Review Article

Protein supplementation versus incretin-based therapies: Implications for muscle and fat mass during exercise-supported weight loss

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Abstract

Incretin–based therapies promote weight loss primarily through appetite suppression, delayed gastric emptying, and improvements in glycemic regulation, resulting in rapid and clinically meaningful reductions in body mass. In contrast, protein-focused interventions support fat loss through enhanced satiety, preservation of diet-induced thermogenesis, and direct stimulation of muscle protein synthesis, typically producing slower but more metabolically stable changes in body composition. For physically active individuals, the interaction between these strategies and exercise introduces additional physiological considerations beyond total weight loss. Exercise, particularly resistance training, increases the demand for adequate substrate availability to support skeletal muscle maintenance, remodeling, and functional adaptation. Within this context, incretin–based therapies, induced reductions in energy intake may challenge lean mass preservation if not carefully managed, whereas protein-based strategies may align more naturally with the anabolic and recovery requirements of training. Importantly, these approaches also differ in the temporal pattern of fat loss, the extent to which lean mass is affected, and the durability of weight loss once active intervention slows or ceases, factors that are especially relevant for individuals pursuing long-term exercise adherence and performance. This review synthesizes current evidence on incretin–based therapies and protein-based dietary strategies through an exercise-relevant lens, focusing on three underexamined determinants: skeletal muscle preservation, pace of fat loss, and weight-loss maintenance. Rather than positioning these approaches as competing or hierarchical, the review aims to clarify what physiological trajectories individuals may encounter when integrating each strategy with exercise. Understanding these trajectories may help practitioners and physically active individuals make more informed, context-specific decisions when selecting fat-loss interventions.

Key Words: Incretin-based therapies, Protein diets, Muscle Health, Fat loss strategies

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and newer incretin-based injectable therapies have emerged as cornerstone pharmacological strategies for the management of obesity and type 2 diabetes mellitus (T2DM) (Jastreboff et al., 2022; Rubino et al., 2021; Wilding et al., 2021). These agents induce clinically meaningful weight loss and confer substantial cardiometabolic benefits, including improvements in glycemic control and reductions in cardiovascular risk (Ard et al., 2021; Gerstein et al., 2019; Marso et al., 2016). However, alongside their increasing clinical uptake, concerns have been raised regarding their effects on body composition, particularly lean body mass (LBM) or skeletal muscle mass (SMM), given that weight loss induced by GLP-1–based therapies may include a nontrivial proportion of fat-free mass (FFM) loss (Anyiam et al., 2025; Bikou et al., 2024; Locatelli et al., 2024).

Exercise, particularly resistance training, represents a foundational strategy for preserving SMM and functional capacity during weight loss. Exercise activates a complex network of mechanical, metabolic, hormonal, and molecular pathways that promote muscle protein synthesis, neuromuscular adaptation, mitochondrial function, and anti-inflammatory responses. Across healthy and clinical populations, structured exercise interventions have consistently demonstrated efficacy in maintaining or improving muscle structure and function, even under conditions of energy restriction (Arciero et al., 2014; Minett et al., 2020). As such, exercise is widely recommended as a core component of obesity management strategies aimed at improving both metabolic health and body composition.

In practice, many individuals with obesity engage in exercise programs while simultaneously seeking adjunct strategies to accelerate fat loss and improve adherence. Within this context, GLP-1–based therapies are increasingly used alongside exerci-

-se due to their potent appetite-suppressive effects and capacity to induce rapid early weight reduction (Jastreboff et al., 2022; Wilding et al., 2021). Nevertheless, the marked reduction in energy intake associated with these agents raises important questions regarding their compatibility with exercise-driven goals, particularly with respect to muscle preservation, training recovery, and long-term functional outcomes (Bikou et al., 2024; Locatelli et al., 2024).

Dietary protein intake represents a central nutritional strategy that directly intersects with both exercise adaptation and body composition regulation. Higher-protein diets have been shown to enhance satiety, increase diet-induced thermogenesis, preserve FFM, and support skeletal muscle remodeling during weight loss (Leidy et al., 2015; Moon & Koh, 2020; Paddon-Jones et al., 2008). Protein intake also stimulates anorexigenic gut hormones such as Glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), while suppressing ghrelin, thereby contributing to appetite regulation through endogenous pathways (Moon & Koh, 2020; Pesta & Samuel, 2014). Importantly, when combined with exercise, protein supplementation has been associated with superior preservation of lean mass and improved body composition outcomes compared with energy restriction alone (Arciero et al., 2014).

