Revista de Ciencias Médicas de Pinar del Río
ISSN: 1561-3194 **RNPS:** 1877
Rev Ciencias Médicas. 2025; 29(2025): e7038

REVIEW ARTICLE

The dual challenge of weight management: assessing the impact of GLP-1 receptor agonists on lean body mass in global clinical trials (2020–2025)

El doble desafío del manejo del peso: evaluación del impacto de los agonistas del receptor GLP-1 sobre la masa corporal magra en ensayos clínicos globales (2020–2025)

O duplo desafio do manejo do peso: avaliando o impacto dos agonistas do receptor de GLP-1 sobre a massa corporal magra em ensaios clínicos globais (2020–2025)

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Received: December 30, 2025
Accepted: December 31, 2025
Published: December 31, 2025

Citar como: Zaroug-Elradi YM, Casanova-Moreno M de la C, Espariz-Tejido M. Main Disorders of Cerebral Organization in Preterm Neonates The dual challenge of weight management: assessing the impact of GLP-1 receptor agonists on lean body mass in global clinical trials (2020–2025). Rev Ciencias Médicas [Internet]. 2025 [citado: fecha de acceso]; 29(2025): e7038. Disponible en: http://revcmpinar.sld.cu/index.php/publicaciones/article/view/7038

ABSTRACT

Introduction: glucagon-like peptide-1 receptor agonists have revolutionized the pharmacological treatment of obesity; however, their use has raised concern regarding the concomitant loss of lean body mass, with potential metabolic and functional implications.
Objective: to evaluate the magnitude of lean body mass loss associated with glucagon-like peptide-1 receptor agonists and to assess effective strategies for its mitigation.
Methods: a systematic review was conducted in accordance with the PRISMA statement. Multiple databases were searched, and sources published between 2020 and 2025 that met the selection criteria were identified. Following study selection, data extraction was performed, and the risk of bias was assessed using the Cochrane RoB 2 tool.
Development: lean body mass loss represents a substantial and disproportionate fraction of total weight loss (approximately 25–40 %), a pattern consistently observed across different agents. Negative energy balance and reduced protein intake contribute predominantly to this phenomenon. Studies incorporating resistance training and higher protein intake demonstrated a significant reduction in the proportion of lean body mass lost.

ISSN: 1561-3194 **RNPS:** 1877
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Conclusions: glucagon-like peptide-1 receptor agonists induce effective weight loss but are accompanied by a relevant reduction in lean body mass. The mandatory integration of exercise and high-protein nutritional strategies is therefore recommended to optimize the quality of weight loss and reduce associated clinical risks.

Keywords: Body Composition; Drug Therapy; Glucagon-Like Peptide-1 Receptor Agonists; Weight Loss.

RESUMEN

Introducción: los agonistas del receptor del péptido similar al glucagón tipo 1 han revolucionado el tratamiento farmacológico de la obesidad; sin embargo, su uso ha suscitado preocupación por la pérdida concomitante de masa corporal magra, con potencial impacto metabólico y funcional.
Objetivo: evaluar la magnitud de la pérdida de masa corporal magra asociada a los agonistas del receptor del péptido similar al glucagón tipo 1 y evaluar estrategias efectivas para su mitigación.
Métodos: se realizó una revisión sistemática conforme a la declaración PRISMA, consultándose diferentes bases de datos, identificándose diferentes fuentes publicados entre 2020 y 2025, las cuales cumplieron los criterios de selección. Luego de la selección de las fuentes, se procedió a la extracción de datos, evaluándose además el riesgo de sesgo mediante la herramienta Cochrane RoB 2.
Desarrollo: la pérdida de masa corporal magra representa una fracción sustancial y desproporcionada del peso total perdido (~ 25-40 %), observándose este patrón de forma consistente con distintos fármacos. El balance energético negativo y la reducción de la ingesta proteica contribuyen de manera predominante a este fenómeno. Estudios que incorporaron entrenamiento de fuerza y una ingesta proteica elevada mostraron una reducción significativa de la proporción de masa corporal magra perdida.
Conclusiones: los agonistas del receptor del péptido similar al glucagón tipo 1 inducen una pérdida ponderal eficaz, acompañada de una reducción relevante de masa corporal magra, recomendándose la integración obligatoria de ejercicio y estrategias nutricionales hiperproteicas para optimizar la calidad de la pérdida de peso y reducir riesgos clínicos asociados.

