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Muscle-preserving therapies in the era of pharmacological weight loss

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Significance

Modern incretin-based therapies produce unprecedented weight loss, bringing renewed focus to the accompanying reduction in lean soft tissue (LST). Although often adaptive, LST loss raises concerns in populations at higher risk of functional decline, including older adults and individuals with severe obesity. This article summarizes the latest evidence on emerging muscle-preserving therapies, including myostatin/activin inhibitors, selective androgen receptor modulators, and next-generation multiagonists, and evaluates their potential to improve the quality of weight loss produced by contemporary obesity medications. Key safety considerations and persisting knowledge gaps are highlighted, including the uncertain clinical relevance of LST preservation and the need for trials powered for functional outcomes. These developments may help shape therapies that optimize both cardiometabolic health and physical capability.

Introduction

Modern GLP-1 receptor agonists (RAs) and dual GLP-1/GIP agonists produce ~15%-20% weight loss,[1] with up to 40% of the lost weight consisting of lean soft tissue (LST).[2] The clinical significance of this LST reduction has not been established. Nonetheless, concerns about the risk of developing sarcopenic obesity—the coexistence of excess adiposity and reduced muscle mass and function—have prompted the development of pharmacological agents aimed at preserving muscle mass (Figure 1).

Investigational agents for muscle preservation during pharmacological weight loss

Myostatin/activin pathway inhibitors

Bimagrumab, a monoclonal antibody that blocks activin type II receptors, thereby inhibiting signaling by myostatin, activins, and related negative regulators of skeletal muscle growth, was first shown to increase LST while reducing fat mass in adults with type 2 diabetes (T2D) and overweight or obesity.[3] In the Phase 2b BELIEVE trial (NCT05616013), 507 adults with overweight or obesity were randomized to bimagrumab (10 or 30 mg at weeks 4, 16, 28, and 40), semaglutide (1.0 or 2.4 mg weekly), or their combinations for 48 weeks. The high-dose combination produced a mean weight loss of 24.2 kg (−20.2%), compared with 16.5 kg (−14.8%) with semaglutide 2.4 mg at 48 weeks. Compared with semaglutide 1.0 mg alone (−2.6 kg), the combination blunted LST loss by ~58%-81%. When added to semaglutide 2.4 mg (−3.9 kg), attenuation was ~67%-69%.[4] Combination therapy produced weight loss that was largely attributable to reductions in fat mass[5] (Figure 2). Improvements in physical function assessed by patient-reported outcome measures were also observed.[4] These results confirm that activin receptor blockade may enhance the quality of GLP-1 RA-induced weight loss. It is worth noticing that muscle spasms were reported by 57%-64% of participants in the bimagrumab plus semaglutide groups.[4] Studies evaluating the combination of bimagrumab and tirzepatide in people with obesity are ongoing (NCT05933499; NCT06643728), whereas a similar trial in individuals with obesity and T2D has been withdrawn (NCT06901349).

Two myostatin/activin antibodies—trevogrumab (antimyostatin) and garetosmab (antiactivin A)—have been evaluated as adjuncts to semaglutide in 599 adults with obesity without diabetes in the Phase 2 COURAGE trial (NCT06299098). At 26-weeks, the combination of semaglutide, trevogrumab, and garetosmab yielded a greater weight loss (−13.4%) as compared with semaglutide alone or semaglutide plus trevogrumab 200 or 400 mg (~−10%). LST loss with semaglutide alone (−6.5%) was attenuated by ~42%-49% with the addition of trevogrumab, and by ~69% with the triple combination.[6] Thus, adding myostatin/activin blockade can blunt LST loss associated with semaglutide and shift weight loss toward a greater contribution from fat mass[6] (Figure 2). Approximately half of participants in the triple combination group experienced muscle spasms, and adverse events leading to drug discontinuation occurred in nearly one third.

