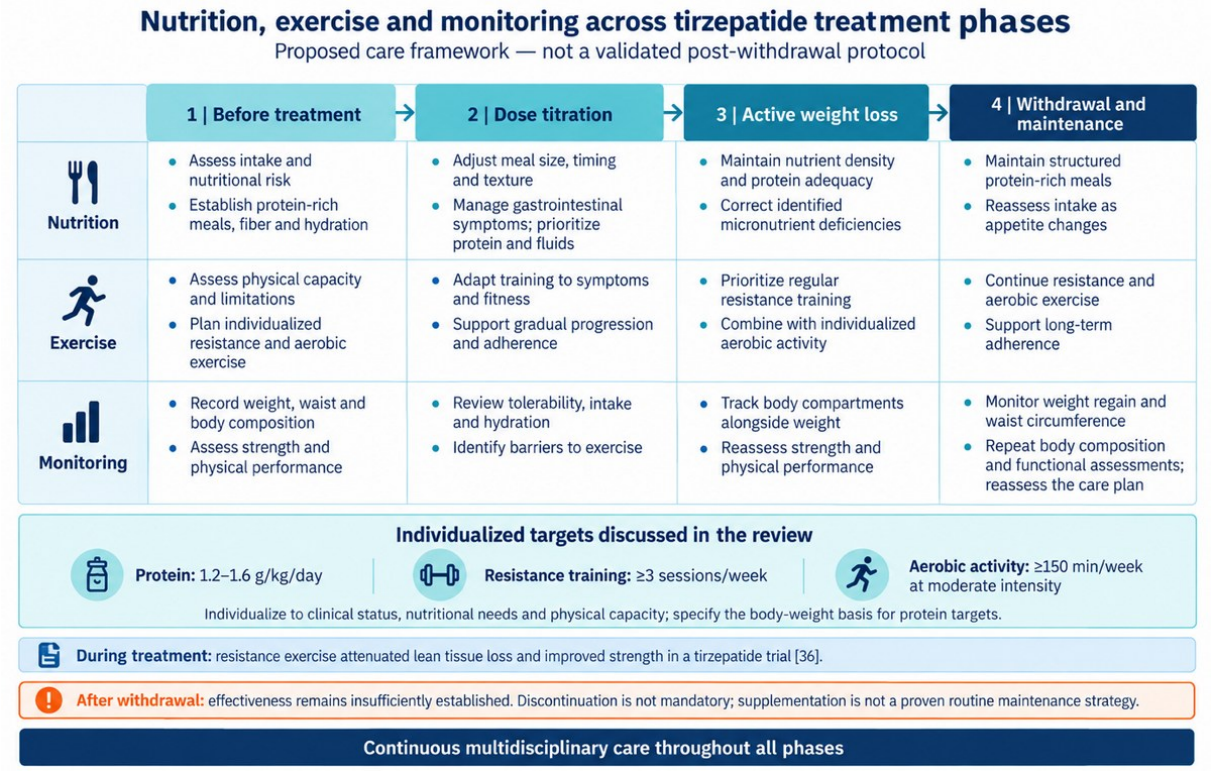
Figure 2. Proposed framework for nutritional care, exercise, and clinical monitoring across tirzepatide treatment phases.



Legend: The framework outlines priorities before treatment, during dose titration and active weight loss, and after withdrawal when applicable. Nutritional care emphasizes adequate protein intake, nutrient density, hydration, and management of gastrointestinal symptoms. Exercise combines resistance training with aerobic activity, while monitoring includes body weight, body composition, muscle strength, and physical performance. The targets shown are discussed in the review and should be individualized according to clinical status, nutritional requirements, and physical capacity. During active tirzepatide treatment, a randomized trial found that resistance exercise attenuated lean tissue loss and improved strength (Green *et al.*, 2026). The effectiveness of these strategies after tirzepatide withdrawal remains insufficiently established. Treatment discontinuation is not mandatory, and supplementation is not presented as a proven routine strategy for preventing post-withdrawal weight regain. Sources: Mechanick *et al.*, 2025; Jensen *et al.*, 2024; Mozaffarian *et al.*, 2025; Locatelli *et al.*, 2024; Green *et al.*, 2026; Zambrano-Villacres *et al.*, 2026; Mollero *et al.*, 2026; Cava *et al.*, 2017; Jakicic *et al.*, 2024; Sardeli *et al.*, 2018.

