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Skeletal muscle loss and sarcopenia in obesity pharmacotherapy

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Pharmacological therapies with incretin-based 'multi-agonists' are rapidly advancing the therapeutic landscape for obesity. The loss of skeletal muscle mass with these potent weight-loss agents is emerging as a possible side effect. It is therefore important to determine whether multi-agonists increase the risk of sarcopenia in susceptible patients.

Over the past decade, incretin-based pharmacotherapy — specifically, the class of glucagon-like peptide 1 receptor (GLP-1R) agonists and successor multi-agonists — have created much excitement in the obesity field[1]. These agents are generally based on the proven action of GLP-1R to suppress appetite and reduce food intake. Further agonistic actions on related receptors, including glucose-dependent insulinotropic peptide receptor (GIPR), glucagon receptor (GCGR) and amylin receptor, promote synergistic effects such as improved appetite suppression, enhancement of energy expenditure and hepatic lipolysis[1]. Potent incretin-based multi-agonist drug candidates are now being developed at pace in several drug-development pipelines. By modulating multiple energy balance pathways, these agents can reduce total body weight by 10–25%[1], which rivals what can be achieved with surgical interventions. However, skeletal muscle preservation during weight-loss treatment is emerging as an important consideration for the development of these drugs.

Comprising ~40% of total body weight, skeletal muscle serves many functions including locomotion, maintenance of posture and balance, respiration, and essential metabolic roles such as nutrient storage, energy metabolism and heat production. The contribution of skeletal muscle to energy expenditure is therefore important for driving sustainable body-weight loss. However, body-weight loss by any modality is associated with loss of lean tissue and skeletal muscle mass (SMM). Sarcopenia — defined as low muscle strength together with low muscle quantity or quality — is acknowledged to be an important risk factor for disability, morbidity and mortality[2]. Further complicating matters is sarcopenic obesity, an entity in which complex metabolic crosstalk between adipose tissue and skeletal muscle leads to muscle inflammation, lipotoxicity and weakness[2] in patients with obesity.

Phase III trials have provided an initial insight into the effect of new weight-loss pharmacotherapies on lean body mass (LBM) and SMM. In the STEP-1 trial, a subanalysis of 140 people with obesity without diabetes given semaglutide at a dose of up to 2.4 mg once weekly over 68 weeks showed that ~40% (6.92 kg) of the total body-weight loss came from lean mass (as measured by dual-energy X-ray absorptiometry (DXA))[3]. This proportion of LBM to total body-weight loss observed is consistent with semaglutide 1.0 mg once weekly in the SUSTAIN 8 trial[4]. Despite these findings, the proportion of LBM relative to total body weight increased in both studies. In these post hoc analyses, no assessment of muscle strength is reported, as this was not an outcome of the original studies. Other studies of lower dose semaglutide have shown minimal effects on SMM or hand grip strength. Interestingly, in humans, GLP-1 infusions recruit skeletal muscle microvasculature and lead to improved tissue oxygenation and metabolism[5]. Therefore, the effect of GLP-1R agonism on skeletal muscle might afford a protective effect in the face of energy restriction.

The GLP-1R–GIPR co-agonist tirzepatide has shown impressive results in the SURMOUNT-1 trial with a mean total body-weight loss of 15–21% in people with overweight or obesity without diabetes over 72 weeks[6]. A DXA subgroup analysis of 255 participants showed that ~25% (5.67 kg) of the total body-weight loss came from LBM. Despite this finding, the ratio of total fat mass to total lean mass decreased more in the tirzepatide group, and physical activity scores were increased[6]. Tirzepatide has also been shown to improve muscle quality with reduced fat infiltration[7].

Therefore, the loss of fat mass after GLP-1R (with or without GIPR)-mediated weight loss might ameliorate any negative effect of obesity on muscle function, as well as lead to overall improvements in mobility. Together, clinical trials demonstrate LBM loss with GLP-1R- and GLP-1R–GIPR-directed pharmacotherapy, but the evidence is weak that this translates to reduced muscle strength or sarcopenia; indeed, there is evidence for improved muscle composition and overall physical ability and activity.