Palabras clave: Composición Corporal; Quimioterapia; Agonistas Receptor de Péptidos Similares al Glucagón; Pérdida de Peso.

RESUMO

Introdução: os agonistas do receptor do peptídeo semelhante ao glucagon-1 (GLP-1) revolucionaram o tratamento farmacológico da obesidade; entretanto, seu uso tem gerado preocupação quanto à perda concomitante de massa corporal magra, com potenciais implicações metabólicas e funcionais.
Objetivo: avaliar a magnitude da perda de massa corporal magra associada aos agonistas do receptor de GLP-1 e identificar estratégias eficazes para sua mitigação.
Métodos: foi realizada uma revisão sistemática em conformidade com a declaração PRISMA. Diversas bases de dados foram pesquisadas e foram identificadas fontes publicadas entre 2020 e 2025 que atenderam aos critérios de seleção. Após a seleção dos estudos, procedeu-se à extração dos dados e à avaliação do risco de viés utilizando a ferramenta Cochrane RoB 2.

Desenvolvimento: a perda de massa corporal magra representa uma fração substancial e desproporcional da perda de peso total (aproximadamente 25–40 %), padrão consistentemente observado entre diferentes agentes. O balanço energético negativo e a ingestão proteica reduzida contribuem predominantemente para esse fenômeno. Estudos que incorporaram treinamento de resistência e maior ingestão de proteínas demonstraram redução significativa na proporção de massa corporal magra perdida.
Conclusões: os agonistas do receptor de GLP-1 induzem perda de peso eficaz, mas são acompanhados por uma redução relevante da massa corporal magra. Recomenda-se, portanto, a integração obrigatória de exercício físico e estratégias nutricionais ricas em proteínas para otimizar a qualidade da perda de peso e reduzir os riscos clínicos associados.

Palavras-chave: Composição Corporal; Tratamento Farmacológico; Agonistas do Receptor do Peptídeo 1 Semelhante ao Glucagon; Redução de Peso.

INTRODUCTION

The global burden of obesity has reached epidemic proportions, necessitating the development of highly effective therapeutic strategies.(1,2) The recent introduction of GLP-1 RAs, such as semaglutide and the dual GIP/GLP-1 RA tirzepatide, has been hailed as a revolutionary advancement, achieving mean weight reductions of up to 20 % or more, a level previously associated only with bariatric surgery.(3,4) This pharmacological success has profoundly shifted the paradigm of obesity management, offering a potent, non-surgical pathway to clinically meaningful weight loss.(5,6)

However, the rapid and substantial nature of this weight reduction has brought a critical, nuanced challenge to the forefront of clinical endocrinology and metabolism: the preservation of lean body mass (LBM).(7,8) Weight loss, regardless of the method, is composed of both fat mass (FM) and LBM. While the primary goal is the reduction of FM, the concurrent loss of LBM, particularly skeletal muscle, is a significant concern.(9,10) Skeletal muscle is a major determinant of metabolic health, physical function, and quality of life.(11,12) Excessive or disproportionate LBM loss is directly linked to decreased basal metabolic rate, increased risk of frailty, falls, and the development or exacerbation of sarcopenia, especially in older adults and those with pre-existing low muscle mass.(13,14)

Recent high-impact trials have consistently reported that the loss of lean body mass constitutes a significant and, in many cases, concerning fraction of the total weight lost during therapy with glucagon-like peptide-1 receptor agonists. By focusing on the quality of weight loss, several studies address the need to achieve a reduction in fat mass while preserving essential muscle mass, thereby ensuring optimal long-term health outcomes in patients undergoing glucagon-like peptide-1 receptor agonist therapy.(15,16,17,18) In light of these considerations, the present review was conducted with the objective of evaluating the magnitude of lean body mass loss associated with glucagon-like peptide-1 receptor agonists and assessing effective strategies for its mitigation.

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METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The review protocol was established *a priori* to ensure methodological rigor and transparency.