6. CONCLUSIONS

Tirzepatide therapy promotes substantial weight loss and metabolic benefits, primarily through reductions in adipose mass, although these are accompanied by lean mass loss. Discontinuation of the medication highlights the chronic and relapsing nature of obesity, leading

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to progressive weight regain and partial reversal of improvements in cardiometabolic markers. This trajectory is not fully counteracted by maintaining conventional behavioral interventions alone.

Although adequate nutritional support and resistance training are recommended to help preserve lean tissues, substantial gaps remain concerning the tissue composition of regained weight and effective maintenance protocols following incretin-based therapy withdrawal. Sustainable clinical management therefore requires continuous multidisciplinary strategies and recognition that long-term treatment is often necessary. Future research should examine changes in body composition and neuromuscular capacity throughout the full treatment and withdrawal cycle.

REFERENCES

ADAMIDIS, N.; DESALERMOS, A.; PAPADOPOULOU, N.; ADAMIDI, S.; KOUTRAKOS, T.; KYVENTIDOU, M.; GEORGAKOPOULOU, V. E.; ADAMIDIS, S. Short-Term Effects of Tirzepatide in Obese Adults: A Real-World Prospective Study. Cureus, v. 17, n. 6, p. e85970, 2025. DOI: 10.7759/cureus.85970.

AL OZAIRI, E.; IRSHAD, M.; ALKANDRI, J.; MASHANKAR, A.; GRAY, S. R.; LE ROUX, C. W. Weight Loss-Dependent Changes in Body Composition and Bone Health in People With Obesity and Type 1 Diabetes Treated With Liraglutide, Semaglutide, or Tirzepatide. Diabetes/Metabolism Research and Reviews, v. 42, n. 6, p. e70213, 2026. DOI: 10.1002/dmrr.70213.

ALHADEFF, A. L.; RUPPRECHT, L. E.; HAYES, M. R. GLP-1 Neurons in the Nucleus of the Solitary Tract Project Directly to the Ventral Tegmental Area and Nucleus Accumbens to Control for Food Intake. Endocrinology, v. 153, n. 2, p. 647-658, 2012. DOI: 10.1210/en.2011-1443.

ALHARBI, S. H. Anti-Inflammatory Role of Glucagon-Like Peptide 1 Receptor Agonists and Its Clinical Implications. Therapeutic Advances in Endocrinology and Metabolism, v. 15, p. 20420188231222367, 2024. DOI: 10.1177/20420188231222367.

AMERICAN DIABETES ASSOCIATION. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes - 2024. Diabetes Care, v. 47, supl. 1, p. S145-S157, 2024. DOI: 10.2337/dc24-S008.

ANGELOPOULOS, N.; RIZOULIS, A.; BONIAKOS, A.; FOUSTERIS, E.; MENTZELOPOULOU, V.; ZIANNI, D.; LIVADAS, S.; PAPARODIS, R. Early changes in body composition with tirzepatide in adults with obesity: a real-world BIA study. Nutrition, v. 150, p. 113286, 2026. DOI: 10.1016/j.nut.2026.113286.

ARONNE, L. J.; SATTAR, N.; HORN, D. B. *et al.* Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA, v. 331, n. 1, p. 38-48, 2024. DOI: 10.1001/jama.2023.24945.

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BEIROA, D.; IMBERNON, M.; GALLEGO, R. *et al.* GLP-1 Agonism Stimulates Brown Adipose Tissue Thermogenesis and Browning Through Hypothalamic AMPK. Diabetes, v. 63, n. 10, p. 3346-3358, 2014. DOI: 10.2337/db14-0302.

BOLAND, B. B.; LAKER, R. C.; O'BRIEN, S. *et al.* Peptide-YY(3-36)/Glucagon-Like Peptide-1 Combination Treatment of Obese Diabetic Mice Improves Insulin Sensitivity Associated With Recovered Pancreatic Beta-Cell Function and Synergistic Activation of Discrete Hypothalamic and Brainstem Neuronal Circuitries. Molecular Metabolism, v. 55, p. 101392, 2022. DOI: 10.1016/j.molmet.2021.101392.

BRAGA, A. T. G.; BRAGA, N. C.; DE L. SEIXAS, V.; GONÇALVES, D. M. Agonismo duplo GIP/GLP-1 e manutenção da massa magra: revisão integrativa a respeito da tirzepatida e sugestão de um modelo alimentar amazônico. In: PATHWAYS TO HEALTH: INNOVATIONS AND APPROACHES IN HEALTH SCIENCES. Seven Editora, 2026. p. 604-619. DOI: 10.56238/sevened2026.009-046.

