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INVITED EDITORIAL

Body composition in glucagon-like peptide-1 receptor agonist therapy: Absolute loss, relative changes, and outcomes

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Obesity, as one of the most prevalent chronic diseases globally, has well-documented adverse health effects.[1] Originally developed for their insulin-regulating properties, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained widespread attention in both clinical and public domains due to their significant weight-loss effects. Against the backdrop of the increasing prevalence of obesity and metabolic dysfunction-associated steatotic liver disease, the widespread use of GLP-1 RAs has raised important clinical questions regarding their impact on body composition, particularly on non-adipose tissues. Excessive loss of skeletal muscle may impair metabolic health, reduce physical function, and increase the risk of sarcopenia, frailty, and falls. Existing evidence on body composition changes during GLP-1 RA treatment presents certain complexities, with diverse indicators (such as lean body mass [LBM], fat-free mass [FFM], and skeletal muscle mass [SMM]) used to assess muscular impact. The clinical significance of these changes requires careful distinction between functional outcomes and structural alterations. This article compares the effects of different GLP-1 RAs on body composition during weight loss and analyzes key factors influencing these changes, aiming to optimize clinical strategies and identify future research directions.

Changes in Diverse Body Composition Indicators during GLP-1 RA Therapy

One of the key metrics for assessing muscular impact is LBM, defined as total body FFM minus total bone mineral content, also known as lean soft tissue mass. LBM typically decreases during weight loss induced by GLP-1 RAs, with the extent of reduction influenced by study design, specific agent, and treatment duration. Randomized controlled trials indicate that the use of tirzepatide or semaglutide can lead to an LBM reduction of 2.3–5.6 kg,[2–4] and real-world studies similarly observed decreases of 2.7 kg after liraglutide and 3.53 kg after semaglutide.[5,6] Nonetheless, weight loss is primarily driven by fat reduction, while the evidence for excessive depletion of LBM remains inconclusive. Other studies describe more modest LBM declines of about 1.1–1.3 kg (≈3.2% of lean soft tissue) with agents such as exenatide, semaglutide, and liraglutide.[7–9] Some studies even report well-preserved LBM, as exemplified by only a marginal decrease of 0.1 kg after 12 weeks of oral semaglutide treatment,[10] and no significant change following 52 weeks of exenatide therapy.[11] Moreover, despite potential reductions in limb LBM, the overall proportion of lean tissue may still increase.[12] In certain populations, such as hemodialysis patients, LBM showed a slight increasing trend after 6 months of semaglutide treatment.[13]

FFM is defined as the component of total body mass remaining after the subtraction of fat mass. Changes in FFM vary across studies, with its trend influenced by treatment duration, mode of intervention, and accompanying measures. Some studies have demonstrated an absolute increase in FFM, such as significant growth observed after 26 weeks of oral semaglutide treatment.[14] Conversely, other studies indicate varying degrees of reduction in FFM. For example, a decrease of approximately 1.15 kg after 52

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weeks of GLP-1 RA therapy,[15] or a loss of 1.43 kg following 3 months of combined semaglutide treatment.[16] It is noteworthy that the relative reduction in FFM is generally smaller than that in fat mass.[17] Moreover, subcutaneous injection may lead to a more significant reduction compared to oral administration.[18] Meanwhile, while combined dietary education can enhance overall weight loss, it also results in greater loss of SMM compared to pharmacotherapy alone.[19] This highlights the necessity of prevention of muscle loss for maintaining FFM and SMM.

SMM serves as a more precise indicator for assessing muscle health. Available data show that the reduction in SMM is generally less pronounced than the overall decline in fat-free mass. For instance, following semaglutide treatment, SMM decreased by 0.88–0.99 kg, whereas the corresponding reduction in fat-free mass was 1.15–1.43 kg.[15,16] A similar trend was observed in a liraglutide study, where the decline in muscle mass (–3.6%) was significantly lower than the reduction in fat mass (–11.1%).[20] It is noteworthy that structural changes do not necessarily equate to functional impairment. Some studies have reported that despite a decrease in muscle mass, key functional measures such as handgrip strength can be preserved.[21] Other research has even documented concurrent increases in both SMM and FFM.[14] These findings suggest that although GLP-1 RA therapy may lead to a modest reduction in SMM, current studies have not consistently observed clinically significant functional impairment.

Potential Explanations for the Discrepant Effects of GLP-1 RAs on Body Composition

The observed heterogeneity in study results may be attributed to a combination of the following factors. First, differences in the baseline characteristics of the study populations may have a potential influence. While standardized study designs can effectively control for confounding factors, attention should also be paid to the representativeness of the sample and the generalizability of the findings. For example, enrolling more patients with conditions that may affect muscle metabolism, such as cardiovascular diseases or diabetic complications, could increase the risk of lean mass loss. Second, the degree of standardization in concomitant lifestyle interventions is also an important variable. Consistent dietary and exercise regimens are beneficial for the preservation of lean mass. Furthermore, differences in body composition assessment methods may introduce systematic errors. Although techniques such as dual-energy X-ray absorptiometry and magnetic resonance imaging are considered the "gold standard," bioelectrical impedance analysis is widely used due to its practicality and accessibility. However, the latter method is susceptible to physiological factors such as hydration status and body temperature, as well as measurement conditions, which may increase measurement variability and consequently affect the comparability of data across studies. Finally, due to significant heterogeneity in intervention measures and assessment methods across different studies, direct comparisons should be approached with caution.

Balancing Body Composition Changes and Metabolic Health in GLP-1 RA Therapy

To assess the clinical significance of body composition changes during GLP-1 RA-induced weight loss, we should not focus solely on the absolute value of LBM. While GLP-1 RA treatment leads to a reduction in LBM, current evidence does not consistently demonstrate significant impairment in muscle mass or function. Moreover, the overall metabolic benefits for most patients are likely to outweigh the risks associated with lean mass loss alone. It should be noted that current research on muscle function is relatively limited; therefore, future research should aim to fill this gap. Consequently, in vulnerable subpopulations with risk factors for sarcopenia, such as advanced age, frailty, sedentary lifestyle, or inadequate nutrition, the potential risks associated with GLP-1 RAs should not be overlooked. Systematic assessment of muscle function, along with increased monitoring frequency, should also be strengthened accordingly.

Therefore, in weight loss management, the focus of body composition monitoring should shift from merely tracking lean mass to preserving or improving muscle health, with greater emphasis on muscle strength and functional metrics to better balance metabolic gains against potential risks. According to current guidelines, for patients diagnosed with sarcopenia, it is recommended to establish a systematic monitoring protocol that includes at least an annual functional assessment (such as grip strength and gait speed testing) after diagnosis. Given the likelihood of long-term GLP-1 RA therapy, it is crucial to introduce more objective and comprehensive methods for assessing muscle health. These should encompass evaluations of muscle quantity, composition, function, mobility, and strength. Concurrently, individualized interventions centered on optimizing energy and protein intake alongside regular resistance training should be implemented, thereby minimizing the risk of therapy-related muscle loss.[22,23]

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