As weight loss strategies are increasingly integrated with exercise-based lifestyle interventions, the choice between pharmacological and nutritional approaches has become a practical and physiological decision rather than a purely therapeutic one. Incretin-based therapies (GLP-1 receptor agonists and newer dual incretin agonists) and protein-based dietary strategies both produce meaningful fat loss, yet they differ substantially in how weight loss unfolds over time, how SMM is affected, and how well reductions are maintained once active weight loss slows. For individuals engaging in regular exercise, these factors may outweigh absolute weight loss magnitude. This review therefore focuses on three determinants that are often underemphasized in obesity research, muscle mass preservation, pace of fat loss, and weight-loss maintenance, to critically evaluate protein strategies and incretin–based therapy in an exercise-relevant framework. This approach aims to clarify the physiological adaptations that may emerge when each strategy is combined with regular physical activity.

Materials and Methods

Search strategy

This article was conducted as a narrative review aimed at examining the physiological and practical characteristics of protein-based and incretin–based weight-loss strategies in the context of exercise. Relevant literature was identified through searches of PubMed, Scopus, and Google Scholar up to February 2026. Search terms included combinations of “GLP-1 receptor agonist”, “incretin therapy”, “semaglutide”, “tirzepatide”, “protein supplementation”, “high-protein diet”, “skeletal muscle mass”, “lean body mass”, “fat mass”, “weight loss”, “weight maintenance”, “satiety”, and “exercise”. Priority was given to randomized controlled trials, meta-analyses, systematic reviews, and major clinical studies conducted in adults. Mechanistic studies and selected animal investigations were also considered when relevant to the physiological pathways discussed. Studies were included if they reported outcomes related to body composition, muscle mass preservation, fat loss, weight-loss maintenance, appetite regulation, or exercise-related adaptations. Owing to the narrative nature of this review, a formal systematic screening process and quantitative quality assessment of individual studies were not performed. Therefore, the findings should be interpreted within the inherent limitations of narrative reviews.

The role of exercise in supporting muscle health and adaptation

Exercise is a primary strategy for maintaining and improving SMM, strength, and metabolic health across the lifespan. Resistance training is a particularly potent stimulus for muscle protein synthesis and hypertrophy, producing cumulative adaptations that increase muscle size and functional capacity when performed regularly (Damas et al., 2016). Although endurance exercise elicits different physiological adaptations, it also contributes to muscle health through improvements in oxidative capacity, metabolic flexibility, and overall physical function (Phillips, 2014). Importantly, exercise remains effective during periods of energy restriction and weight loss, helping to preserve lean mass and physical performance. Current evidence indicates that appropriately programmed concurrent resistance and endurance training can provide complementary benefits without necessarily compromising hypertrophic adaptations (Murach & Bagley, 2016). In addition to its effects on body composition, regular exercise improves insulin sensitivity, reduces chronic low-grade inflammation, and enhances cardiometabolic health, making it a cornerstone component of obesity management and long-term weight maintenance (Brandt & Pedersen, 2010; Forbes et al., 2012).

The relevance of exercise to the present review lies in its interaction with both nutritional and pharmacological weight-loss strategies. Because preservation of muscle mass and functional capacity is a major consideration during fat loss, evaluating protein supplementation and GLP-1–based therapies within an exercise-supported framework may provide a more clinically meaningful perspective than considering either intervention in isolation.

Effects of incretin–based injectable therapies on fat mass

GLP-1RAs and newer incretin-based injectable therapies consistently induce substantial reductions in total and regional fat mass (FM), representing a central mechanism underlying their clinical efficacy in obesity and T2DM. Across randomized controlled trials and real-world studies, weight loss achieved with GLP-1RAs is predominantly driven by FM reduction rather than loss of lean tissue, with particularly pronounced effects on visceral adipose tissue (Bhandarkar et al., 2025; Jendle et al., 2009; Jiao et al., 2025). Meta-analytic evidence demonstrates that GLP-1RAs significantly reduce both visceral and subcutaneous adipose tissue, with a preferential effect on visceral fat depots, which are strongly linked to cardiometabolic risk. Vergès reported that exenatide- and liraglutide-based interventions resulted in a mean reduction of approximately 11% in visceral adipose tissue compared with an 8% reduction in subcutaneous fat. Similarly, treatment with high-dose semaglutide (2.4 mg/week) over 68 weeks produced marked total FM loss alongside significant decreases in regional visceral adiposity (Kadowaki et al., 2025; Vergès, 2024). These findings are clinically relevant, as visceral fat reduction is associated with improvements in insulin sensitivity, lipid metabolism, and systemic inflammation.

Mechanistically, accumulating evidence supports both indirect and direct effects of GLP-1RAs on adipose tissue biology. Indirectly, GLP-1RAs reduce energy intake through central appetite regulation, enhancing satiety, fullness, and eating control while reducing hunger and preference for energy-dense foods (Gibbons et al., 2021; Kadouh et al., 2020). These central effects contribute to sustained negative energy balance, with ad libitum energy intake consistently lower during GLP-1RA treatment without compensatory increases in appetite (Gibbons et al., 2021).