BRANCATO, D.; MAGGIO, V.; VACCARO, F.; MURATORE, E.; PIRRELLO, D.; CITTADINI, E.; PATTI, A. M.; DI FALCO, F.; AGNELLO, L.; CIACCIO, M.; RIZZO, M. Real-world effectiveness of 6-month tirzepatide therapy on body weight and composition in adults with overweight and obesity. J Diabetes Complications, v. 40, n. 11, p. 109419, 2026. DOI: 10.1016/j.jdiacomp.2026.109419.

CARIOU, B.; LINGE, J.; NEELAND, I. J.; DAHLQVIST LEINHARD, O.; PETERSSON, M.; FERNÁNDEZ LANDÓ, L.; BRAY, R.; RODRÍGUEZ, Á. Effect of tirzepatide on body fat distribution pattern in people with type 2 diabetes. Diabetes Obes Metab, v. 26, n. 6, p. 2446-2455, 2024. DOI: 10.1111/dom.15566.

CAVA, E.; YEAT, N. C.; MITTENDORFER, B. Preserving Healthy Muscle During Weight Loss. Advances in Nutrition, v. 8, n. 3, p. 511-519, 2017. DOI: 10.3945/an.116.014506.

CHEN, C.; YING, Z.; TANG, Q.; ZHAO, L.; LU, Y.; FAN, X.; XU, L.; SI, S.; LI, Y.; XU, J.; WANG, Y.; DONG, Y.; LI, X.; CHEN, Y. Weight loss maintenance after tirzepatide cessation in people with overweight/obesity: a real-world follow-up of the phase 3 SURMOUNT-CN trial. Life Metabolism, v. 4, n. 5, p. loaf024, 2025. DOI: 10.1093/lifemeta/loaf024.

CORSO, H.; GRAYBEAL, A. J.; HOELSCHER, E.; ROBERSON, S.; CURRAN, B.; JOHNSON, C.; JOHNSON, K. E. Effects of tirzepatide therapy on body weight and body composition in adults with overweight and obesity. Frontiers in Endocrinology, v. 17, p. 1834580, 2026. DOI: 10.3389/fendo.2026.1834580.

COTTAM, M. A.; CASLIN, H. L.; WINN, N. C.; HASTY, A. H. Multiomics Reveals Persistence of Obesity-Associated Immune Cell Phenotypes in Adipose Tissue During Weight Loss and Weight Regain in Mice. Nature Communications, v. 13, n. 1, p. 2950, 2022. DOI: 10.1038/s41467-022-30646-4.

DESAI, I.; WEWEGE, M. A.; JONES, M. D. *et al.* The Effect of Creatine Supplementation on Resistance Training-Based Changes to Body Composition: A Systematic Review and Meta-Analysis. Journal of Strength and Conditioning Research, v. 38, n. 10, p. 1813-1821, 2024. DOI: 10.1519/JSC.0000000000004862.

This article is published in open access under the Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original author and source are credited.

EISA, N.; BAROOD, O. Lean Mass Changes With Incretin Therapy Versus Lifestyle Intervention: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Diabetes, Obesity and Metabolism, v. 28, n. 6, p. 4818-4827, 2026. DOI: 10.1111/dom.70666.

FARIA, S. L.; SANTOS, A.; MAGRO, D. O. *et al.* Gut Microbiota Modifications and Weight Regain in Morbidly Obese Women After Roux-en-Y Gastric Bypass. Obesity Surgery, v. 30, n. 12, p. 4958-4966, 2020. DOI: 10.1007/s11695-020-04956-9.

FLANAGAN, E. W.; SPANN, R.; BERRY, S. E. *et al.* New Insights in the Mechanisms of Weight-Loss Maintenance: Summary From a Pennington Symposium. Obesity, v. 31, n. 12, p. 2895-2908, 2023. DOI: 10.1002/oby.23905.

GARVEY, W. T.; FRIAS, J. P.; JASTREBOFF, A. M.; LE ROUX, C. W.; SATTAR, N.; AIZENBERG, D.; MAO, H.; ZHANG, S.; AHMAD, N. N.; BUNCK, M. C.; BENABBAD, I.; ZHANG, X. M.; SURMOUNT-2 INVESTIGATORS. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet, v. 402, n. 10402, p. 613-626, 2023. DOI: 10.1016/S0140-6736(23)01200-X.

