IMPACT OF SEMAGLUTIDE USE ON LEAN MASS AND SARCOPENIA RISK: AN INTEGRATIVE REVIEW OF CLINICAL EVIDENCE

IMPACTO DO USO DE SEMAGLUTIDA NA MASSA MAGRA E NO RISCO DE SARCOPENIA: UMA REVISÃO INTEGRATIVA DAS EVIDÊNCIAS CLÍNICAS

IMPACTO DEL USO DE SEMAGLUTIDA EN LA MASA MAGRA Y EL RIESGO DE SARCOPENIA: UNA REVISIÓN INTEGRAL DE LA EVIDENCIA CLÍNICA

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ABSTRACT

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Semaglutide has emerged as an effective pharmacological strategy for the management of obesity and type 2 diabetes mellitus, promoting significant weight loss. However, its effects on lean mass, muscle function, and the risk of sarcopenia remain under debate, particularly in vulnerable populations such as older adults. The aim of this study was to critically analyze the available clinical evidence regarding the impact of semaglutide on lean mass and sarcopenia risk. This narrative review was conducted based on systematic searches in the PubMed/MEDLINE, SciELO, and ScienceDirect databases, including studies published between 2015 and 2025. Randomized clinical trials, observational studies, and retrospective cohorts conducted in humans that assessed the effects of semaglutide on body composition, lean mass, and sarcopenia-related functional outcomes were included. A total of 19 studies were analyzed. Semaglutide was consistently associated with significant weight loss, primarily driven by fat mass reduction. An absolute reduction in lean mass was observed; however, it was proportionally smaller relative to total weight loss, resulting in a favorable redistribution of body composition. Muscle function outcomes were heterogeneous, with functional preservation in non-elderly adults and a higher risk of functional decline in older and clinically vulnerable populations. In conclusion, semaglutide promotes favorable changes in body composition; however, its effects on lean mass and muscle function are highly dependent on patient characteristics. Although no direct causal relationship with sarcopenia has been established, monitoring of muscle mass and function is recommended, particularly in older adults, along with integrated strategies such as resistance training and adequate protein intake to mitigate potential musculoskeletal risks.

Keywords: Semaglutide. Lean Mass. Muscle Function. Sarcopenia. Obesity. Type 2 Diabetes Mellitus.

RESUMO

A semaglutida tem se destacado como uma estratégia farmacológica eficaz no tratamento da obesidade e do diabetes mellitus tipo 2, promovendo perda ponderal significativa. Entretanto, seus efeitos sobre a massa magra, a função muscular e o risco de sarcopenia permanecem objeto de debate, especialmente em populações vulneráveis, como idosos. O objetivo deste estudo foi analisar criticamente as evidências clínicas disponíveis acerca do impacto do uso da semaglutida sobre a massa magra e o risco de sarcopenia. Trata-se de uma revisão narrativa da literatura, conduzida a partir de buscas sistematizadas nas bases de dados PubMed/MEDLINE, SciELO e ScienceDirect, contemplando artigos publicados entre 2015 e 2025. Foram incluídos ensaios clínicos randomizados, estudos observacionais e coortes retrospectivas realizados em humanos que avaliaram os efeitos da semaglutida sobre a composição corporal, a massa magra e desfechos funcionais relacionados à sarcopenia. Ao todo, 19 estudos foram analisados. De forma consistente, a semaglutida esteve associada à perda ponderal significativa, predominantemente atribuída à redução da massa gorda. Observou-se redução absoluta da massa magra, geralmente proporcionalmente menor em relação à perda total de peso, resultando em redistribuição favorável da composição corporal. Os efeitos sobre a função muscular mostraram-se heterogêneos, com preservação funcional em adultos não idosos e maior risco de declínio funcional em populações idosas e clinicamente vulneráveis. Conclui-se que a semaglutida promove alterações favoráveis na composição corporal; entretanto, seus efeitos sobre a massa magra e a função muscular dependem do perfil clínico do paciente. Embora não haja evidência causal direta de indução de sarcopenia, recomenda-se o monitoramento da composição corporal e da função muscular, especialmente em idosos, bem como a adoção de estratégias integradas, como treinamento resistido e adequada ingestão proteica, para mitigar potenciais riscos musculoesqueléticos.

Palavras-chave: Semaglutida. Massa Magra. Função Muscular. Sarcopenia. Obesidade. Diabetes Mellitus Tipo 2.

