Muscle matters: the effects of medically induced weight loss on skeletal muscle

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The importance of skeletal muscle mass is increasingly being recognised in the medical field.[1] The crucial roles of skeletal muscle have come to the forefront of public attention due to data on the use of GLP-1 receptor agonists, which are effective for weight loss, but can cause substantial muscle loss. Studies suggest muscle loss with these medications (as indicated by decreases in fat-free mass [FFM]) ranges from 25% to 39% of the total weight lost over 36–72 weeks.[2] This substantial muscle loss can be largely attributed to the magnitude of weight loss, rather than by an independent effect of GLP-1 receptor agonists, although this hypothesis must be tested. By comparison, non-pharmacological caloric restriction studies with smaller magnitudes of weight loss result in 10–30% FFM losses.[3] In context, on an annual basis, the decline in muscle mass with GLP-1 receptor agonists is several times greater than what would be expected from age-related muscle loss (0·8% per year based on 8% muscle loss per decade from ages 40–70 years). Dismissing the importance of muscle loss can create a disconnect between patients' increased awareness of muscle and the role it plays in health, and clinicians who downplay these concerns, affecting adherence to and the development of optimised treatment plans.

It is hypothesised that substantial decreases in FFM due to short-term weight loss do not impact physical function,[2] such as muscle strength. Although muscle mass and strength are positively correlated, they do not always change proportionally due to factors, such as obesity, metabolic abnormalities, or older age.[4] It is possible that, despite the reduction in total muscle mass, muscle composition might improve, thereby enhancing muscle quality. If this is the case, it can improve body composition, which might maintain or even enhance muscle functions, such as strength. Muscle composition includes myosteatosis (ie, fat infiltration into muscle), which is linked to adverse health outcomes, and muscle quality refers to the ratio of muscle strength to muscle mass. The hypothesis of improving muscle composition with decreasing muscle mass should be explored in future research.

Although data on GLP-1 receptor agonists is scarce, evidence from bariatric and metabolic surgery suggests muscle loss does not necessarily compromise strength.[5] However, strength is only one aspect of muscles' importance. In addition to being a functional organ, muscle plays crucial metabolic roles that extend far beyond movement and strength[6] (figure). These roles are often overlooked when broadly discussing the effects of weight loss on muscle mass. As a metabolic organ, muscle acts as a reservoir for amino acids, including those involved in responding to stress, trauma, and infection. Muscle tissue also synthesises and stores glutamine, a key amino acid involved in nitrogen transport and immune function. Furthermore, muscle mass greatly influences glucose homoeostasis by taking up glucose in response to insulin, thus maintaining normoglycaemia. Muscle-derived myokines—signalling molecules produced and released by muscle cells—serve as endocrine factors that modulate systemic metabolism, energy balance, and inflammation. As such, muscles are also essential for immune system functions; myokines regulate the production and release