Beyond appetite suppression, GLP-1RAs exert direct actions on adipose tissue metabolism. Experimental studies demonstrate that liraglutide and semaglutide reduce adipocyte size, suppress lipogenic gene expression, and upregulate pathways involved in lipolysis and thermogenesis (Szekeres et al., 2024; Vergès, 2024). In rodent and cellular models, GLP-1RAs promote browning of white adipose tissue, characterized by increased uncoupling protein-1 (UCP-1) expression, enhanced mitochondrial respiration, and increased oxygen consumption in both white and brown adipose depots (Vergès, 2024). These effects appear to be mediated, at least in part, through activation of sympathetic pathways, interleukin-6 signaling, thyroid hormone activation via type 2 deiodinase, and modulation of AMP-activated protein kinase (AMPK), dependent energy-sensing mechanisms (Hopkins & Blundell, 2016; Vergès, 2024).

Human evidence regarding brown adipose tissue activation is more heterogeneous. While some imaging studies failed to demonstrate increases in brown adipose tissue volume following liraglutide or exenatide treatment, others observed significant increases in metabolic activity and glucose uptake within existing brown fat depots, suggesting functional rather than volumetric adaptations (Vergès, 2024). These findings indicate that GLP-1RA–induced FM reduction in humans is primarily driven by decreased energy intake and improved adipocyte metabolic function rather than robust recruitment of new thermogenic tissue.

Clinical studies further confirm that FM reduction is preserved across diverse populations, including older adults and individuals with prediabetes or obesity-related comorbidities. Observational and interventional studies with liraglutide and Semaglutide demonstrate consistent reductions in total body fat, trunk fat, and visceral fat area, often with relative preservation of lean mass (Aladel et al., 2023; Silver et al., 2023; Zizka et al., 2024). Newer dual and multi-agonist therapies, such as Tirzepatide and GLP-1/GIP or GLP-1/glucagon receptor co-agonists, further amplify FM loss through enhanced fat oxidation and ketogenesis, highlighting the evolving potential of incretin-based pharmacotherapy for targeted adiposity reduction (Corbin et al., 2023; Corrao et al., 2024).

Influence of incretin–based injectable therapies on muscle mass

Lean mass loss during incretin–induced weight reduction

Weight loss induced by GLP-1RAs is primarily mediated through appetite suppression and delayed gastric emptying via central hypothalamic and brainstem pathways, resulting in sustained negative energy balance (Rossi et al., 2026). As observed with other weight loss interventions, reductions in total body mass during GLP-1RA therapy are accompanied by concomitant losses in FFM. Meta-analytic data indicate that approximately 20–25% of total weight loss originates from lean tissue, with skeletal muscle comprising a substantial proportion of this component (Anyiam et al., 2025; Rossi et al., 2026).

In individuals with obesity, GLP-1RA treatment has been associated with statistically significant reductions in muscle mass measures; however, these losses are consistently smaller than the corresponding reductions in FM and appear less pronounced than those reported following bariatric surgery or very-low-calorie dietary interventions (Anyiam et al., 2025). In patients with T2DM or obesity reductions in muscle mass are generally modest and significant along with substantial weight and FM loss (Anyiam et al., 2025; Jiao et al., 2025).