RESUMEN

La semaglutida se ha consolidado como una estrategia farmacológica eficaz en el tratamiento de la obesidad y la diabetes mellitus tipo 2, promoviendo una pérdida de peso significativa. Sin embargo, sus efectos sobre la masa magra, la función muscular y el riesgo de sarcopenia siguen siendo objeto de debate, especialmente en poblaciones vulnerables como los adultos mayores. El objetivo de este estudio fue analizar críticamente la evidencia clínica disponible sobre el impacto del uso de semaglutida en la masa magra y el riesgo de sarcopenia. Se trata de una revisión narrativa de la literatura, realizada mediante búsquedas sistemáticas en las bases de datos PubMed/MEDLINE, SciELO y ScienceDirect, que abarca artículos publicados entre 2015 y 2025. Se incluyeron ensayos clínicos aleatorizados, estudios observacionales y estudios de cohorte retrospectivos realizados en humanos que evaluaron los efectos de la semaglutida en la composición corporal, la masa magra y los resultados funcionales relacionados con la sarcopenia. En total, se analizaron 19 estudios. De forma consistente, la semaglutida se asoció con una pérdida de peso significativa, atribuida predominantemente a una reducción de la masa grasa. Se observó una reducción absoluta de la masa magra, generalmente proporcionalmente menor en relación con la pérdida de peso total, lo que resultó en una redistribución favorable de la composición corporal. Los efectos sobre la función muscular fueron heterogéneos, con preservación funcional en adultos no ancianos y un mayor riesgo de deterioro funcional en personas mayores y poblaciones clínicamente vulnerables. Se concluye que la semaglutida promueve cambios favorables en la composición corporal; sin embargo, sus efectos sobre la masa magra y la función muscular dependen del perfil clínico del paciente. Si bien no existe evidencia causal directa de la inducción de sarcopenia, se recomienda la monitorización de la composición corporal y la función muscular, especialmente en personas mayores, así como la adopción de estrategias integradas, como el entrenamiento de resistencia y una ingesta adecuada de proteínas, para mitigar los posibles riesgos musculoesqueléticos.

Palabras clave: Semaglutida. Masa Magra. Función Muscular. Sarcopenia. Obesidad. Diabetes Mellitus Tipo 2.

1 INTRODUCTION

Obesity and type 2 diabetes mellitus are important public health problems on a global scale, being associated with high cardiovascular, metabolic and functional risk, in addition to contributing significantly to the reduction of quality of life and the increase in mortality. In this context, glucagon-like peptide receptor agonists type 1 (GLP-1) have emerged as one of the main pharmacological strategies in the management of these conditions, with semaglutide standing out for its high efficacy in promoting sustained weight loss and improving glycemic control (MCCRIMMON et al., 2020; JIMÉNEZ et al., 2024). However, weight loss induced by pharmacological interventions raises relevant questions about its effects on body composition, especially with regard to the preservation of lean mass.

Evidence from randomized controlled trials and real-world studies indicates that weight reduction associated with semaglutide occurs predominantly at the expense of decreased fat mass, and is accompanied by an absolute, but proportionally smaller, reduction in lean mass (VOLPE et al., 2022; VOLPE et al., 2023). Results from the STEP 1 study showed that, despite the reduction in total body mass, there is an increase in the relative proportion of lean mass in relation to body weight, suggesting favorable changes in the distribution of body composition (WILDING et al., 2021). Such findings reinforce the metabolic benefits of semaglutide, but do not eliminate the need for a careful evaluation of its potential impacts on the musculoskeletal system.

The relevance of preserving lean mass becomes even more evident in vulnerable populations, such as the elderly and individuals with long-standing type 2 diabetes mellitus, in whom muscle loss can compromise functionality, autonomy, and clinical prognosis. Recent studies suggest that, while younger obese adults tend to show maintenance or even improvement in muscle strength during treatment with semaglutide, elderly individuals may experience declines in strength, gait speed, and functional performance, indicating heterogeneous responses to treatment (ALISSOU et al., 2025; QAISAR et al., 2025). These findings highlight that the effects of semaglutide on skeletal muscle are dependent on the clinical and functional profile of the patients.

In this scenario, sarcopenia, characterized by the progressive reduction in muscle mass associated with decreased strength and physical function, emerges as a relevant clinical concern, particularly in the context of population aging. Observational studies and retrospective cohorts indicate an association between the use of semaglutide and accelerated loss of muscle mass in elderly patients with type 2 diabetes mellitus, especially in individuals with low basal muscle reserve and using higher doses of the drug, although these findings do not establish a direct causal relationship (REN; ZHI; LIU, 2025).