Several other co-agonists and triple agonists that also target the GCGR are currently in later phases of drug development and nearing clinical deployment[1]. For example, the once-weekly tri-agonist retatrutide leads to a remarkable 24.2% total body-weight loss over a 48-week treatment period[8]. Owing to hepatic GCGR activity, the GLP-1R–GCGR and GLP-1R–GCGR–GIPR multi-agonists reduce circulating levels of amino acids. What is presently not clear is whether the hypoaminoacidaemia triggered by these agents leads to enhanced loss of muscle mass and hence functional muscle weakness in humans in the long term. It is also not known whether hypoaminoacidaemia can be rescued with simple interventions, such as a high-protein diet.

One key factor that impedes research in this area is the lack of standardization of metrics for skeletal muscle assessment. Various measurements of SMM, including surrogate evaluations, are often reported in clinical studies (for example, fat-free mass or LBM). Importantly, LBM provides a composite measurement of muscle, ligaments, tendon, organ tissues and water, with fat-free mass also typically including bone mass; thus, these measurements are not 'pure' measures of SMM. Imaging modalities also vary widely, and include DXA and, bioelectrical impedance analysis, in addition to more skeletal muscle-focused modalities such as MRI or CT. Although SMM and its surrogates are often reported, strength assessments are not routinely reported in trials of weight-loss pharmacotherapy, as noted above.

Box 1 | Unanswered questions for weight-loss pharmacotherapy and skeletal muscle

Is there a reduction in both muscle mass and function (that is, sarcopenia) with weight-loss drugs?

Which muscle outcome measures are best used in clinical trials?

Does the risk of sarcopenia increase with advancing age, obesity, MAFLD or MLTC?

Is the risk of muscle loss increased with GCGR-targeted multi-agonists?

How best do we deploy exercise and dietary protein supplementation strategies?

Are muscle anabolic agents a solution to protect skeletal muscle?

GCGR, glucagon receptor; MAFLD, metabolic associated fatty liver disease; MLTC, multiple long-term conditions.

Muscle mass per se is a poor indicator of strength, and strength is a better predictor of the negative outcomes of sarcopenia: hence, reduced muscle strength — supported by changes in muscle mass, quality or physical performance — is at the forefront in international consensus definitions of sarcopenia[2]. Going forwards, skeletal muscle assessment should be standardized across large trial designs to aid comparability. Whole-body DXA, MRI or CT imaging are validated tools to assess SMM described in international sarcopenia guidelines[2]. More sophisticated methods such as *Z*-scores for MRI-assessed fat-free tissue muscle volume have been suggested[9]. Muscle quality can also be assessed with cross-sectional imaging studies that specifically detail muscle architecture and composition[2]. For muscle strength and physical performance assessments, combinations of chair–stand, grip strength, gait speed and the short physical performance battery tests can be used[2].

A key question faced by multi-agonist weight-loss drugs is the effect on skeletal muscle in those at increased risk of sarcopenia, or with established sarcopenia. In addition to advancing age and obesity, risk factors for sarcopenia include multiple-long term conditions, inactivity and nutritional status[2]. Investigating weight-loss pharmacotherapy in populations with reduced SMM and strength is therefore warranted. If weight-loss pharmacotherapy does cause SMM loss and perhaps worsens sarcopenia, is it possible to prevent this? Although it seems sensible to recommend adjunctive increased dietary protein intake with exercise, no clear consensus exists on the amount or type of dietary protein. Furthermore, the optimal frequency, type and intensity of exercise intervention is unclear and warrants further investigation, particularly as many patients will have established sarcopenia or other disabilities that might preclude full-bore physical activity.

Several compounds specifically for muscle anabolism are also currently being investigated to be given alongside weight-loss pharmacotherapy. One of these, bimagrumab (a monoclonal antibody to activin receptor II), is currently being investigated as a complementary therapy to semaglutide[10]. The actual need for and the long-term effects of such anabolic agents will need to be clearly established.

In summary, the focus of weight-loss pharmacotherapy must shift from simple weight loss towards healthy weight loss and preservation of SMM, strength and quality. Further investigation is warranted into the effects of multi-agonists on skeletal muscle, particularly in patients with sarcopenia (Box 1). This approach will ultimately enable more effective and personalized weight-loss therapy in the future.

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Competing interests

T.M-M T. was previously a shareholder in and consultant for Zihipp Ltd, an Imperial College spinout company developing new therapies for obesity. D.C.D.H. declares no competing interests.