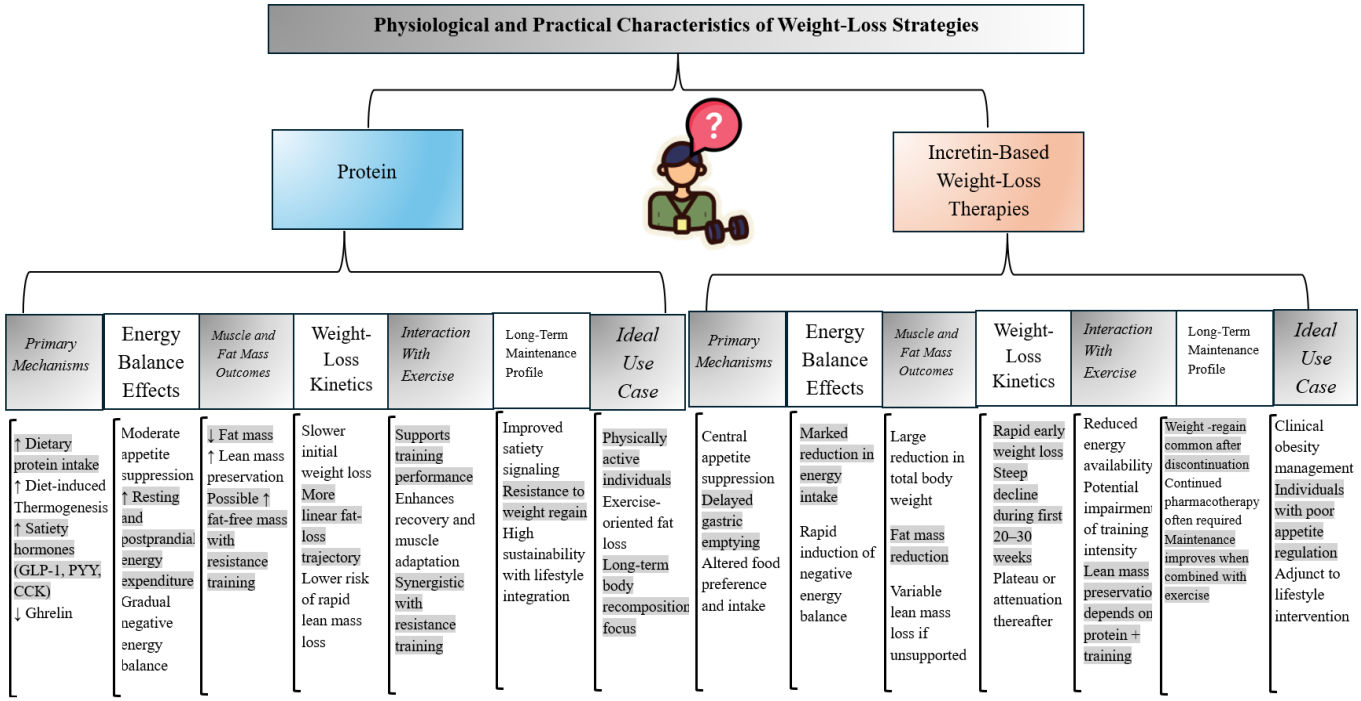

Figure 1. Physiological and practical characteristics of protein- and GLP-1–based weight-loss strategies, including their primary mechanisms, effects on energy balance and body composition, weight-loss kinetics, interaction with exercise, long-term maintenance profile, and ideal use cases. GLP-1: glucagon-like peptide-1; PYY: peptide YY; CCK: cholecystokinin.

Nevertheless, concerns remain regarding accelerated skeletal muscle loss and increased risk of sarcopenia in vulnerable populations, particularly older adults and individuals with pre-existing obesity, T2DM, or physical frailty (Bikou et al., 2024; Sargeant et al., 2019). Rapid weight loss in these populations may exacerbate age-related anabolic resistance and predispose to sarcopenic obesity, underscoring the need for careful clinical monitoring (Ceasovschih et al., 2025).

Mechanisms contributing to muscle loss during GLP-1RA therapy

Muscle loss during GLP-1RA-induced weight reduction is multifactorial. Appetite suppression frequently leads to reduced protein intake, particularly in older adults, diminishing substrate availability for muscle protein synthesis (Rossi et al., 2026). Sustained caloric deficit lowers circulating insulin and insulin-like growth factor-1, attenuating Phosphoinositide 3-kinase /Protein kinase B/ mechanistic target of rapamycin (PI3K/Akt/mTOR) signaling and shifting muscle protein balance toward catabolism (Rossi et al., 2026).

Negative energy balance and weight loss may also activate the hypothalamic pituitary adrenal axis, increasing cortisol concentrations and stimulating ubiquitin proteasome mediated proteolysis (Rossi et al., 2026). Furthermore, reduced habitual physical activity during treatment reported by some patients due to fatigue or altered energy perception may reduce mechanical loading of skeletal muscle, further impairing anabolic signaling (Rossi et al., 2026).

Evidence for direct and indirect muscle-preserving effects

Despite these concerns, accumulating preclinical and translational evidence suggests that GLP-1RAs may exert direct protective effects on skeletal muscle under certain conditions. In rodent models, GLP-1RAs such as exendin-4, liraglutide, semaglutide, and dulaglutide have been shown to improve muscle contractile properties, restructure the extracellular matrix, and enhance metabolic efficiency through AMPK activation (Scheen, 2025). Semaglutide has also been shown to attenuate skeletal muscle atrophy in diabetic and chronic liver disease models by suppressing ubiquitin–proteasome system activity and promoting myogenic differentiation (Szekeres et al., 2024).

GLP-1RAs may further support muscle preservation by improving skeletal muscle microvascular perfusion. Human studies demonstrate that GLP-1RA infusion increases skeletal muscle microvascular blood flow by approximately 30%, potentially enhancing delivery of oxygen, amino acids, and anabolic hormones to myocytes (Szekeres et al., 2024). Additionally, GLP-1 receptor signaling has been shown to directly stimulate myogenesis via cAMP-dependent pathways in skeletal muscle cells (Szekeres et al., 2024). Anti-inflammatory and antioxidant effects of GLP-1RAs may further mitigate muscle catabolism. Reductions in circulating pro-inflammatory cytokines such as TNF-α and IL-6 may partially counteract proteolytic signaling, particularly in obesity-associated inflammatory states (Gonzalez-Luis et al., 2025; Rossi et al., 2026).

