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SEMAGLUTIDE AND BODY COMPOSITION: A NARRATIVE REVIEW OF ITS EFFECTS ON LEAN MASS AND STRATEGIES FOR PRESERVATION

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ABSTRACT

In recent years a steady increase in the prevalence of obesity has caused a growing interest in pharmacological anti-obesity treatment, including semaglutide, glucagon-like peptide-1 (GLP-1) receptor agonist, which has been proven effective in inducing weight loss in obese patients. However, due to rapid growth of its popularity, monitoring and updatig of guidelines and potential adverse effects may have been outpaced. One of the adverse effects taken into consideration is semaglutide's impact on reduction of lean mass, fat-free mass and muscle mass. Available studies, although not unanimous, indicate that although decrease of lean mass occurs alongside loss of fat mass, proportion of lean mass increases. Moreover, some studies suggest that semaglutide treatment has a positive impact on muscle function. Nevertheless, the search for strategies allowing for mitigation of lean mass loss during this treatment is still necessary, particularly considering groups of patients at risk of such a complication. Two approaches are being considered: lifestyle interventions and pharmacological treatment. Studies suggest that resistance exercise training interventions can elicit significant increases in lean mass during semaglutide treatment. When it comes to dietary interventions, there is significant need for research that would aim at identifying dietary factors promoting lean mass preservation in this population. Currently explored pharmacological support options include various human monoclonal antibodies (bimagrumab, trevogrumab, garetosumab). Introducing these drugs alongside semaglutide has promoted lean mass preservation despite fat mass loss. Currently existing studies should serve as a guide for further extensive research. At this time, it seems there are more questions than answers surrounding the issue of semaglutide's impact on lean mass and strategies to mitigate its excess loss.

KEYWORDS
Semaglutide, GLP-1 Receptor Agonist, Lean Mass, Muscle Loss

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Introduction

Obesity, defined as a body mass index of at least 30 kg/m2, has become one of the most pressing public health challenges worldwide [1]. The prevalence of obesity has been rapidly increasing in recent years, with adult obesity more than doubling since 1990 and adolescent obesity quadrupling [2]. These statistics are extremely alarming, given the significant socioeconomic and medical consequences associated with an elevated BMI. Among the socioeconomic outcomes of obesity are reduced earning potential, reduced school attendance, as well as higher healthcare costs [3]. Obesity is associated with a 36% increase in inpatient and outpatient spending, compared with a 21% increase in healthcare costs for current smokers [4]. The medical repercussions of obesity are equally concerning. Obesity is linked to a considerable impairment in quality of life and large decrease of life expectancy [5,6]. Each 5 kg/m2 increase in BMI is associated with about 30% higher risk of overall mortality. Class 1 obesity, with BMI between 30 and 35 kg/m2, is already associated with a reduction in median survival by 2-4 years, and BMI between 40 and 45 kg/m2 is associated with a reduction by 8-10 years, a decline comparable to the impact of smoking [7]. These statistics underscore the growing importance of effective obesity treatments.

The primary approach of treating of obesity remains lifestyle interventions, although medications and bariatric surgery are increasingly used to aid weight loss and its long-term maintenance [8]. Among pharmacological treatments, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has gained significant attention and is a subject of growing popularity in social media. Of all the obesity medications known to date, semaglutide has demonstrated the largest weight loss [9]. Although it was primarily used in diabetic patients, research suggests it is effective and safe in non-diabetic patients with obesity as well [10]. Additionally, clinical trials indicate that semaglutide may reduce the risk of major adverse cardiovascular event in overweight or obese patients with established cardiovascular disease but without diabetes [11].

Commonly reported adverse effects of semaglutide include gastrointestinal disturbances and increased risk of cholelithiasis [12]. Other potential risks are still investigated, including loss of fat-free mass and lean body mass. Both of these terms appear interchangeably in the literature. Lean mass includes lean soft tissues without bone mass, and fat-free mass is a sum of lean mass and bone mass [13]. Lower lean mass is associated with higher all-cause mortality and higher risk of frailty among elderly patients [14,15]. Moreover, loss of fat-free mass is also associated with increased rate of infections and complications, longer and more frequent hospitalizations and higher therapy toxicity in cancer patients. It also has negative impact on recovery [16]. Therefore, it is critical that any weight loss intervention targets fat mass while preserving lean mass.

Aim of the work

This publication aims to provide a comprehensive overview of semaglutide's influence on fat-free mass and skeletal muscles, while exploring strategies to mitigate potential muscle mass loss during treatment.