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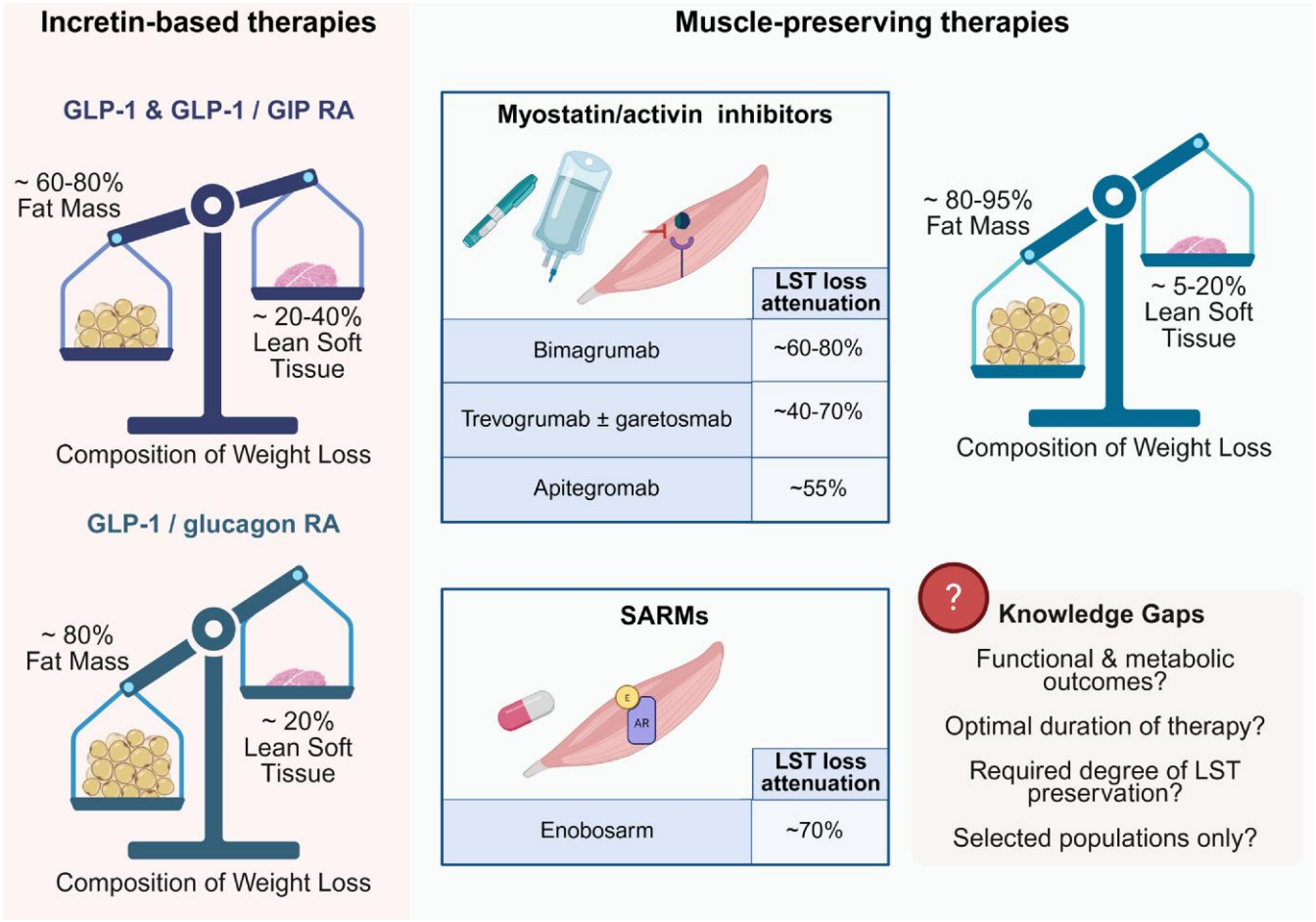

Figure 1 Incretin-based therapies induce substantial weight loss, accompanied by variable loss of LST. Muscle-preserving strategies may attenuate LST loss and shift weight reduction toward fat mass, but whether they confer meaningful benefit, particularly in selected at-risk populations, remains an important knowledge gap. AR, androgen receptor; E, enobosarm; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; LST, lean soft tissue; RA, receptor agonist. Created in BioRender. Conte, C. (2025) https://BioRender.com/mweerxb.