Clinical interpretation and the role of exercise

While GLP-1–based therapies induce substantial weight loss, the proportion of lean mass loss appears context-dependent and modified by age, baseline muscle mass, comorbidities, nutritional intake, and physical activity levels (Bikou et al., 2024; Sargeant et al., 2019). Importantly, resistance exercise has been repeatedly highlighted as a critical adjunct strategy to preserve or even increase lean mass during incretin-based weight loss therapy (Locatelli et al., 2024). Supervised resistance training interventions exceeding 10 weeks have demonstrated clinically meaningful gains in lean mass and strength, potentially offsetting pharmacotherapy-associated muscle loss (Locatelli et al., 2024)

Importantly, reductions in lean mass observed during GLP-1 receptor agonist–induced weight loss should be interpreted within the broader context of body-weight reduction. Lean mass measured by techniques such as dual-energy X-ray absorptiometry includes not only skeletal muscle but also body water, connective tissue, and organ mass (Heymsfield et al., 2026). Consequently, decreases in lean mass do not necessarily reflect proportional losses of contractile muscle tissue. Moreover, the proportion of lean mass lost during GLP-1RA-mediated weight reduction appears to fall within the range commonly reported for other successful weight-loss interventions (Anyiam et al., 2025; Chaston et al., 2007).

Protein supplementation as a nutritional approach to fat reduction

Dietary protein supplementation has emerged as a well-established nutritional strategy for reducing FM while preserving lean tissue during weight loss. Evidence from large randomized controlled trials indicates that fat loss generally exceeds lean mass loss across a range of macronutrient distributions; however, higher protein intakes may confer specific advantages for body composition, metabolic health, and satiety (de Souza et al., 2012; Larsen et al., 2018). Although absolute FM reductions are often comparable between protein-enriched and control diets under isoenergetic conditions, protein intake appears to modulate regional fat depots, appetite regulation, and cardiometabolic risk factors.

Effects on total and regional fat mass

Clinical and experimental studies consistently demonstrate that protein-rich diets reduce total FM, with several trials reporting greater reductions in FM and percent body fat compared with normal-protein diets (Antonio et al., 2015; Haghighat et al., 2020; Haghighat et al., 2021). Importantly, protein supplementation has been associated with preferential reductions in visceral and hepatic fat, fat depots strongly linked to cardiometabolic risk (Bel Lassen et al., 2021; Evangelista et al., 2021; Xu et al., 2020). In individuals with obesity, high-protein interventions have shown superior improvements in visceral adiposity and metabolic markers compared with standard-protein diets, even in the absence of greater total weight loss (Evangelista et al., 2021). Evidence from bariatric and post-weight-regain populations further suggests that whey protein supplementation promotes FM loss while preserving FFM, highlighting its clinical relevance in vulnerable groups (Lopes Gomes et al., 2017). Long-term dietary protein enrichment has also been shown to reduce body fat percentage and waist circumference while supporting SMM, particularly in populations with normal-weight obesity or low baseline muscle mass (Haghighat et al., 2020; Haghighat et al., 2021).

Mechanisms underpinning protein-induced fat loss

The fat-reducing effects of protein supplementation are mediated by multiple complementary mechanisms. One key contributor is the thermic effect of food, which is substantially higher for protein (≈15–30%) than for carbohydrates or fat, leading to increased diet-induced thermogenesis and total energy expenditure (Moon & Koh, 2020; Pesta & Samuel, 2014). Meta-analytic data indicate that each incremental increase in dietary protein proportion further augments thermogenesis, thereby facilitating a sustained negative energy balance. Protein intake also exerts potent effects on appetite regulation through gut-derived and central pathways. High-protein diets stimulate the secretion of anorexigenic hormones, including GLP-1, CCK, and PYY, while suppressing ghrelin, resulting in enhanced satiety and reduced ad libitum energy intake (Moon & Koh, 2020; Pesta & Samuel, 2014). These effects are mediated by nutrient sensing in enteroendocrine cells and vagal afferent signaling, as well as central activation of hypothalamic pro-opiomelanocortin pathways.

At the tissue level, high-protein diets (HPD) influence adipose metabolism through increased lipolysis, enhanced fat oxidation, and activation of both uncoupling protein 1 (UCP1) -dependent and UCP1-independent futile cycles, including creatine-driven substrate cycling and triglyceride turnover (Madsen et al., 2018). Rodent studies further suggest that protein intake promotes browning of white adipose tissue and favorable remodeling of adipocyte metabolism, contributing to resistance against diet-induced obesity (Madsen et al., 2018; Petzke et al., 2014).

Interaction with lean mass preservation and exercise

Beyond fat loss, protein supplementation plays a critical role in preserving FFM during energy restriction. Multiple studies demonstrate that higher protein intake attenuates lean mass loss during weight reduction, an effect particularly relevant in older adults and physically active individuals (Cheraghpour et al., 2017; Moon & Koh, 2020). Whey protein supplementation, especially when combined with resistance or multimodal exercise training,

enhances improvements in total and regional body composition, including greater reductions in visceral fat and improvements in insulin sensitivity (Arciero et al., 2014). At the cellular level, protein intake supports muscle remodeling by stimulating satellite cell proliferation and muscle protein synthesis, reinforcing its dual role in fat reduction and muscle maintenance (Mobley et al., 2017).