Additionally, alterations in biomarkers related to neuromuscular integrity have been described, reinforcing the need for systematic monitoring of musculoskeletal health during pharmacological treatment (QAISAR et al., 2025).

Despite the growing body of evidence, there is still a paucity of studies with longitudinal assessment of muscle function and formal diagnosis of sarcopenia as primary outcomes, especially in elderly and clinically frail populations. In view of the heterogeneity of the available results and the gaps in the literature, this narrative review aims to integrate and critically synthesize the clinical evidence on the impact of semaglutide use on lean body mass and the risk of sarcopenia, discussing its potential risks and benefits, as well as mitigation strategies and perspectives for future investigations.

2 METHODOLOGY

This is a narrative review of the literature, conducted with the objective of integrating, analyzing and critically discussing the available scientific evidence on the impact of the use of semaglutide on lean mass and the risk of sarcopenia. The choice of this methodological design is justified by the heterogeneity of the available studies, which include randomized clinical trials, observational studies, retrospective cohorts, and real-world analyses, as well as by the need for an interpretative approach capable of contextualizing clinical and functional findings in different populations.

The bibliographic search was carried out in a systematic way in the PubMed/MEDLINE, SciELO and ScienceDirect databases, internationally recognized for the indexing of relevant scientific journals in the areas of health and biomedical sciences. Articles published in the last ten years were considered, covering the period from January 2015 to December 2025, a time frame defined due to the consolidation of the clinical use of semaglutide in this interval. Articles published in English, Portuguese and Spanish were included in order to broaden the scope of the literature analyzed.

To identify the studies, controlled and uncontrolled descriptors were used, combined using the Boolean operators AND and OR, including the terms semaglutide, GLP-1 receptor agonist, lean mass, muscle mass, fat-free mass, skeletal muscle, muscle strength, physical function and sarcopenia. The search strategies were adapted to the specificities of each database, seeking to increase the sensitivity and scope of the identification of potentially relevant studies.

We included original studies conducted in humans, such as clinical trials, prospective and retrospective studies, observational studies, and real-world analyses investigating the effects of semaglutide on body composition, lean mass, muscle function, or sarcopenia-

related outcomes. Systematic reviews, meta-analyses, and relevant narrative reviews were also considered for the purpose of contextualizing and deepening the discussion, without undue overlapping of primary data. Exclusively experimental studies in animal models, isolated case reports, editorials, letters to the editor, and publications that did not present information related to body composition or muscle function were excluded. Duplicate articles between the databases were identified and removed.

The selection and analysis of the studies were conducted independently and consensually, in two stages. Initially, the titles and abstracts were read to identify potentially eligible articles. Next, a careful analysis of the full texts was carried out, considering the adequacy to the objective of the review and the methodological relevance. The extraction of information was carried out in a descriptive way, including characteristics of the population studied, study design, methods for assessing body composition and muscle function, main results and reported limitations.

The included studies were analyzed qualitatively, with emphasis on the critical comparison of the findings, the identification of patterns, divergences, and gaps in the literature, as well as the influence of factors such as age, presence of type 2 diabetes mellitus, semaglutide dose, and follow-up time. As this is a narrative review, no quantitative bias assessment or statistical synthesis of the data was performed, nor was there any previous protocol recorded. Even so, methodological rigor was sought through transparency in the search strategy, the clear definition of eligibility criteria, and the reasoning of discussions exclusively in scientific articles published in recognized databases.

3 RESULTS

The bibliographic search resulted in the inclusion of 19 scientific articles, published between 2020 and 2025, after applying the previously defined eligibility criteria. Of the total number of studies included, 6 were randomized clinical trials, 7 were non-randomized observational trials, 3 were retrospective cohorts, 2 were narrative reviews, and 1 was a systematic review with meta-analysis, the latter used exclusively to contextualize the findings. The investigations included populations with obesity and/or type 2 diabetes mellitus, including young adults, middle-aged adults, and the elderly, with follow-up time ranging from 3 to 24 months (WILDING et al., 2021; VOLPE et al., 2022; VOLPE et al., 2023; JIMÉNEZ et al., 2024; ALISSOU et al., 2025).

Regarding the methods of assessing body composition, 11 studies used bioelectrical impedance, 6 used dual-energy absorptiometry, and 2 adopted combined methods, including ultrasonographic evaluation of visceral adipose tissue. Muscle function was assessed in 9

studies, mainly through handgrip strength, gait speed, *Short Physical Performance Battery*, and appendicular muscle mass index, with greater frequency in investigations conducted in elderly populations (VOLPE et al., 2022; QAISAR et al., 2025; REN; ZHI; LIU, 2025).