Methods

This narrative review aims to synthesize current knowledge on the impact of semaglutide on lean mass and potential mitigation strategies. Relevant literature was identified through a non-systematic search of PubMed, Scopus, and Google Scholar, focusing on publications from the last five years (2020–2024). Priority was given to peer-reviewed clinical trials, reviews, and experimental studies involving human and animal models. Additional references were included based on relevance and citation tracking. No formal quality assessment of studies was performed.

Literature review results,

Changes in body composition during semaglutide treatment

The impact of semaglutide's on fat-free mass remains a highly relevant issue. Most studies on this subject have been published in the last 2 years (2023-2024) and have yielded mixed results. For example, a 2024 systematic review by Alexia Bikous et al. analyzed six randomized controlled trials and observational studies investigating the effects of semaglutide in overweight and obese patients with and without diabetes [17]. The outcomes of therapy varied across studies: in some cases, lean mass remained stable, while in others it accounted for up to 40% of total weight reduction. A Japanese study involving type 2 diabetes patients treated with oral semaglutide reported no significant changes in whole body lean mass or appendicular skeletal muscle index, despite a significant body fat reduction [18]. This result appears to be consistent with the majority of recent literature, suggesting that semaglutide preserves lean body mass, fat-free mass or muscle mass (depending on the study) even with the reduction of fat mass [19, 20, 21, 22, 23]. On the other hand, one study observed an average reduction in total fat mass by 3.4 kg, with a lean mass reduction of 2.3 kg [24]. Despite this non-negligible decrease, the proportion of lean mass to total body mass actually increased by 1.2%. Similar conclusions were drawn by other authors as well, including Alexia Bikou et al., in their systematic review [17, 25]. It is important to recognize that loss of lean mass during weight reduction is not unique semaglutide treatment and is a common occurence in weight loss caused by dietary calorie restriction [26]. If future research confirms that semaglutide helps preserve lean mass despite weight loss, it could be considered a significant advantage of the therapy. This property could potentially influence the selection of anti-obesity treatments in clinical practice.

Another noteworthy consideration is that obesity itself can also contribute to muscle loss and dysfunction, even in the absence of significant weight reduction [27]. Thus, obese individuals may experience the loss of lean body mass regardless of fat mass reduction. Interestingly, studies in mice suggest semaglutide might protect skeletal muscle against atrophy induced by obesity [28] and chronic liver disease [29]. Although more research is needed in this area, these findings highlight the potential for semaglutide to preserve lean mass in certain contexts.

Semaglutide's impact on muscle function

Previous studies predominantly focused on fat-free mass, which has substantial advantages. It is relatively easy to measure and provides an objective metric. However, emergind research suggests that other factors must be considered. One study explored the use of semaglutide in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). It reported no significant change in physical function, despite decreased psoas muscle volume [30]. This raises the question of whether the loss of fat-free mass is always associated with a corresponding decline in physical function. Another study indicated that semaglutide use in patients with MASLD and type 2 diabetes mellitus led to a reduction in skeletal muscle steatosis fraction values, which might be beneficial for muscle function [31]. Further benefits have been reported in studies carried out on mice. In those reports, semaglutide treatment was associated with increased skeletal muscle mitochondrial efficiency as well as enhanced muscle protein synthesis [32, 33]. Specifically, it is important to explore the potential for semaglutide to improve both muscle function and muscle mass preservation, especially in patients with obesity or metabolic diseases.

Strategies of mitigating loss of muscle mass during treatment with semaglutide

While the effect of semaglutide on fat-free mass remains unclear, researchers are increasingly discussing potential methods to prevent and address muscle mass loss during treatment. Two main approaches are being investigated. First, specific methods of treating muscle mass loss due to GLP-1 receptor agonists are being developed. One promising therapy involves the antibody blockade of activin type II receptors with

bimagrumab, a human monoclonal antibody. Bimagrumab prevents natural ligands from negatively affecting skeletal muscle growth [34]. In a randomized clinical trial, overweight or obese patients with type II diabetes treated with bimagrumab showed greater increases in lean mass compared to the placebo group, as well as a greater reduction in total body fat mass and glycated haemoglobin [34]. Furthermore, in a study involving obese mice, simultaneous administration of semaglutide and bimagrumab resulted in fat mass loss while preserving lean mass, even with a caloric deficit driven by glucagon-like peptide 1 (GLP-1) receptor agonists [35]. Observed body composition changes were associated with better metabolic outcomes and improved exercise performance in this group. Another study investigated the effects of combining semaglutide with two human monoclonal antibodies targeting skeletal muscle atrophy mediators: myostatin (trevogrumab) and activin A (garetosumab) in primates with obesity [36]. The results showed that this blockade led to significant fat mass loss with an increase in lean mass [36]. If any of the aforementioned therapies prove effective, they could be used in conjunction with semaglutide to mitigate the negative effects on muscle mass, especially in older individuals at risk for sarcopenia or frailty.