Are protein strategies more effective than incretin agents for satiety and fat loss?

Both GLP-1–based pharmacological therapies and protein-based nutritional strategies are effective approaches for reducing FM. However, their comparative implications extend beyond the magnitude of weight loss alone. In this section, we examine three key dimensions that are critical for evaluating the clinical and physiological relevance of these interventions: (1) SMM preservation, (2) the pace of fat loss, and (3) long-term weight-loss maintenance. Skeletal muscle preservation and weight maintenance represent fundamental physiological determinants of metabolic health, functional capacity, and long-term cardiometabolic risk. The pace of fat loss, while often underemphasized, is a salient factor influencing lean mass retention, adaptive metabolic responses, and individual acceptability when selecting a weight-loss strategy. Together, these dimensions provide a framework for assessing not only the efficacy but also the sustainability and health consequences of nutritional versus pharmacological approaches to fat loss (Figure 1).

Muscle mass preservation

Preserving SMM is a critical determinant of metabolic health, physical function, and long-term outcomes during fat-loss interventions. Both protein-based and GLP-1–based strategies offer mechanisms to support muscle preservation, though their modes of action differ. HPD supply essential amino acids that directly stimulate muscle protein synthesis, enhance thermogenesis, and reduce proteolysis, thereby supporting LBM during negative energy balance (Antonio et al., 2015; Cheraghpour et al., 2017; Moon & Koh, 2020). Whey protein supplementation, particularly when combined with resistance exercise, has been shown to increase satellite cell proliferation and optimize skeletal muscle function, further mitigating lean mass loss during caloric restriction (Arciero et al., 2014; Mobley et al., 2017).

GLP-1RAs, while primarily designed to reduce adiposity, have demonstrated muscle-preserving effects in both preclinical and clinical studies. Mechanisms include the modulation of anabolic and catabolic signaling pathways, such as PI3K/Akt/mTOR and AMPKPeroxisome proliferator-activated receptor-gamma coactivator, inhibition of proteolysis via the ubiquitin-proteasome system, and promotion of myogenic differentiation (Ceasovschih et al., 2025; Gonzalez-Luis et al., 2025; Rossi et al., 2026). Furthermore, GLP-1RAs enhance skeletal muscle perfusion and nutrient delivery, supporting protein synthesis and functional capacity (Wang et al., 2025; Szekeres et al., 2024). Clinical trials consistently indicate that while total body weight and FM are reduced, reductions in SMM remain relatively modest—typically less than 20% of total weight loss—highlighting a protective effect compared with other interventions such as bariatric surgery or very-low-calorie diets (Anyiam et al., 2025; Jiao et al., 2025). Overall, both strategies can contribute to muscle preservation, though HPD provide a more direct anabolic stimulus, whereas GLP-1RAs may require careful monitoring of protein intake and nutritional status to minimize potential muscle loss.

Pace of fat loss and weight maintenance

The pace of weight loss represents a critical yet often underappreciated determinant of long-term success, influencing adaptive thermogenesis, hormonal responses, lean tissue retention, and behavioral adherence. Beyond total weight reduction, the temporal pattern of weight change, particularly the early rate of loss and subsequent stabilization, plays a meaningful role in determining maintenance outcomes (Astrup & Rossner, 2000; Solmi et al., 2018). GLP-1RAs induce weight loss primarily through central nervous system–mediated reductions in appetite, energy intake, and hunger, alongside enhanced satiety and altered food preferences (Ard et al., 2021). Visual inspection of longitudinal weight-loss trajectories across major GLP-1RA trials suggests a characteristic biphasic pattern: an early phase marked by a relatively rapid rate of weight loss, approximately 0.5–1.0 $kg \cdot week^{-1}$ during dose escalation and early maintenance, followed by a progressive attenuation in loss rate beyond approximately week 30.This pattern is well illustrated in the STEP-1 trial, in which semaglutide 2.4 mg produced continuous weight loss over 68 weeks, with the steepest decline occurring during the first 20–30 weeks, followed by a slower, plateau-like phase thereafter (Wilding et al., 2021). Similar temporal dynamics have been observed with tirzepatide, where large early reductions were achieved by week 72, but long-term maintenance depended on ongoing treatment exposure (Jastreboff et al., 2022; Rubino et al., 2021).

Importantly, continued pharmacological support appears central to weight-loss maintenance with GLP-1RAs. Withdrawal or substitution with placebo results in substantial weight regain, highlighting the reliance of this strategy on sustained drug-mediated appetite suppression (Rubino et al., 2021). While GLP-1RAs are effective and generally well tolerated, gastrointestinal side effects, although typically mild and transient, may indirectly influence dietary intake patterns and adherence over time (Ard et al., 2021).