GASOYAN, H.; BUTSCH, W. S.; SCHULTE, R.; CASACCHIA, N. J.; LE, P.; BOYER, C. B.; GRIEBELER, M. L.; BURGUERA, B.; ROTHBERG, M. B. Changes in weight and glycemic control following obesity treatment with semaglutide or tirzepatide by discontinuation status. Obesity (Silver Spring), v. 33, n. 9, p. 1657-1667, 2025. DOI: 10.1002/oby.24331.

GELONEZE, B.; DE LIMA-JÚNIOR, J. C.; VELLOSO, L. A. Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) in the Brain-Adipocyte Axis. Drugs, v. 77, n. 5, p. 493-503, 2017. DOI: 10.1007/s40265-017-0706-4.

GREEN, D. J.; HAYNES, A.; UNDERWOOD, D. R. *et al.* Resistance exercise to attenuate lean mass loss during tirzepatide therapy for obesity: a randomized controlled trial. Nature Medicine, 2026. DOI: 10.1038/s41591-026-04752-5.

HAFIDA, S.; APOVIAN, C. Physiology of the Weight-Reduced State and Its Impact on Weight Regain. Endocrinology and Metabolism Clinics of North America, v. 51, n. 4, p. 795-815, 2022. DOI: 10.1016/j.ecl.2022.06.002.

HALIM, M. A.; DEGERBLAD, M.; SUNDBOM, M. *et al.* Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility Through Myenteric Neuronal Mechanisms in Humans. Journal of Clinical Endocrinology & Metabolism, v. 103, n. 2, p. 575-585, 2018. DOI: 10.1210/jc.2017-02006.

HEISE, T.; DEVRIES, J. H.; URVA, S.; LI, J.; PRATT, E. J.; THOMAS, M. K.; MATHER, K. J.; KARANIKAS, C. A.; DUNN, J.; HAUPT, A.; MILICEVIC, Z.; COSKUN, T. Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes. Diabetes Care, v. 46, n. 5, p. 998-1004, 2023. DOI: 10.2337/dc22-1710.

HOFFMAN, K.; GILLESPIE, P.; SMITH, C. Impact of Glucagon-Like Peptide-1/Glucose-Dependent Insulinotropic Polypeptide Therapy and Nutrition Counseling on Body Composition. Journal of Nutrition, v. 156, n. 7, p. 101618, 2026. DOI: 10.1016/j.tjnut.2026.101618.

This article is published in open access under the Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original author and source are credited.

HORN, D. B.; ARONNE, L. J.; WHARTON, S.; BAYS, H. E.; LE ROUX, C. W.; SRINATH, R.; GOMEZ-VALDERAS, E.; ARAD, A. D.; DAS, S.; DUNN, J. P.; RIBEIRO, A.; GLASS, L. C.; LEE, C. J. Tirzepatide for maintenance of bodyweight reduction in people with obesity in the USA (SURMOUNT-MAINTAIN): a multicentre, double-blind, randomised, placebo-controlled trial. Lancet, v. 407, n. 10545, p. 2305-2318, 2026. DOI: 10.1016/S0140-6736(26)00656-2.

JABBOUR, G.; SALMAN, A. Bariatric Surgery in Adults With Obesity: The Impact on Performance, Metabolism, and Health Indices. Obesity Surgery, v. 31, p. 1767-1789, 2021. DOI: 10.1007/s11695-020-05182-z.

JAKICIC, J. M.; ROGERS, R. J.; CHURCH, T. S. Physical Activity in the New Era of Antiobesity Medications. Obesity, v. 32, n. 2, p. 234-236, 2024. DOI: 10.1002/oby.23930.

JASTREBOFF, A. M.; ARONNE, L. J.; AHMAD, N. N.; WHARTON, S.; CONNERY, L.; ALVES, B.; KIYOSUE, A.; ZHANG, S.; LIU, B.; BUNCK, M. C.; STEFANSKI, A.; SURMOUNT-1 INVESTIGATORS. Tirzepatide Once Weekly for the Treatment of Obesity. New England Journal of Medicine, v. 387, n. 3, p. 205-216, 2022. DOI: 10.1056/NEJMoa2206038.

JENSEN, S. B. K.; BLOND, M. B.; SANDSDAL, R. M. *et al.* Healthy Weight Loss Maintenance With Exercise, GLP-1 Receptor Agonist, or Both Combined Followed by One Year Without Treatment: A Post-Treatment Analysis of a Randomised Placebo-Controlled Trial. EClinicalMedicine, v. 69, p. 102475, 2024. DOI: 10.1016/j.eclinm.2024.102475.