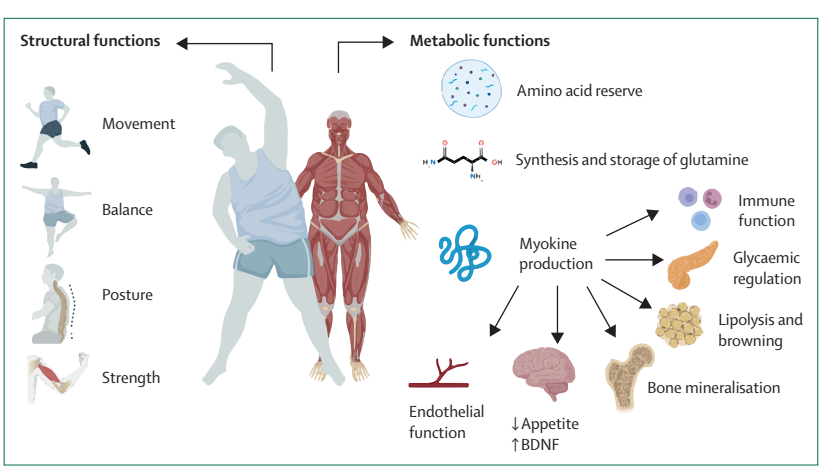

Figure: **Selected key roles of skeletal muscle as a structural versus metabolic organ**
The dual role of muscle as both a structural/functional and metabolic organ. Functionally, muscles are essential for movement, balance, posture, and strength, which are vital for physical function. Metabolically, muscle serves as a reservoir for amino acids that are crucial for stress response, trauma recovery, and infection management. Muscle also plays a key role in glucose homoeostasis and synthesises glutamine, an important amino acid for nitrogen transport and immune function. The figure further emphasises the role of muscle-derived myokines—signalling molecules that function as endocrine factors—facilitating communication between muscle and various organs. This inter-organ crosstalk highlights muscle's central role in overall metabolic health. Myokines enhance endothelial function, regulate appetite by interacting with BDNF and contribute to bone health by promoting bone mineralisation. Additionally, myokines support lipolysis and the browning of white adipose tissue, which increases metabolic activity and energy expenditure. Adapted from Severinsen et al.[7] Created with BioRender. We thank Julia Montenegro and Leticia Ramos da Silva for their assistance in creating the figure. BDNF=brain-derived neurotrophic factor.

of compounds involved in immune cell proliferation, activation, and distribution.[7] In fact, muscles and the immune system share a crucial bidirectional relationship. Given the metabolic and immune system functions of muscle, it is not surprising that low muscle mass has been consistently shown to be an independent predictor of poor health outcomes. Low muscle mass is associated with decreased immunity, increased risk of infections, reduced wound healing, physical impairment and disability, poor quality of life, and shorter survival, among other adverse effects.[8]

Low muscle mass can occur at any age, independent of body weight.[9] Although most individuals with obesity have normal or increased muscle mass, some might have sarcopenic obesity, where obesity coexists with poor muscle health. Drug-induced weight loss without concurrent strategies to prevent substantial muscle loss can lead to, or exacerbate, sarcopenic obesity across the lifespan. Sarcopenic obesity is prevalent and linked to poor health outcomes, such as increased risk of cardiovascular disease and higher morality rates. Furthermore, many individuals seek to discontinue GLP-1 receptor agonists after initial weight loss, often due to weight loss plateau or loss of insurance coverage. In general, subsequent weight regain usually increases fat mass rather than muscle mass. This pattern of weight cycling, which can be more pronounced than that observed with diet-induced weight loss alone, might be a key factor in developing sarcopenic obesity. Repeated cycles of weight loss and regain in adults with obesity are linked to decreased muscle mass and strength and a higher risk of sarcopenic obesity.[10] Additionally, patients receiving GLP-1 receptor agonists are at increased risk for multiple factors contributing to muscle loss and sarcopenia, including metabolic dysfunction, inflammation, poor dietary intake, low physical activity, and comorbidities. The marked weight loss induced by these medications could therefore further exacerbate these risks.

In summary, GLP-1 receptor agonists have revolutionised obesity treatment and shown substantial benefits by effectively reducing fat mass and improving fat to fat-free tissue ratios, leading to metabolic benefits. However, the potential effects of muscle mass loss as now observed remain a concern. These highly effective medications should be used strategically in a multimodal approach to improve the quality of weight loss by optimising body composition. This strategy can be accomplished with concurrent nutrition and exercise interventions. Additionally, ongoing studies are exploring ways to prevent or mitigate muscle loss with drugs, such as bimagrumab (NCT05616013) and enobosarm (NCT06282458), which could offer solutions for preserving muscle mass in individuals undergoing weight loss treatments.

At the time of writing, there are no data to establish whether treatment with GLP-1 receptor agonists is associated with physical frailty or sarcopenia. These effects would require long-term studies, which are not yet available, and the studies conducted to date were not designed to answer these questions. Regulatory agencies should provide more comprehensive guidelines for monitoring and evaluating body composition changes, mandate well-designed body composition studies, and enhance post-marketing surveillance. These measures would help ensure that any medication for obesity is safe, effective, and promotes muscle health with optimised body composition through quality weight loss.

CMP has previously received honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestlé Health Science, Pfizer, AMRA Medical, and Novo Nordisk; served as a steering committee member (from 2013 to 2015) and received research funding in 2013 from GTx, the developer of Enobosarm. SMP reports grants or research contracts from the US National Dairy Council, the Canadian Institutes for Health Research, Dairy Farmers of Canada, Roquette Freres, Ontario Centre of Innovation, Nestle Health Sciences, Myos, National Science and Engineering Research Council, and the US National Institutes of Health; reports personal fees from Nestle Health Sciences; reports non-financial support from Enhanced Recovery outside the submitted work; has patents licensed to Exerkine, but reports no financial gains. MCG has previously received honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, and Nestlé Health Science Brazil. SBH serves on the Medical Advisory Boards of Tanita Corporation, Novo Nordisk, Abbott, and Medifast.

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