In contrast to the rapid early weight loss observed with GLP-1–based therapies, protein-centered dietary strategies generally produce a more moderate but linear pace of weight loss, with greater emphasis on long-term stability. Across randomized controlled trials, (HPD) consistently reduce body weight and FM, though early weight-loss velocity is typically slower than pharmacological interventions (Evangelista et al., 2021; Wycherley et al., 2012). Notably, modest increases in dietary protein intake have been associated with improved weight-loss maintenance and reduced weight regain, even when long-term weight-loss magnitude varies (Leidy et al., 2015). Mechanistically, protein exerts sustained effects on satiety, thermogenesis, and FFM preservation, contributing to lower metabolic adaptation and improved energy balance over time (Evert & Franz, 2017; Paddon-Jones et al., 2008).

Evidence from long-term interventions indicates that protein-based approaches can maintain clinically meaningful weight loss without reliance on continuous escalation or pharmacological support (Bel Lassen et al., 2021; de Souza et al., 2012). Importantly, while early weight loss may be less dramatic, this slower trajectory does not appear to compromise long-term outcomes and may, in fact, enhance adherence and sustainability. Contrary to the common assumption that slower weight loss necessarily improves maintenance, evidence suggests that greater initial weight loss is often positively associated with long-term success, provided that adequate maintenance strategies are implemented (Astrup & Rossner, 2000; Nackers et al., 2010). However, the mechanisms sustaining weight loss differ substantially between strategies. GLP-1–based approaches rely heavily on continued pharmacological modulation of appetite and energy intake, whereas protein-based strategies embed maintenance within physiological and behavioral adaptations. Collectively, these findings indicate that pace of weight loss should be viewed as a strategic variable rather than a universal goal. GLP-1RAs offer rapid early reductions with high efficacy but require long-term continuation to sustain benefits, while protein-based strategies favor metabolic stability and durability, even at the cost of slower initial progress.

Protein- or incretin–based fat-loss strategies at the crossroads of exercise

When fat loss is pursued in the context of regular exercise, nutritional and pharmacological strategies interact differently with training capacity, body-composition adaptations, and long-term adherence. Protein-based dietary strategies and GLP-1–based injectable therapies represent two mechanistically distinct approaches that can both reduce FM, yet their practical consequences during exercise-supported weight loss differ in meaningful ways.

Figure 1 summarizes the principal physiological and practical characteristics of protein- and GLP-1–based weight-loss strategies, including their primary mechanisms, effects on energy balance, muscle and FM outcomes, weight-loss kinetics, long-term maintenance profiles, interactions with exercise, and potential use cases. Increasing dietary protein intake within an energy-restricted diet primarily supports fat loss through enhanced satiety, increased diet-induced thermogenesis, and preservation of FFM. In individuals who engage in resistance or combined training, higher protein intake aligns with the anabolic stimulus of exercise by supporting muscle protein synthesis and attenuating losses in SMM during caloric deficit (de Souza et al., 2012; Paddon-Jones et al., 2008).

Weight reduction under protein-based strategies typically progresses at a moderate pace, but this slower trajectory is often accompanied by greater metabolic stability, sustained training performance, and improved feasibility of long-term weight maintenance. Importantly, protein-driven fat loss does not suppress appetite to the extent observed with pharmacological agents, which may preserve normal hunger signaling and reduce the risk of compensatory overeating following weight loss (Leidy et al., 2015; Wycherley et al., 2012). GLP-1RAs induce fat loss predominantly through central appetite suppression, reduced energy intake, delayed gastric emptying, and altered food reward pathways. In the presence of exercise, these agents often produce rapid early weight loss, particularly during the dose-escalation phase, with clinically meaningful reductions in FM observed within the first 20–30 weeks of treatment (Jastreboff et al., 2022; Wilding et al., 2021).

However, the strong anorectic effects of GLP-1–based therapies may also reduce spontaneous energy intake to levels that challenge adequate protein consumption, potentially increasing the risk of lean mass loss if resistance training and protein intake are not carefully managed. Gastrointestinal adverse effects, although typically transient, may further limit training intensity or nutritional consistency during early treatment phases (Ard et al., 2021). Long-term maintenance of weight loss appears strongly dependent on continued pharmacotherapy or structured post-treatment support (Rubino et al., 2021; Wang et al., 2023).

At the intersection of exercise and fat loss, protein-based strategies emphasize physiological compatibility with training adaptations, favoring muscle preservation and metabolic resilience, albeit with slower initial fat loss. In contrast, GLP-1–based therapies prioritize efficacy and speed, delivering substantial early reductions in FM but requiring careful integration with exercise and nutrition to mitigate potential losses in lean tissue and to support weight-loss maintenance.

Beyond physiological considerations, practical factors may also influence the selection of weight-loss strategies. Protein supple-

-mentation is widely available, relatively inexpensive, and can generally be incorporated into dietary programs with minimal medical supervision. In contrast, GLP-1 receptor agonists require prescription-based treatment and ongoing clinical oversight and may be associated with substantial financial costs, depending on healthcare systems and insurance coverage. Accessibility, affordability, treatment burden, tolerability, and individual preference may therefore influence the feasibility and long-term implementation of either approach. Together, these distinctions suggest that the choice between protein-based and GLP-1–based strategies during exercise-supported fat loss should be guided not solely by the magnitude of weight reduction, but by the desired balance between pace, muscle preservation, training sustainability, and long-term weight stability.