JORDAN, G.; YOUNG, S.; ALEMÁN, J. O. Weight Loss Pharmacotherapy: Current and Future Therapies. Gastrointestinal Endoscopy Clinics of North America, v. 34, n. 4, p. 591-608, 2024. DOI: 10.1016/j.giec.2024.06.006.

KADOWAKI, T.; KIYOSUE, A.; SHINGAKI, T.; OURA, T.; YOKOTE, K. Efficacy and safety of once-weekly tirzepatide in Japanese patients with obesity disease (SURMOUNT-J): a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Lancet Diabetes Endocrinol, v. 13, n. 5, p. 384-396, 2025. DOI: 10.1016/S2213-8587(24)00377-2.

LIN, F.; YU, B.; LING, B.; LV, G.; SHANG, H.; ZHAO, X.; JIE, X.; CHEN, J.; LI, Y. Weight loss efficiency and safety of tirzepatide: A Systematic review. PLoS One, v. 18, n. 5, p. e0285197, 2023. DOI: 10.1371/journal.pone.0285197.

LINNEMANN, A. K.; NEUMAN, J. C.; BATTIOLA, T. J.; WISINSKI, J. A.; KIMPLE, M. E.; DAVIS, D. B. Glucagon-Like Peptide-1 Regulates Cholecystokinin Production in Beta-Cells to Protect From Apoptosis. Molecular Endocrinology, v. 29, n. 7, p. 978-987, 2015. DOI: 10.1210/me.2015-1030.

LIU, B. N.; LIU, X. T.; LIANG, Z. H.; WANG, J. H. Gut Microbiota in Obesity. World Journal of Gastroenterology, v. 27, n. 25, p. 3837-3850, 2021. DOI: 10.3748/wjg.v27.i25.3837.

LOCATELLI, J. C.; COSTA, J. G.; HAYNES, A. *et al.* Incretin-Based Weight Loss Pharmacotherapy: Can Resistance Exercise Optimize Changes in Body Composition? Diabetes Care, v. 47, n. 10, p. 1718-1730, 2024. DOI: 10.2337/dci23-0100.

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LOOK, M.; DUNN, J. P.; KUSHNER, R. F. *et al.* Body Composition Changes During Weight Reduction With Tirzepatide in the SURMOUNT-1 Study of Adults With Obesity or Overweight. Diabetes, Obesity and Metabolism, v. 27, n. 5, p. 2720-2729, 2025. DOI: 10.1111/dom.16275.

MARTIN, C. K.; CARMICHAEL, O. T.; CARNELL, S. *et al.* Tirzepatide on Ingestive Behavior in Adults With Overweight or Obesity: A Randomized 6-Week Phase 1 Trial. Nature Medicine, v. 31, p. 3141-3150, 2025. DOI: 10.1038/s41591-025-03774-9.

MARTINS, C.; NYMO, S.; COUTINHO, S. R.; REHFELD, J. F.; HUNTER, G. R.; GOWER, B. A. Association Between Fat-Free Mass Loss, Changes in Appetite, and Weight Regain in Individuals With Obesity. Journal of Nutrition, v. 153, n. 5, p. 1330-1337, 2023. DOI: 10.1016/j.tjnut.2023.03.026.

MCGUANE, C.; FARHADHAR, N.; SHARIEFF, K. A.; PETROSKY, S. N.; ALABASI, K. Nutritional Care for Adults With Obesity Treated With Glucagon-Like Peptide (GLP)-1 and Dual Glucose-Dependent Insulinotropic Polypeptide (GIP)/GLP-1 Receptor Agonists: A Review of Evidence, Gaps, and Clinical Implications. Cureus, v. 18, n. 5, p. e109731, 2026. DOI: 10.7759/cureus.109731.

MECHANICK, J. I.; BUTSCH, W. S.; CHRISTENSEN, S. M. *et al.* Strategies for Minimizing Muscle Loss During Use of Incretin-Mimetic Drugs for Treatment of Obesity. Obesity Reviews, v. 26, n. 1, p. e13841, 2025. DOI: 10.1111/obr.13841.

MELSON, E.; ASHRAF, U.; PAPAMARGARITIS, D.; DAVIES, M. J. What Is the Pipeline for Future Medications for Obesity? International Journal of Obesity, v. 49, n. 3, p. 433-451, 2025. DOI: 10.1038/s41366-024-01473-y.

MOIZ, A.; LEVETT, J. Y.; FILION, K. B.; PERI, K.; REYNIER, P.; EISENBERG, M. J. Long-Term Efficacy and Safety of Once-Weekly Semaglutide for Weight Loss in Patients Without Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. American Journal of Cardiology, v. 222, p. 121-130, 2024. DOI: 10.1016/j.amjcard.2024.04.041.

