


PERSPECTIVE

Semaglutide versus caloric restriction-induced weight loss: insights into effects on skeletal muscle mass and function

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The advent of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has revolutionized obesity therapeutics, delivering weight loss far beyond what lifestyle interventions achieve. Clinical trials of a potent GLP-1RA, semaglutide, have demonstrated 10%–15% weight loss with improvements in cardio-metabolic outcomes (Drucker, 2025), fuelling adoption of GLP-1RAs as front-line pharmacotherapies for obesity. However, studies have consistently reported that, along with loss of fat mass, GLP-1RAs promote a significant loss of lean mass, raising concerns about long-term consequences for skeletal muscle quality and function (McCrimmon et al., 2020; Wilding et al., 2021). Skeletal muscle is a key metabolic organ essential for protection against frailty, disability and mortality. Therefore, loss of muscle function could have long-lasting negative implications. Additionally, because most people regain weight after GLP-1RA treatment cessation, it remains unclear how weight regain affects recovery of lean mass and skeletal muscle function. Two critical questions that must be addressed are: (1) Does the loss of lean mass from GLP-1RA treatment represent a unique effect of these drugs, or does it simply reflect the expected effect of weight

loss in general? and (2) Does GLP-1RA treatment impair skeletal muscle function along with lean mass loss?

In this issue of the *Journal of Physiology*, Jeromson et al. address these questions by comparing the effect of semaglutide treatment with pair-fed controls whose caloric intake was matched to that of semaglutide-treated animals. This design allowed authors to determine whether reductions in muscle mass and function were intrinsic to semaglutide treatment or simply attributable to weight loss due to caloric restriction. Four weeks of semaglutide treatment led to substantial weight loss comprising loss of both fat and lean mass, a nearly 38% decline in grip strength and no changes in fibre size in soleus muscle. Importantly, these phenotypes were similar to pair-fed mice, suggesting that semaglutide-induced loss of lean mass and muscle function largely reflects the outcome of caloric restriction rather than a distinct pharmacological effect.

Another clinically relevant finding was observed after treatment discontinuation. In both semaglutide-treated and pair-fed mice, once body weights returned to pretreatment levels, lean and fat mass rebounded, and grip strength was restored. This suggests that muscle mass and function can recover as weight is regained. Importantly, this recovery occurred despite continuous exposure to an obesogenic diet, highlighting the inherent resilience of skeletal muscle function in relatively young animals. It is worth noting that reductions in lean mass also reflect decreases in the masses of other organs besides skeletal muscle. This broader view underscores that semaglutide-driven lean mass loss is not confined to skeletal muscle, though muscle function carries unique importance for health outcomes. Remarkably, the restoration of lean mass after weight regain was due to a rebound in the mass of all organs measured as well as the different types of skeletal muscle.

Although this work represents an important advancement in the field, several gaps remain. As noted by the authors, this study was conducted in relatively young obese mice. Muscle mass and function decline with age, and the capacity to recover after cycles of weight loss and regain may reduce with age (Prokopicis et al., 2025).

Testing GLP-1RA effects in aged animal models will be crucial for translation to older human populations most vulnerable to sarcopenia. Another limitation noted by the authors is that muscle fibre analysis was performed only in the soleus, a muscle dominated by type I oxidative fibres. Type II glycolytic fibres, which produce greater force and power but fatigue quickly and are more susceptible to atrophy under caloric restriction (Ham et al., 2022), were not analysed here. In addition, muscle function was evaluated exclusively by grip strength. Although robust and widely used this metric captures only one aspect of muscle function. Complementary approaches such as *in vivo* force production, treadmill endurance or rotarod testing could provide a more comprehensive functional profile.

Beyond methodological limitations several conceptual gaps remain. One important consideration is how strength should be interpreted relative to body weight. Compared to obese controls grip strength declined, but it is unclear whether the strength scaled appropriately to the newly established lower body weight. This distinction matters for understanding functional efficiency. Future work comparing semaglutide-treated or pair-fed mice to chow-fed animals of equivalent body weight would determine whether reduced muscle strength is truly maladaptive or simply reflects normalization towards leaner physiology. Another question is the role of diet composition itself. Studies in mice are typically conducted with a single type of diet, whereas humans consume a wide variety of diets that may interact with GLP-1RA therapy in complex ways. Exploring how different macronutrient backgrounds shape lean mass dynamics and muscle function will be an important next step. Finally other than a source of strength, skeletal muscle is the body's largest metabolic organ, central to substrate utilization and energy balance. Whether semaglutide-associated changes in muscle impair metabolic flexibility, an ability to shift fuel selection, remains to be determined.

Overall, this study provides an essential perspective of semaglutide's effect on skeletal muscle. It suggests that the loss of muscle function and mass during treatment is not unique to GLP-1RA

pharmacology but rather reflects the biology of caloric restriction, and these deficits can be reversed upon weight regain. Simultaneously, these studies highlight important gaps in our understanding of the impact of GLP-1RA on lean mass, such as age-related vulnerability, fibre-type specificity, proportional strength scaling to body weight and metabolic consequences of muscle loss. Addressing these questions will determine the role of GLP-1RAs in affecting structural and functional integrity that underpins health and quality of life.

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Additional information

Competing interests

No potential conflicts of interest relevant to this article are reported.

Author contributions

H.S.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. J.E.A.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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