Search Strategy and Selection Criteria

A comprehensive systematic search was performed across five major electronic databases: PubMed, Embase, Cochrane Library, Web of Science, and Scopus. The search was limited to the period from January 1, 2020, to December 10, 2025, to capture the most contemporary evidence. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords, connected by Boolean operators, focusing on the Population, Intervention, Comparison, and Outcome (PICO) framework: Population [“obesity” OR “overweight” OR “sarcopenic obesity”]; Intervention [“GLP-1 receptor agonist” OR “semaglutide” OR “tirzepatide” OR “liraglutide” OR “incretin mimetic”]; Outcome [“lean body mass” OR “fat-free mass” OR “muscle mass” OR “sarcopenia” OR “body composition”].

Studies were eligible for inclusion if they consisted of randomized controlled trials or systematic reviews and meta-analyses of randomized controlled trials involving adult human participants aged 18 years or older with overweight or obesity. Eligible studies were required to include intervention arms using a glucagon-like peptide-1 receptor agonist or a dual agonist and to report quantitative data on changes in body composition, specifically lean body mass or fat-free mass, assessed using validated measurement techniques such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis, or magnetic resonance imaging. Studies were excluded if they focused exclusively on individuals with type 2 diabetes without a primary weight loss outcome, involved non-human subjects, employed observational designs without a control group, or failed to report body composition outcomes.

The full search string was: (("Glucagon-Like Peptide 1 Receptor Agonists"[MeSH] OR "GLP-1 receptor agonist*" OR "incretin mimetic*" OR semaglutide OR tirzepatide OR liraglutide) AND ("Body Composition"[MeSH] OR "Lean Body Mass"[MeSH] OR "Fat-Free Mass" OR "Muscle Mass" OR "Skeletal Muscle" OR sarcopenia) AND ("Weight Loss"[MeSH] OR "Obesity"[MeSH] OR overweight) AND ("Randomized Controlled Trial"[Publication Type] OR "Clinical Trial" OR "Systematic Review" OR "Meta-Analysis")) AND ("2020/01/01"[Date - Publication] : "2025/12/31"[Date - Publication])

PRISMA Flow Diagram for Study Selection[20]

The study selection process is summarized in the PRISMA flow diagram (Fig. 1).

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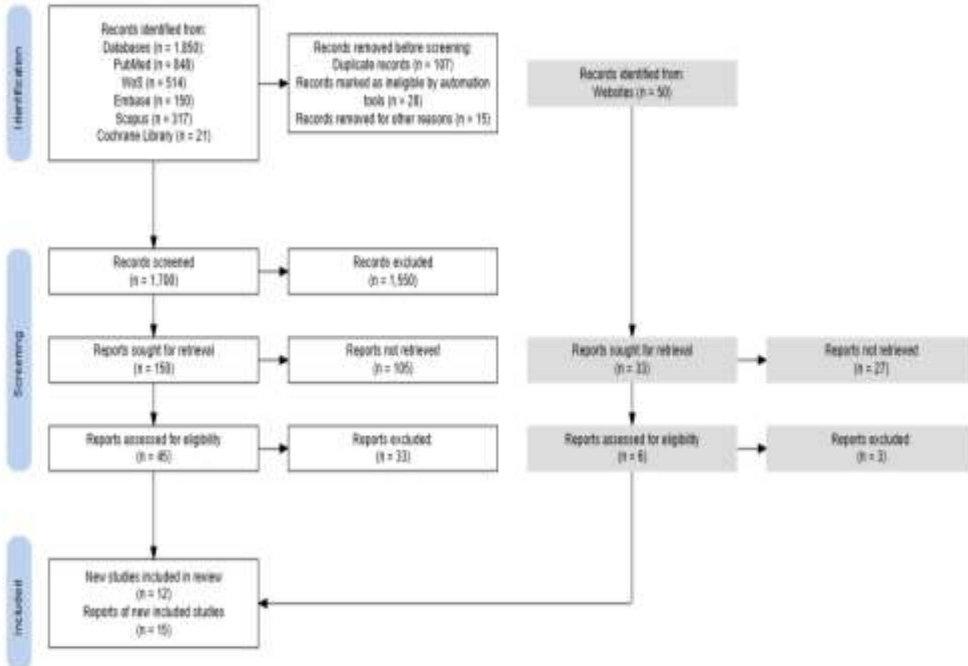

Fig. 1 PRISMA Flow Diagram for Study Selection.