MOIZ, A.; FILION, K. B.; TSOUKAS, M. A.; YU, O. H.; PETERS, T. M.; EISENBERG, M. J. Mechanisms of GLP-1 Receptor Agonist-Induced Weight Loss: A Review of Central and Peripheral Pathways in Appetite and Energy Regulation. American Journal of Medicine, v. 138, n. 6, p. 934-940, 2025. DOI: 10.1016/j.amjmed.2025.01.021.

MOLLERO, E. L. M.; DOZZANI, I.; BIAMONTE, E. *et al.* Beyond Weight Loss: Skeletal Muscle Health During Incretin-Based Therapy in Patients With Diabesity. Nutrients, v. 18, n. 16, p. 2654, 2026. DOI: 10.3390/nu18162654.

MOZAFFARIAN, D.; AGARWAL, M.; AGGARWAL, M. *et al.* Nutritional Priorities to Support GLP-1 Therapy for Obesity: A Joint Advisory From the American College of Lifestyle Medicine, the American Society for Nutrition, the Obesity Medicine Association, and The Obesity Society. American Journal of Clinical Nutrition, v. 122, p. 344-367, 2025. DOI: 10.1002/oby.24336.

NATIONAL WEIGHT CONTROL REGISTRY. Research Findings. Available at: http://www.nwcr.ws/Research/published%20research.htm. Accessed: October 15, 2026.

This article is published in open access under the Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original author and source are credited.

NEELAND, I. J.; LINGE, J.; BIRKENFELD, A. L. Changes in Lean Body Mass With Glucagon-Like Peptide-1-Based Therapies and Mitigation Strategies. Diabetes, Obesity and Metabolism, v. 26, supl. 4, p. 16-27, 2024. DOI: 10.1111/dom.15728.

OLANIYI, A. O.; GOGINENI, K. K.; OLANIYI, H.; SABIR, H.; AGBONROFO EBOIGBE, G.; YERIMA, S. R.; GABRIELS, N. Long-Term Clinical Outcomes and Real-World Effectiveness of Tirzepatide in Adults With Overweight or Obesity: A Systematic Review. Cureus, v. 18, n. 8, p. e114962, 2026. DOI: 10.7759/cureus.114962.

OWENS, D. J.; SHARPLES, A. P.; POLYDOROU, I. *et al.* A Systems-Based Investigation Into Vitamin D and Skeletal Muscle Repair, Regeneration, and Hypertrophy. American Journal of Physiology-Endocrinology and Metabolism, v. 309, n. 12, p. E1019-E1031, 2015. DOI: 10.1152/ajpendo.00375.2015.

PATERNÒ, V.; GERACI, G.; PITICCHIO, T.; LE MOLI, R.; BURGIO, S.; COSTANZO, G.; SAMBATARO, G.; BARATTA, R.; BARBAGALLO, F.; PALLOTTI, F. Mediterranean diet adherence and tirzepatide: real-world evidence on adiposity indices and insulin resistance beyond weight loss. Frontiers in Endocrinology, v. 16, p. 1700894, 2026. DOI: 10.3389/fendo.2025.1700894.

POWNALL, H. J.; SCHWARTZ, A. V.; BRAY, G. A. *et al.* Changes in Regional Body Composition Over 8 Years in a Randomized Lifestyle Trial: The Look AHEAD Study. Obesity, v. 24, p. 1899-1905, 2016. DOI: 10.1002/oby.21577.

PROKOPIDIS, K.; CACCIATORE, S.; ANTON, S. D.; BATSIS, J. A. Risk of Protein Intake Deficiency During Treatment With GLP-1 and GIP/GLP-1 Receptor Agonists: Considerations for Secondary Sarcopenia. Advances in Therapy, 2026. Published online: 22 Aug. 2026. DOI: 10.1007/s12325-026-03750-w.

RAKHSHA, S. S.; SHAHINFAR, H.; EBRAHIMI-MOUSAVI, S. *et al.* Comparative Effects of Antidiabetic Drugs on Body Composition: A Systematic Review and Network Meta-Analysis. Diabetes, Obesity and Metabolism, v. 28, n. 9, p. 7689-7704, 2026. DOI: 10.1111/dom.70957.

