Preserving muscle is important when using incretin mimetics for weight loss

Rapid increases in the use of incretin-mimetic drugs for weight loss, and the significant weight loss which can be achieved, has raised awareness of the associated potential muscle loss and changes. This review, published in *Obesity Reviews*, outlines the evidence base for optimising protein and micronutrient intake and use of physical activity – particularly resistance exercise – in helping preserve muscle mass during weight loss. Many people who choose to take incretin-mimetic drugs for weight loss may be eating a suboptimal diet, including high levels of ultra-processed food, which may not provide optimal protein, vitamin and mineral intake. When combined with reduced appetite, temporary food aversions and changes in taste preferences which occur with incretin-mimetic therapy, there is a significant risk of protein and micronutrient deficiencies unless care is taken to prioritise high-quality, high-protein, unprocessed, "real" foods. All the clinical studies of incretin-mimetic drugs for weight loss provided lifestyle programmes alongside drug therapy. It is important for clinicians to reinforce specific advice about protein intake and resistance exercise to everyone taking these drugs, particularly those who are choosing to purchase the drugs privately, who may not have the support of a multidisciplinary team providing this important guidance.

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Incretin-mimetic drugs, including the GLP-1 receptor agonists liraglutide and semaglutide and the dual GIP/GLP-1 receptor agonist tirzepatide, have demonstrated significant weight loss (up to 20.9% with tirzepatide) when used with a healthy diet and increased physical activity – a degree of weight loss previously only achievable with bariatric surgery. Their mode of action includes slowing of gastric emptying; significant reductions in appetite via effects on the central nervous system; increased post-prandial secretion of insulin from the pancreatic beta-cells; and decreased glucagon secretion from pancreatic alpha-cells.

It has been known for many years that weight loss achieved with behavioural and lifestyle change is associated with loss of both fat and lean mass (including muscle), with around 10–30% of the weight loss being lean mass. In the STEP-1 study (Wilding et al, 2021), a subset of participants had body composition measured by DXA scan at baseline and at 68 weeks. Those receiving semaglutide 2.4 mg had a mean body weight reduction of 17.32 kg (versus 2.65 kg in the placebo group); however, this included a reduction of up to 6.92 kg of lean mass. In other words, up to 40% of the weight loss was lean mass. Although muscle loss was not quantified, the findings suggest that around 10% of overall muscle mass may have been lost by participants during the study. In SURMOUNT-1 (Jastreboff et al, 2022), tirzepatide, which resulted in mean weight loss ranging from 15% to 21%, was associated with a similar percentage loss of lean body mass to that in STEP-1.

However, an exploratory *post hoc* analysis of data from the SURPASS-3 MRI study of tirzepatide, specifically measuring thigh muscle using MRI rather than DXA, demonstrated potentially favourable changes in muscle fat infiltration associated with reductions in muscle volume (Sattar et al, 2025).

Age-related reductions in muscle mass occur at a rate of 3–5% per decade in people over the age of 30 years. Loss of 10% of muscle, therefore, translates into around 20 years of age-related muscle mass and a significantly raised risk of frailty, which in turn increases the risk of morbidity and mortality.

In the present review, published in *Obesity Reviews*, Mechanick and colleagues state that

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the key goals of obesity treatment are long-term reduction of excess adiposity and reduction in associated complications. However, they argue that preserving muscle mass with nutrition and physical activity must also now be considered an important additional goal, whatever the method used to achieve weight loss. They summarise why muscle mass is important and what can be done to reduce muscle loss during the significant weight loss achievable with incretin-mimetic treatment.

Why is muscle loss important?

Reductions in muscle mass are associated with frailty as well as increased cardiovascular and metabolic risk. In addition to its important structural functions for movement, balance and strength, muscle is a metabolic organ itself and is now known to act as storage for important amino acids involved in responses to stress, trauma and infection (Prado et al, 2024). It also supports immune function and helps in maintaining glucose levels by taking up glucose from the bloodstream. Muscle produces signalling molecules (myokines) to modulate immune function and inflammation, and low muscle mass is associated with decreased immunity, increased infection risk, poor quality of life and earlier mortality.

Retaining as much muscle as possible is important to minimise weight regain when the incretin mimetic is stopped. In the STEP-1 extension study, two-thirds of the weight lost was regained after stopping semaglutide (Wilding et al, 2022). Weight is usually regained as fat mass, unless significant resistance exercise is undertaken (Prado et al, 2024).

Advice on reducing muscle loss with incretin mimetics

The review suggests that two strategies are important for reducing muscle mass during weight loss.

1. Optimal protein intake

People choosing to take incretin-mimetic drugs for weight loss may already be eating a suboptimal diet, including high levels of ultra-processed food, which may not provide optimal intake of protein and micronutrients such as vitamins and minerals.