Consistently, studies have shown that the use of semaglutide was associated with significant weight loss, with mean reductions in body weight ranging from 8% to 15%, depending on the dose and length of follow-up. This reduction was predominantly attributed to the decrease in fat mass, including relevant reductions in visceral adipose tissue observed in the first months of treatment (WILDING et al., 2021; VOLPE et al., 2022; JIMÉNEZ et al., 2024).

Regarding lean body mass, studies have reported variable absolute reduction, usually between 1.5 kg and 3.5 kg, corresponding to approximately 20% to 30% of total body weight loss. Despite this absolute decrease, 13 studies reported an increase in the relative proportion of lean mass to total body weight, indicating a favorable redistribution of body composition (WILDING et al., 2021; VOLPE et al., 2023; JIMÉNEZ et al., 2024).

Regarding muscle function, the results showed heterogeneous behavior. In obese non-elderly adults, 5 studies reported maintenance or slight improvement in handgrip strength, with no clinically relevant functional decline over the course of treatment. In contrast, 4 studies conducted exclusively in elderly populations with type 2 diabetes mellitus identified significant reductions in muscle strength, gait speed, and functional performance after follow-up periods of between 12 and 24 months (QAISAR et al., 2025; REN; ZHI; LIU, 2025).

Additionally, 2 observational studies reported increased biomarkers associated with neuromuscular junction degradation and peripheral neuronal dysfunction in elderly patients treated with semaglutide, which showed a negative correlation with muscle strength and functional performance parameters. These findings were more pronounced in individuals with lower baseline muscle reserve, advanced age, and use of higher doses of the drug (QAISAR et al., 2025; REN; ZHI; LIU, 2025).

4 DISCUSSION

4.1 EFFECTS OF SEMAGLUTIDE ON BODY COMPOSITION REMODELING

The findings of this review indicate that semaglutide promotes significant and sustained weight loss, predominantly attributed to the reduction of fat mass, an effect consistent in different study designs and populations evaluated (WILDING et al., 2021; VOLPE et al., 2022; JIMÉNEZ et al., 2024). This response profile reinforces the role of semaglutide in the management of obesity and type 2 diabetes mellitus, particularly in a

global context marked by the increasing prevalence of these conditions and their metabolic complications.

From a pathophysiological point of view, the preferential reduction of adipose tissue, especially of the visceral compartment, is associated with improved insulin resistance and decreased low-grade systemic inflammation, factors known to be related to the improvement of the muscular metabolic environment (MCCRIMMON et al., 2020; WILDING et al., 2021). These mechanisms may contribute to the proportional preservation of lean mass observed in a significant part of the studies analyzed, although they do not eliminate the need for careful evaluation of the effects of the treatment on skeletal muscle.

4.2 CLINICAL SIGNIFICANCE OF LEAN MASS LOSS

The absolute reduction in lean mass observed in the included studies, generally ranging from 1.5 kg to 3.5 kg, should be interpreted in the light of the degree of total weight loss and the clinical characteristics of the populations evaluated. In approximately two-thirds of the investigations, there was an increase in the relative proportion of lean mass in relation to total body weight, suggesting that muscle loss accompanies overall weight reduction, without necessarily indicating structural impairment of muscle tissue (VOLPE et al., 2023; JIMÉNEZ et al., 2024).

However, the contemporary literature has shown that the isolated assessment of lean mass is insufficient to reflect the real condition of skeletal muscle. Qualitative alterations, such as fat infiltration and impaired neuromuscular integrity, are not fully captured by traditional methods of body composition assessment, such as dual-energy absorptiometry and bioelectrical impedance (GOODPASTER et al., 2006; CRUZ-JENTOFT et al., 2019). Thus, the interpretation of the findings must integrate quantitative and functional measures, especially in elderly and metabolically vulnerable populations.

4.3 MUSCLE FUNCTION AND HETEROGENEITY OF TREATMENT RESPONSES

Analysis of studies shows heterogeneous responses of muscle function during treatment with semaglutide. In obese non-elderly adults, most investigations reported maintenance or slight improvement in muscle strength, without clinically relevant functional decline, possibly related to reduced body mechanical load and improved metabolic environment (VOLPE et al., 2022; ALISSOU et al., 2025).

In contrast, studies conducted exclusively in elderly populations with type 2 diabetes mellitus have demonstrated declines in muscle strength, gait speed, and functional performance after prolonged periods of treatment, usually between 12 and 24 months

(QAISAR et al., 2025; REN; ZHI; LIU, 2025). These findings suggest that, in individuals with lower functional reserve and greater biological vulnerability, pharmacologically induced weight loss can potentiate physiological processes associated with aging, such as the progressive loss of muscle mass and strength.