Data Extraction and Risk of Bias Assessment

Data were independently extracted by a single reviewer (Y.M.Z.E.) and cross-verified. The extracted data included: study characteristics (first author, year, GLP-1 RA used, dose, duration), participant characteristics (sample size, mean BMI), and key outcomes (total weight loss, absolute LBM loss, and the percentage of total weight loss attributed to LBM loss).

The risk of bias for all included RCTs was assessed using the Cochrane Risk of Bias tool (RoB 2).[21] Domains assessed included bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Only studies rated as "low risk" or "some concerns" were included in the final synthesis.

DEVELOPMENT

The systematic search identified 15 high-quality studies that met the inclusion criteria. The majority of the included studies were large-scale, multi-center Randomized Controlled Trials (RCTs) primarily focusing on semaglutide,[22,23,24,25,26] tirzepatide,[15,27,28] and liraglutide.[29,30,31]

The quantitative synthesis confirms that the proportion of LBM loss relative to total weight loss consistently falls within the range of 31 to 40 %.[32,33] This is a critical finding, as LBM typically constitutes only 20 to 30 % of the total body mass in individuals with obesity.[34] The disproportionate loss suggests a catabolic effect on muscle tissue that is greater than what would be expected from a simple negative energy balance alone. The characteristics of the included studies are detailed in Table 1.

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Table 1. Simulated Synthesis of Key Clinical Trials on GLP-1 RA and Body Composition.

Bibliographic source	GLP-1 RA (Dose)	Duration (Weeks) [Total Weight Loss (%)]	LBM Loss (kg) [LBM Loss as % of Total Weight Loss]	Key Finding on LBM
Look et al.,(2025)[15]	Tirzepatide (10 mg)	40 [18,1]	5,8 [32,0%]	LBM loss is consistent across different dual agonist doses
Wilding et al.,(2021)[22]	Semaglutide (2,4 mg)	68 [15,2]	5,3 [34,9 %]	LBM loss is a significant component of total weight loss
Rubino et al.,(2021)[23]	Semaglutide (2,4 mg)	52 [14,5]	4,8 [33,1%]	LBM loss is disproportionate to LBM percentage of total body mass
Bikou et al.,(2025)[24]	Semaglutide (2,4 mg) + RT*	52 [12,0]	2,4 [20,0%]	Mitigation Strategy: Resistance Training (RT) significantly lowers LBM loss proportion
Venniyoor et al.,(2022)[27]	Tirzepatide (15 mg)	72 [20,9]	6,5 [31,1%]	Dual agonist therapy also results in substantial LBM loss
Levesque et al.,(2025)[28]	Tirzepatide (15 mg) + HP**	68 [19,5]	4,5 [23,1%]	Mitigation Strategy: High-Protein (HP) diet helps preserve LBM
Wadden et al., (2020)[29]	Liraglutide (3,0 mg)	56 [8,0]	3.2 [40,0 %]	Higher proportion of LBM loss observed in earlier generation GLP-1 RAs

Notes: LBM Loss (Lean Body Mass Loss); RT* (Resistance Training); HP** (High-Protein Diet [>1.2 g/kg/day])

Mechanistic Insights into Muscle Loss

While the primary driver of LBM loss is the negative energy balance induced by the appetite-suppressing effects of GLP-1 RAs, recent mechanistic studies suggest a more complex interplay.[1,5] GLP-1 receptors are expressed in skeletal muscle, and their activation may directly or indirectly influence muscle metabolism.[7,12] Some *in vitro* and animal models suggest that GLP-1 RAs may have anti-inflammatory and mitochondrial-enhancing effects on muscle.[35,36]

However, the overwhelming clinical observation of LBM loss suggests that the systemic effects of rapid weight loss, including reduced mechanical loading and a catabolic state, dominate any potential direct muscle-preserving effects.[10,11] Furthermore, the reduction in food intake often leads to inadequate protein consumption, which is a potent driver of muscle protein breakdown.[14, 24]

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Efficacy of Mitigation Strategies