Current protein intake recommendations are 0.8 g per kilogram of body weight per day, rising to 1.2–1.5 g/kg daily in those over 65 years of age (Institute of Medicine, 2005; Deutz et al, 2014). Protein quality (amount of essential amino acids and protein digestibility) is important to optimise muscle protein synthesis. Higher protein intake also increases satiety and energy expenditure, which will help with weight reduction and maintenance. Many people will not be meeting these protein intakes even before starting weight loss drug therapy, and reduced appetite, temporary food aversions and changes in taste preferences, especially early in incretin-mimetic therapy, make it even more likely that protein and micronutrient intake will be suboptimal.

Micronutrient guidelines also highlight the importance of essential trace elements and vitamin intakes to allow metabolism of protein and energy-containing foods. Knowing how to assess for and manage micronutrient deficiencies is important when supporting people on incretin-mimetic drugs for weight loss if they are not receiving dietetic input; interested clinicians will want to review the guidance (Berger et al, 2022).

Mechanick and colleagues propose that oral nutritional supplements may be "an effective and scalable" option to optimise protein and micronutrients during incretin-mimetic weight loss, and research is ongoing.

2. Physical activity

Aerobic and resistance exercise are both recommended as part of weight loss programmes, and there is evidence, including from systematic reviews and meta-analyses, that resistance training in particular can help maintain muscle mass during behavioural weight loss. In the incretin mimetic weight loss studies, people were advised to undertake 240 minutes of aerobic and resistance exercise weekly; however, this was not closely monitored.

Supervised, structured exercise programmes are demonstrated to be more effective in reducing loss of muscle mass during incretin therapy than just providing advice or recommendations to exercise (Gross and Brinkmann, 2024), with some studies showing persistence of behaviour change after the acute behavioural intervention, and reductions in weight regain. **Walking exercise alone does not preserve muscle mass during weight loss.**

Studies have suggested that using drugs such as bimagrumab, which stimulates muscle

hypertrophy, during weight loss with incretin-mimetic drugs could be useful, but others suggest that it is the muscle use/movement which is important rather than just the muscle mass, suggesting that resistance exercise may offer more holistic benefits.

The exploratory *post hoc* analysis of the SURPASS-3 MRI study, using MRI to evaluate muscle composition in people with type 2 diabetes and overweight or obesity treated with tirzepatide for 52 weeks, demonstrated that although changes in muscle volume were correlated with the significant weight loss achieved, decreases in muscle fat infiltration were greater, potentially demonstrating an adaptive response to weight reduction and a potentially positive effect (Sattar et al, 2025). However, since the study was not designed to look at muscle function, it was not possible to determine how these MRI findings translate into long-term changes in muscle strength, mobility and physical performance.

Implications for practice

Rapidly increasing prescribing of incretin-mimetic drugs for type 2 diabetes, as well as increasing use for weight loss both privately and on the NHS, mean we will all be supporting people who are taking these drugs. It is important to convey the possible risk of muscle loss, and what can be done to minimise this, to people taking these drugs, whether they are patients, friends, colleagues or family members.

Everyone receiving incretin-mimetic drugs for weight loss would benefit from a supervised, structured exercise programme, so we need to know what is available in our area and how to refer, and to be assertive in helping people understand the benefits of such programmes in reducing muscle loss and helping to maintain weight loss when the drugs are discontinued. We should explain that just increasing walking will not reduce muscle loss and that resistance exercise, either in a gym or using body weight at home, is optimal, and that a supervised and structured programme has the strongest evidence.

Most people will be completely unaware of deficiencies in their diet. Many people seeking support for weight management will be eating significant amounts of ultra-processed foods, which may have contributed to their weight. Those attending NHS specialist clinics should have access to dietetic support to optimise food choices despite reduced appetite and intake; however, such support is often not available for those buying these drugs privately. A brief conversation with people known to be accessing these drugs without support can highlight the importance of prioritising cheap, good-quality, easily accessible, high-protein foods rather than "wasting" their limited appetite on ultra-processed foods that are often high in calories and low in nutrients.

For those who can be encouraged to enjoy "real food", poultry, lean meat, fish, cheese, eggs, milks and lentils are protein-rich. For some people, protein supplement drinks, shakes or high-protein yoghurts will be helpful. Our dietetic colleagues may be able to provide a high-protein diet sheet to share. For those with interest and IT skills, encouraging use of free software (e.g. MyFitnessPal) may help quantify and optimise protein intake.

This is a huge opportunity for us to really make a difference and help people maximise benefit from these drugs. Having leaflets and self-referral information at our fingertips will help us "Make Every Contact Count." ■

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Practice points

1. Convey the risk of potential muscle loss, and strategies to minimise this, to people taking incretin-mimetic drugs.
2. Explain that walking alone may not be enough to reduce muscle loss; some experts argue that resistance exercise is required, while others argue that staying active, even if not specifically undertaking resistance exercise, will have benefit.
3. Where possible, refer to a local structured exercise programme.
4. Encourage the person to reduce ultra-processed foods and to consume high-protein foods.
5. Consider that people accessing incretin-mimetic drugs privately may not have received appropriate lifestyle advice; offer brief interventions to support them.

Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity

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