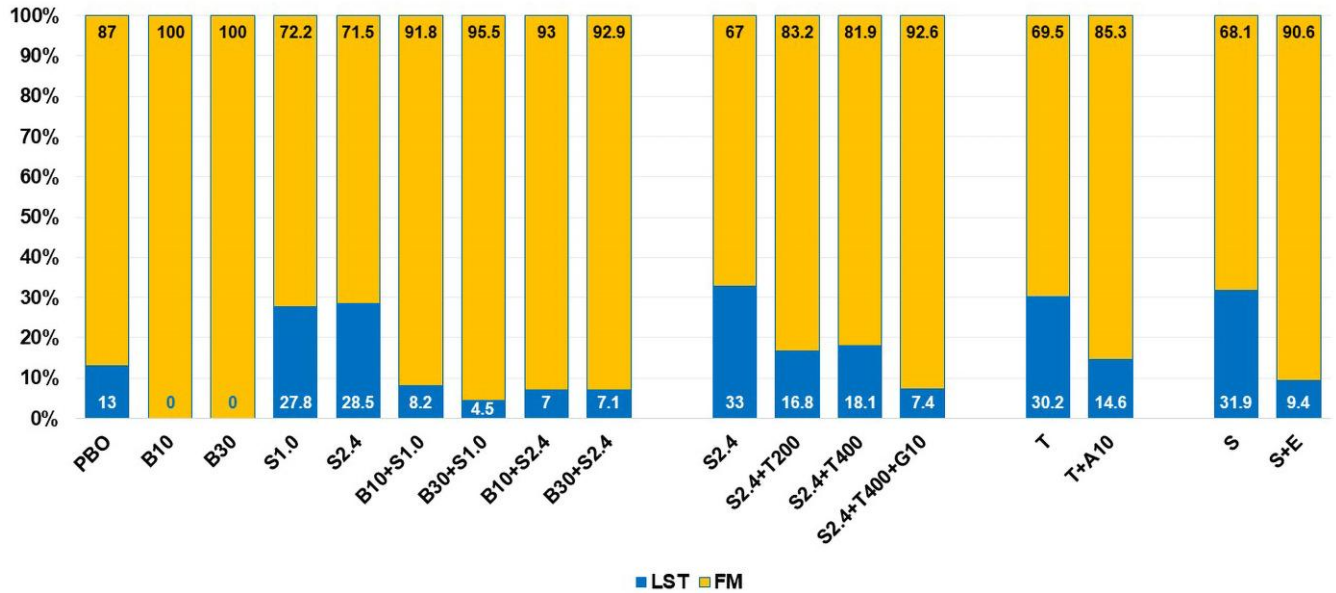

Figure 2 Proportion of total weight lost as LST or fat mass (FM) in phase 2 studies that assessed the efficacy of muscle-preserving therapies in combination with incretin-based agents for the management of excess adiposity. LST Abbreviations: A10, apitegromab 10 mg; B10, bimagrumab 10 mg; B30, bimagrumab 30 mg; E, enobosarm 3 and 6 mg combined (median values, reported for illustrative purposes only); G10, garetosmab 10 mg; PBO, placebo; S1.0, semaglutide 1 mg; S2.4, semaglutide 2.4 mg; S, semaglutide (dosage not specified); T, tirzepatide (dosage not specified); T200, trevogrumab 200 mg; T400, trevogrumab 400 mg.

Apitegromab (SRK-439) is a selective inhibitor of latent myostatin,[7] which might confer better tolerability as compared with other myostatin inhibitors. In the Phase 2 EMBRAZE trial (NCT06445075), 87 adults receiving tirzepatide plus apitegromab 10 mg for 24 weeks lost 12.3% of body weight compared with 13.4% for tirzepatide alone.[8] Apitegromab attenuated LST loss by ~55% compared with tirzepatide alone (−1.4 vs −3.5 kg, Figure 2) and was reportedly well tolerated.[8]

Selective androgen receptor modulators (SARMs)

Enobosarm is a nonsteroidal oral SARM that stimulates muscle protein synthesis with fewer androgenic side effects than testosterone. The Phase 2b QUALITY trial (NCT06282458) randomized 168 adults aged ≥60 years receiving semaglutide to enobosarm 3 mg, enobosarm 6 mg or placebo for 16 weeks. Enobosarm recipients lost 71% less LST than those on semaglutide alone (−1.2% vs. −4.1%).[9] Fat mass loss was 27% greater in the enobosarm group while total weight loss was similar (~4.4 kg), improving body composition[9] (Figure 2). Enobosarm also reduced the proportion of participants with ≥10% decline in stair-climb power by 55%.[9] These results suggest that SARMs can preserve muscle mass and function during GLP-1-induced weight loss in older people.