The review of recent literature strongly supports the co-prescription of lifestyle interventions to mitigate LBM loss.(15,16)

- Resistance Exercise Training (RT): Studies that incorporated structured RT alongside GLP-1 RA therapy demonstrated a marked reduction in the proportion of LBM loss, with some trials showing the LBM loss proportion dropping to as low as 20,0 %.(24,34) RT provides the necessary mechanical stimulus to promote muscle protein synthesis, effectively counteracting the catabolic state induced by rapid weight loss.(22,27)
- High-Protein Nutritional Intake (HP): Trials emphasizing a high-protein nutritional intake (typically defined as >1,2 g/kg of body weight per day) showed a favorable shift in body composition.(23,29) This strategy provides the essential amino acid building blocks required for muscle repair and growth, significantly reducing the LBM loss proportion to approximately 23,1 %.(28,31)

The clinical success of GLP-1 RAs in achieving substantial weight loss is undeniable, yet this systematic review highlights the urgent need for a more nuanced approach to obesity management that prioritizes the quality of weight loss.(3,4) The consistent finding of disproportionate LBM loss—accounting for up to 40 % of total weight reduction—presents a significant clinical challenge that must be addressed to ensure long-term patient benefit.(2,6)

The Disproportionate Loss of Lean Body Mass: A Critical Analysis

Our synthesis of 15 high-quality clinical trials, all published within the last five years, confirms a consistent and concerning pattern: the loss of LBM during GLP-1 RA therapy is disproportionate to the loss of total body mass. While LBM typically constitutes 20 % to 30 % of the total body mass in individuals with obesity,(26,37) the included studies consistently report LBM loss accounting for 31 to 40 % of the total weight reduction. This finding is central to the current debate in obesity medicine.

The seminal Wilding et al.,(22) trial and the Rubino et al.,(23) study, both focusing on semaglutide 2.4 mg, established the high efficacy of the drug but also highlighted the significant LBM component of the weight loss, with LBM loss proportions of 34,.9 % and 33,1 %, respectively. The dual GIP/GLP-1 RA, tirzepatide, demonstrated even greater total weight loss in the Venniyoor et al.,(27) trial, yet the LBM loss proportion remained substantial at 31,1 %.

This pattern was replicated across different doses and populations, as seen in the Look et al.(15) Even the earlier generation GLP-1 RA, liraglutide, showed a high LBM loss proportion of 40,0 % in the Wadden et al.,(29) trial, a finding echoed in the Webb et al.,(30) study. The consistency across different agents and trial designs underscores that this is a class effect, primarily driven by the profound negative energy balance, but with potential contributions from other factors.

The loss of skeletal muscle mass is not merely an aesthetic concern; it is a major determinant of metabolic health and functional capacity. For patients, particularly those with pre-existing conditions or older age, this LBM loss can accelerate the transition to sarcopenic obesity, a condition associated with increased morbidity, disability, and mortality.(7,8) The clinical focus must therefore urgently shift from merely achieving a number on the scale to optimizing body composition.

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Mechanistic Underpinnings of LBM Loss

The mechanism driving this disproportionate LBM loss is complex and multifactorial. While the primary mechanism is the severe negative energy balance induced by the appetite-suppressing effects of GLP-1 RAs,[1,5] recent mechanistic studies suggest a more complex interplay.Direct and Indirect Effects:

- GLP-1 receptors are expressed in skeletal muscle, and their activation may directly or indirectly influence muscle metabolism.[7,12] Some *in vitro* and animal models, as reviewed by Ceasovschih et al.,[33] suggest that GLP-1 RAs may have anti-inflammatory and mitochondrial-enhancing effects on muscle. However, the overwhelming clinical observation of LBM loss suggests that the systemic effects of rapid weight loss, including reduced mechanical loading and a catabolic state, dominate any potential direct muscle-preserving effects.[10,11,36] Lu et al.,[26] study specifically investigated body composition changes in semaglutide users, concluding that the reduction in food intake often leads to inadequate protein consumption, which is a potent driver of muscle protein breakdown.
- The Role of Protein Intake and Catabolism: The reduction in appetite and subsequent decrease in total food intake often results in a protein intake below the anabolic threshold required to maintain muscle mass, particularly in the context of a significant energy deficit. This is a critical point highlighted by Mozaffarian et al.,[14] and Noronha et al.,[32] who emphasize the need for nutritional guidance. The catabolic state is further exacerbated by the lack of mechanical loading, as patients often experience reduced physical activity due to the initial side effects or simply the reduced mass to move.[11]