RINAMAN, L. Ascending Projections From the Caudal Visceral Nucleus of the Solitary Tract to Brain Regions Involved in Food Intake and Energy Expenditure. Brain Research, v. 1350, p. 18-34, 2010. DOI: 10.1016/j.brainres.2010.03.059.
ROCHIRA, V.; GRECO, C.; BONI, S.; COSTANTINO, F.; DALLA VALENTINA, L.; ZANNI, E.; ITANI, L.; EL GHOCH, M. The Effect of Tirzepatide on Body Composition in People with Overweight and Obesity: A Systematic Review of Randomized, Controlled Studies. Diseases, v. 12, n. 9, p. 204, 2024. DOI: 10.3390/diseases12090204.

SANTANA, A. B. A.; ALMEIDA, M. C.; GONÇALVES, D. M. Agonistas de GLP-1 e GLP-1/GIP no tratamento da obesidade: impacto na preservação de massa magra e risco de sarcopenia. Periódicos Brasil. Pesquisa Científica, v. 4, n. 2, p. 2144–2160, 2025. DOI: 10.36557/2674-9432.2025v4n2p2144-2160.

SARDELI, A. V.; KOMATSU, T. R.; MORI, M. A.; GASPARI, A. F.; CHACON-MIKAHIL, M. P. T. Resistance Training Prevents Muscle Loss Induced by Caloric Restriction in Obese Elderly Individuals: A Systematic Review and Meta-Analysis. Nutrients, v. 10, n. 4, p. 423, 2018. DOI: 10.3390/nu10040423.

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SATTAR, N.; NEELAND, I. J.; DAHLQVIST LEINHARD, O.; FERNÁNDEZ LANDÓ, L.; BRAY, R.; LINGE, J.; RODRIGUEZ, A. Tirzepatide and muscle composition changes in people with type 2 diabetes (SURPASS-3 MRI): a post-hoc analysis of a randomised, open-label, parallel-group, phase 3 trial. Lancet Diabetes Endocrinol, v. 13, n. 6, p. 482-493, 2025. DOI: 10.1016/S2213-8587(25)00027-0.

SENATORSKA, N.; KLESZCZEWSKA, K.; PRUSKA, A. *et al.* Incretin-Based Therapies for Obesity Management: The Impact of Patient Education and Lifestyle Modification on Long-Term Treatment Outcomes. International Journal of Innovative Technologies in Social Science, v. 3, n. 4(48), 2025. DOI: 10.31435/ijitss.4(48).2025.4225.

SEPANDI, M.; SAMADI, M.; SHIRVANI, H. *et al.* Effect of Whey Protein Supplementation on Weight and Body Composition Indicators: A Meta-Analysis of Randomized Clinical Trials. Clinical Nutrition ESPEN, v. 50, p. 74-83, 2022. DOI: 10.1016/j.clnesp.2022.05.020.

SORIĆ, T.; SARIĆ, A.; IVANIŠIN, A. *et al.* Hidden Malnutrition in the GLP-1 Era: Micronutrient Status, Protein Adequacy, and Lean Mass as Emerging Nutritional Considerations - A Narrative Review. Nutrients, v. 18, n. 17, p. 2757, 2026. DOI: 10.3390/nu18172757.

SPRANGER, L.; WEINER, J.; BREDOW, J. *et al.* Thrifty Energy Phenotype Predicts Weight Regain in Postmenopausal Women With Overweight or Obesity and Is Related to FGFR1 Signaling. Clinical Nutrition, v. 42, n. 4, p. 559-567, 2023. DOI: 10.1016/j.clnu.2023.02.020.

STEFAN, N. Does tirzepatide treatment improve skeletal muscle composition? Lancet Diabetes & Endocrinology, v. 13, n. 6, p. 455-457, 2025. DOI: 10.1016/S2213-8587(25)00054-3.

STOLL, F.; KANTOWSKI, T.; LAASER, J. *et al.* Tackling Suboptimal Clinical Response After Metabolic Bariatric Surgery: Impact of Tirzepatide on Weight Loss and Body Composition. Obesity Research & Clinical Practice, v. 19, n. 1, p. 63-69, 2025. DOI: 10.1016/j.orcp.2025.02.004.

TESSELE, B.; DE OLIVEIRA, A. A.; OMIZZOLO, A. F. *et al.* Reganho ponderal e repercussões metabólicas após a descontinuação de terapias baseadas em incretinas. Revista Eletrônica Acervo Médico, v. 26, p. e23715, 2026. DOI: 10.25248/reamed.e23715.2026.