Conclusions

Current evidence indicates that incretin–based injectable therapies induce clinically meaningful and preferential reductions in FM, particularly visceral adiposity, through integrated central and peripheral mechanisms. These effects underpin the substantial cardiometabolic benefits observed with incretin therapy, incretin–based injectable therapies induce weight loss that includes a variable reduction in LBM, with skeletal muscle loss representing a clinically relevant concern in at-risk populations. However, emerging evidence suggests that GLP-1RAs may exert muscle-preserving effects via metabolic, vascular, anti-inflammatory, and myogenic mechanisms, particularly when negative energy balance is appropriately managed. These findings highlight the importance of integrating resistance exercise and adequate protein intake into treatment strategies to optimize body composition and preserve muscle health during GLP-1RA therapy.

The available evidence indicates that protein supplementation is an effective nutritional strategy for supporting fat loss while promoting lean mass retention. Although total weight loss does not consistently exceed that achieved with lower-protein diets, protein-enriched interventions frequently improve body composition, reduce metabolically harmful fat depots, enhance satiety, and improve several cardiometabolic risk factors. In parallel, GLP-1 receptor agonists produce substantial and often greater reductions in body weight and FM through potent effects on appetite regulation and energy intake. Importantly, the two approaches differ not only in efficacy, but also in their physiological profiles, effects on body composition, weight-loss kinetics, and maintenance characteristics. From a temporal perspective, incretin–based therapies are generally characterized by a more rapid initial reduction in body weight, whereas protein-based approaches typically produce a more gradual pattern of fat loss accompanied by improvements in satiety, body composition, and metabolic health. These differing trajectories may influence individual preferences and treatment goals, particularly when preservation of lean mass and exercise participation are important considerations. With respect to long-term weight management, higher dietary protein intake has been associated with favorable effects on appetite regulation, energy expenditure, and resistance to weight regain, whereas maintenance of weight loss achieved with GLP-1 receptor agonists appears to be enhanced by continued treatment and supportive lifestyle interventions.

Collectively, these findings suggest that for individuals who train regularly, fat-loss interventions should be evaluated not only by the magnitude of weight reduction, but by their compatibility with exercise performance, lean mass preservation, and long-term adherence. In this context, taken together, the available evidence suggests that both protein-based nutritional strategies and incretin–based pharmacotherapies can support clinically meaningful fat loss while offering distinct physiological and practical advantages. Protein-based approaches may favor lean mass preservation, support exercise adaptations, and facilitate long-term dietary adherence, whereas incretin –based therapies generally produce larger and more rapid reductions in body weight and FM. Consequently, the selection of either strategy should be guided by individual goals, training status, body-composition priorities, and clinical context.

What is already known on this subject?

• GLP-1 receptor agonists and newer incretin-based pharmacotherapies produce substantial weight loss and improve cardiometabolic health in individuals with obesity and type 2 diabetes.

• Protein-rich dietary strategies are also associated with reductions in body fat and improvements in satiety, energy expenditure, and metabolic regulation.

• Exercise, particularly resistance training, is recognized as a key intervention for preserving SMM and functional capacity during weight loss.

• Concerns have emerged regarding LBM reduction during pharmacologically induced weight loss, especially with rapid reductions in body weight.

• Long-term maintenance of weight loss remains a major challenge regardless of the intervention strategy used.

What this study adds?

• Provides an exercise-oriented comparison between protein supplementation strategies and incretin–based weight-loss therapies rather than evaluating either approach in isolation.

• Introduces a physiology- and practice-based framework centered on three underexplored determinants of weight-loss quality: muscle mass preservation, pace of fat loss, and long-term weight maintenance.

• Synthesizes evidence from nutritional, pharmacological, and exercise science literature to evaluate how different weight-loss strategies influence body composition beyond total weight reduction.

• Highlights the importance of considering the composition, trajectory, and sustainability of weight loss when evaluating interventions in physically active individuals.

• By integrating mechanistic, nutritional, pharmacological, and exercise-related evidence, this review provides a comprehensive framework for assessing weight-loss strategies in exercise-relevant settings.

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Review article.

Compliance with ethical standards

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Author contributions

Conceptualization: F.B., H.A, Methodology: F.B., H.A., Software: F.B., H.A., Validation: F.B., H.A.,; Formal analysis: F.B., H.A.,; Investigation: F.B., H.A.,; Resources: F.B., H.A.,; Data curation: F.B., H.A.,; Writing - original draft: F.B., H.A.,; Writing–review & editing F.B., H.A.,; Visualization: F.B., H.A.,; Supervision: H.A.; Project administration: F.B., H.A.; Funding acquisition: H.A.

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