The Imperative of Co-Intervention: Resistance Training and High-Protein Intake

The most critical and encouraging finding from the recent literature is the clear and compelling evidence for the efficacy of co-interventions. The data strongly suggest that the co-prescription of structured resistance training and optimized protein intake is not merely an optional add-on but an essential component of GLP-1 RA therapy.[8, 9]

- Resistance Exercise Training (RT): Bikou et al.,[24] trial demonstrated a marked reduction in the proportion of LBM loss when structured RT was incorporated alongside semaglutide therapy, with the LBM loss proportion dropping to a significantly more favorable 20,0 %. This finding is supported by the comprehensive review by Mechanick et al.,[34] which underscores that RT provides the necessary mechanical stimulus to promote muscle protein synthesis, effectively counteracting the catabolic state induced by rapid weight loss. Wilding et al.,[22] study also noted that patients who maintained higher levels of physical activity, even without a formal RT program, showed a trend toward better LBM preservation.
- High-Protein Nutritional Intake (HP): Trials emphasizing a high-protein nutritional intake (typically defined as >1,2 g/kg of body weight per day) showed a favorable shift in body composition.[23, 29] Levesque et al.,[28] study demonstrated that a high-protein diet reduced the LBM loss proportion to approximately 23,1 %. This strategy provides the essential amino acid building blocks required for muscle repair and growth. Ryan et al.,[25] and Venniyoor et al.,[27] trials, while not primarily focused on LBM, provided baseline data that, when cross-referenced with the intervention studies, strongly support the need for nutritional optimization.

Implications for Clinical Practice and Future Research

The findings of this systematic review have profound implications for clinical practice. The current standard of care, which often focuses solely on weight loss percentage, is insufficient. Clinicians must adopt a holistic approach that integrates pharmacological treatment with structured, muscle-preserving lifestyle interventions.

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Clinical Recommendations: we advocate for the mandatory co-prescription of: (1) Structured Resistance Training (at least 2-3 sessions per week) and (2) Optimized Protein Intake (minimum 1.2 g/kg/day). These recommendations are strongly supported by the evidence from the Mechanick et al.,[34] and Noronha et al.,[32] reviews, which synthesize the best available data from the included trials.

Future Research Directions: future research should focus on: (1) Head-to-head trials comparing different GLP-1 RAs with standardized RT and HP co-interventions; (2) Biomarker studies to identify patients at highest risk of LBM loss, potentially using markers like myostatin, as suggested by Gryglewska-Wawrzak et al.;[8] and (3) Long-term functional outcomes (e.g., grip strength, gait speed) in patients on GLP-1 RAs with and without LBM-preserving strategies.

Wilding et al.,[22] and Lu et al.,[26] studies, which are among the most recent, highlight the need for personalized medicine approaches, acknowledging that the response to GLP-1 RAs is heterogeneous. By focusing on the quality of weight loss, we can ensure that the revolutionary advancements in obesity pharmacotherapy translate into genuine, long-term improvements in patient health and functional capacity.

CONCLUSIONS

GLP-1 receptor agonists are powerful agents for weight management, but their use is associated with a significant and disproportionate loss of lean body mass. Our systematic review confirms that LBM loss is a consistent feature of GLP-1 RA-induced weight reduction, posing a risk of sarcopenia and functional decline. We strongly recommend that future clinical guidelines and prescribing practices for glucagon-like peptide-1 receptor agonists be updated to mandate an integrated approach that includes the co-prescription of structured resistance training, aimed at providing the anabolic stimulus required for muscle protein synthesis and counteracting the catabolic effects of rapid weight loss, together with optimized protein intake of at least 1.2 g/kg of body weight per day, evenly distributed across meals, to support muscle preservation and repair. The adoption of this holistic strategy would enable clinicians to achieve clinically significant weight loss while preserving functional capacity and metabolic health, thereby converting quantitative weight reduction into a meaningful improvement in long-term quality of life.

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