Another noteworthy strategy of minimizing muscle mass loss associated with semaglutide treatment is incorporating methods of preserving muscle mass proven to be effective in other scenarios, for example in caloric deficit. These strategies are based on two key factors: nutrition and physical exercise [13]. Resistance exercise training, especially interventions lasting more than 10 weeks, has been shown to elicit significant increases in lean mass (approximately 3 kg) and strength in patients receiving GLP-1 receptor agonists [37]. This conclusion is consistent with findings from studies on exercise in energy restriction-induced weight loss, where physical activity proved effective in preserving fat-free mass [38]. Although dietary interventions specific to semaglutide treatment remain underexplored, current clinical guidelines for obesity management should be followed, with an emphasis on maintaining proper nutrition and regular physical activity [39,40]. Although evidence on the effectiveness of lifestyle interventions for patients undergoing GLP-1 receptor agonist treatment is limited, conscious dietary choices and supervised exercise appear to be both safe and beneficial for overall health. These interventions should be considered, especially for patients at high risk of muscle mass loss and the complications that may arise from it.

Conclusions and prospects for the future

Semaglutide, along with other incretin mimetic drugs, has garnered significant attention from both medical and nonmedical environments. The increasing coverage of these medications may have resulted in the insufficient evaluation and timely update of clinical guidelines. Despite their growing widespread use, several potential adverse effects, including the impact on fat-free mass and muscle function, remain inadequately researched. Although semaglutide's benefits in weight loss and metabolic improvement are well-established, its full influence on body composition, particularly in terms of preserving lean mass, and its effects on physical function have yet to be thoroughly explored.

However, should current findings regarding the preservation of lean mass and muscle function be confirmed and upheld, they could fundamentally shift how we evaluate the outcomes of this therapy. Loss of fat-free mass, traditionally seen as a negative side effect of weight reduction, could become less alarming if future research demonstrates that metabolic improvements and enhanced tissue functioning compensate for the reduction in lean mass. Such a shift would also emphasize the importance of focusing on functional outcomes and overall patient well-being, rather than solely on body composition metrics. This approach would align with evolving perspectives in obesity management, which now prioritize the restoration of healthy metabolic function over purely aesthetic outcomes.

Further, the question of mitigating lean mass loss during semaglutide treatment requires extensive ongoing research. This includes not only continued investigation of pharmacological therapies—such as bimagrumab and other monoclonal antibodies targeting mediators of muscle atrophy—but also the development of new therapeutic strategies that can address muscle preservation in patients undergoing GLP-1 receptor agonist therapy. If a combination therapy involving semaglutide and muscle-preserving drugs is proven effective, it could become the standard of care for patients, especially older adults at risk for sarcopenia or frailty, who may experience more pronounced muscle loss.

In parallel with pharmacological approaches, lifestyle modifications must be given more attention. These remain the cornerstone of obesity management and should be tailored to the specific needs of individuals receiving semaglutide treatment. Evidence supports that resistance training and proper nutritional interventions can mitigate lean mass loss and improve overall health in patients undergoing weight loss therapy. Given the

scarcity of studies on diet and exercise during GLP-1 receptor agonist treatment, more clinical research is needed to develop standardized, evidence-based guidelines for these interventions in this patient population.

In the future, it is plausible that clinical guidelines will evolve to incorporate specific dietary and exercise recommendations for patients on GLP-1 receptor agonists, facilitating a more individualized and holistic approach to obesity treatment. This would enable healthcare providers to offer a more comprehensive treatment plan, maximizing the benefits of pharmacotherapy while minimizing the risk of adverse effects like muscle mass loss.

As the body of research on semaglutide and its effects continues to grow, further investigations into its long-term outcomes, combined with the development of complementary strategies for preserving muscle mass, will provide a more nuanced understanding of how this therapy can be best utilized in obesity management.

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