Apelin RAs and exercise mimetics

Apelin is an exercise-induced peptide (exerkine) that promotes muscle anabolism and glucose uptake. Azelaprag, the most advanced apelin RA, showed promising LST preservation in early studies but its development has been hampered by liver safety concerns, leading to discontinuation of the STRIDES trial (NCT06515418).[10] While the appeal of "exercise mimetics" is strong, future programs will need to demonstrate efficacy and safety.

Multiagonists with favorable body-composition profiles

Some next-generation weight-loss drugs are engineered to minimize LST loss without a separate muscle-targeting agent. Pemvidutide is a GLP-1/glucagon dual RA that increases energy expenditure via glucagon signaling. In the 48-week Phase 2 MOMENTUM trial (NCT04881760) of 391 adults with obesity, pemvidutide 2.4 mg weekly produced 15.6% mean weight loss versus 10%-11% with lower doses and 2.2% with placebo.[11] MRI-based body-composition analysis in a 50-participant subgroup demonstrated that 21.9% of weight lost was LST, and 78.1% was attributable to fat.[11] These LST preservation rates compare favorably with those reported for GLP-1 RAs alone. Pemvidutide also improved blood pressure and lipid profiles without cardiovascular safety signals.

Are muscle-preserving drugs actually needed?

The loss of LST is an expected component of volitional weight reduction and appears to be predominantly adaptive in most people with obesity.[12] Typically 20%-30% of weight lost consists of LST, and part of this reflects extracellular water or tissues other than skeletal muscle.[2] The SEMALEAN prospective study showed that high-dose semaglutide led to around 13% weight loss with modest LST decline and improved grip strength.[13] In the phase 3a REDEFINE 1 trial, cagrilintide plus semaglutide produced ~23% weight loss. In a subgroup assessed by DXA, 67% of the weight loss was attributable to reductions in fat mass. Improvements in physical function were also observed, as reflected by patient-reported outcome measures and performance in the sit-to-stand test.[14] These findings suggest that LST reductions during drug-induced weight loss are modest and do not negate the benefits of adiposity reduction.

Nevertheless, certain populations may need additional support. Older adults or people with sarcopenic obesity or conditions such as T2D face higher risks of excess muscle mass loss during weight loss, and individuals unable to perform resistance exercise may struggle to maintain muscle.[12,15] In these groups, myostatin/activin inhibitors, SARMs, or multiagonists might help preserve muscle mass and function, but they remain investigational.

Evidence in people undergoing pharmacological weight loss relatively is limited, most trials are small and short, and available endpoints (eg, DXA-derived LST) do not necessarily reflect functional muscle improvements. Safety concerns have already curtailed development in some classes, and the populations most likely to benefit—older adults or individuals with sarcopenic obesity—are still underrepresented in trials. Other important knowledge gaps remain. It is not known whether muscle-preserving agents should be continued alongside incretin-based medications to sustain their effects on body composition once target weight loss or body composition has been achieved. Moreover, the extent to which LST should be "preserved" is uncertain. Although preferential fat loss improves the quality of weight loss, the optimal degree of LST preservation required to confer meaningful clinical benefit is not yet established.

Larger and longer studies powered for functional and patient-centered outcomes will determine whether these therapies can be meaningfully integrated into obesity care. Until such evidence is available, nonpharmacologic strategies—adequate protein intake and resistance exercise—remain the cornerstone of muscle preservation during weight loss.

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Author contributions

Caterina Conte (Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing)

Conflicts of interest

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Data availability

Not applicable. No new data were generated or analyzed in this study.

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