TINSLEY, G. M.; NADOLSKY, S. Preservation of Lean Soft Tissue During Weight Loss Induced by GLP-1 and GLP-1/GIP Receptor Agonists: A Case Series. SAGE Open Medical Case Reports, v. 13, p. 2050313X251388724, 2025. DOI: 10.1177/2050313X251388724.

TRONIERI, J. S.; FABRICATORE, A. N.; WADDEN, T. A. *et al.* Effects of Dietary Self-Monitoring, Physical Activity, Liraglutide 3.0 mg, and Placebo on Weight Loss in the SCALE IBT Trial. Obesity Facts, v. 13, n. 6, p. 572-583, 2020. DOI: 10.1159/000511130.

TU, M. K.; LEVIN, J. B.; HAMILTON, A. M.; BORODINSKY, L. N. Calcium Signaling in Skeletal Muscle Development, Maintenance and Regeneration. Cell Calcium, v. 59, n. 2-3, p. 91-97, 2016. DOI: 10.1016/j.ceca.2016.02.005.

TURICCHI, J.; O'DRISCOLL, R.; FINLAYSON, G. *et al.* Associations Between the Proportion of Fat-Free Mass Loss During Weight Loss, Changes in Appetite, and Subsequent Weight Change: Results From a Randomized 2-Stage Dietary Intervention Trial. American Journal of Clinical Nutrition, v. 111, n. 3, p. 536-544, 2020. DOI: 10.1093/ajcn/nqz331.

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VAN BAAK, M. A.; MARIMAN, E. C. M. Mechanisms of Weight Regain After Weight Loss - The Role of Adipose Tissue. Nature Reviews Endocrinology, v. 15, n. 5, p. 274-287, 2019. DOI: 10.1038/s41574-018-0148-4.

VAN BAAK, M. A.; MARIMAN, E. C. M. Physiology of Weight Regain After Weight Loss: Latest Insights. Current Obesity Reports, v. 14, n. 1, p. 28, 2025. DOI: 10.1007/s13679-025-00619-x.

VINCIGUERRA, F.; DI STEFANO, C.; GUCCIONE, F.; DEGANO, C.; NIGRO, S.; BARATTA, R.; PIAZZA, L.; NAVARRA, G.; FRITTITTA, L. Tirzepatide for Recurrent Weight Gain after Bariatric Procedures: Real-World Evidence of Efficacy and Safety. Obes Surg, v. 36, n. 7, p. 3697-3704, 2026. DOI: 10.1007/s11695-026-08754-7.

WEST, S.; SCRAGG, J.; AVEYARD, P. *et al.* Weight Regain After Cessation of Medication for Weight Management: Systematic Review and Meta-Analysis. BMJ, v. 392, p. e085304, 2026. DOI: 10.1136/bmj-2025-085304.

WU, H.; YANG, W.; GUO, T.; CAI, X.; JI, L. Trajectory of the Body Weight After Drug Discontinuation in the Treatment of Anti-Obesity Medications. BMC Medicine, v. 23, n. 1, p. 398, 2025. DOI: 10.1186/s12916-025-04200-0.

YAO, Z.; AHMAD, A.; GONG, F.; ZHANG, N.; ZENG, M.; GE, Q. Comparative Efficacy of Semaglutide and Tirzepatide in Chinese Adults with Obesity without Diabetes: A Real-World Observational Study. Diabetes, Metabolic Syndrome and Obesity, v. 19, p. 607678, 2026. DOI: 10.2147/DMSO.S607678.

YEN, I. W.; LI, H. Y. Tirzepatide-Induced Body Composition Changes: Implications From the SURPASS-3 MRI Substudy. Journal of Diabetes Investigation, v. 17, p. 392-394, 2026. DOI: 10.1111/jdi.70232.

ZAMBRANO-VILLACRES, R.; CAMPUZANO-DONOSO, M.; REYTOR-GONZÁLEZ, C. *et al.* Nutrition-First Support for GLP-1 and Dual Incretin Therapy in Obesity: A Practical Framework for Dietary Management, Symptom Tolerability, and Long-Term Weight Maintenance. Nutrients, v. 18, n. 11, p. 1751, 2026. DOI: 10.3390/nu18111751.

ZHAO, L.; CHENG, Z.; LU, Y.; LIU, M.; CHEN, H.; ZHANG, M.; WANG, R.; YUAN, Y.; LI, X. Tirzepatide for Weight Reduction in Chinese Adults With Obesity: The SURMOUNT-CN Randomized Clinical Trial. JAMA, v. 332, n. 7, p. 551-560, 2024. DOI: 10.1001/jama.2024.9217.

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