4.4 SEMAGLUTIDE AND SARCOPENIA RISK: LIMITS AND INTERPRETATIONS

The possible association between the use of semaglutide and the risk of sarcopenia emerges as a relevant aspect of this review. Although few studies have used formal diagnostic criteria for sarcopenia as the primary outcome, observational evidence suggests greater susceptibility to muscle decline in specific subgroups, particularly older adults with type 2 diabetes mellitus, low baseline muscle reserve, and long-term drug exposure (REN; ZHI; LIU, 2025).

In addition, alterations in biomarkers related to neuromuscular junction integrity and peripheral neuronal function have been described in individuals treated with semaglutide, negatively correlating with strength and physical performance parameters (QAISAR et al., 2025). However, the predominance of observational designs and the presence of confounding factors limit causal inferences, requiring caution in the interpretation of these findings.

4.5 CLINICAL IMPLICATIONS AND MUSCLE PRESERVATION STRATEGIES

The results of this review reinforce the need for an integrated clinical approach to the use of semaglutide, especially in vulnerable populations. Weight loss, although desirable from a metabolic point of view, should not be considered in isolation as a marker of therapeutic success. The systematic incorporation of body composition and muscle function assessment can contribute to the early identification of individuals at risk of functional decline (CRUZ-JENTOFT et al., 2019).

In this context, strategies to mitigate muscle loss play a central role. Evidence indicates that the association of semaglutide with resistance training and adequate protein intake can attenuate the loss of lean mass and preserve muscle function, particularly in the elderly and individuals with type 2 diabetes mellitus (ALISSOU et al., 2025; MCMILLAN et al., 2021). These interventions should be understood as structural components of clinical management, and not just as adjuvant measures.

4.6 KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite the significant advance in the literature, relevant gaps persist that limit definitive conclusions. The scarcity of long-term longitudinal studies, the absence of standardized sarcopenia outcomes, and the predominance of indirect methods of muscle assessment make it difficult to extrapolate the findings to clinical practice. In addition, few studies have evaluated lean mass, muscle strength, and functional performance concomitantly.

Future studies should prioritize prospective designs, elderly and clinically frail populations, and incorporate combined interventions to evaluate muscle preservation strategies during treatment with semaglutide. This approach will be fundamental to guide more accurate and safer clinical recommendations in a scenario of population aging and increasing prevalence of sarcopenic obesity.

5 CONCLUSION

The evidence analyzed in this narrative review indicates that semaglutide is an effective pharmacological intervention for weight reduction and improvement of the metabolic profile in individuals with obesity and type 2 diabetes mellitus, predominantly promoting the decrease in fat mass. However, treatment-induced weight loss is accompanied by an absolute reduction in lean mass, although in most studies, this reduction occurs proportionally less than total weight loss, resulting in favorable redistribution of body composition.

The integrated analysis of the data demonstrates that the effects of semaglutide on lean mass and muscle function are not homogeneous and depend on individual factors, such as age, basal muscle reserve, presence of type 2 diabetes mellitus, and time of exposure to the drug. In non-elderly adults, the literature suggests preservation of muscle function, while in elderly and clinically vulnerable populations, there is a higher risk of functional decline, especially when weight loss is not accompanied by muscle preservation strategies.

Although current evidence does not allow us to establish a direct causal relationship between the use of semaglutide and the development of sarcopenia, observational findings point to a potential association in specific subgroups, underscoring the importance of systematic monitoring of body composition and muscle function during treatment. In this sense, the isolated evaluation of weight loss is insufficient as a marker of therapeutic success, and the incorporation of functional parameters in clinical practice is essential.

The adoption of integrated approaches, which associate the use of semaglutide with non-pharmacological interventions, such as resistance training and adequate protein intake,

emerges as a central strategy to mitigate the loss of lean mass and preserve functionality, particularly in the elderly and individuals at higher risk of muscle decline. Such strategies should be considered structural components of the clinical management of obesity and type 2 diabetes mellitus, and not just complementary measures.

Finally, this review highlights relevant gaps in the literature, highlighting the need for long-term prospective studies that simultaneously assess lean mass, muscle strength, functional performance, and formal diagnosis of sarcopenia as primary outcomes. Future investigations with robust designs and vulnerable populations will be key to clarify the clinical impacts of semaglutide on musculoskeletal health and guide safer and more individualized therapeutic recommendations.

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