



Nutrition Support During GLP-1 Receptor Agonist Therapy: Protecting Lean Mass While Intake Falls

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Abstract

Roughly a quarter of the weight lost on incretin-based therapy is lean mass, and that pooled figure conceals a range from about 15 to 60 per cent across trials. Registration data illustrate the spread: 45.2 per cent of weight lost was lean in one semaglutide trial, 25.7 per cent in a tirzepatide trial and 43.4 per cent in a semaglutide substudy, in which lean mass as a proportion of lean plus fat nevertheless increased. Absolute loss and worsening composition are therefore not the same measurement. Function is measured less often and points the other way: in one cohort handgrip strength rose by 4.5 kg at twelve months and sarcopenic obesity fell from 49 to 33 per cent. Analysis of 670,422 users identified a depletive pattern, above 20 per cent weight loss with above 5 per cent lean loss, in 10.3 per cent on tirzepatide against 6.7 per cent on semaglutide.

Keywords: GLP-1 receptor agonists; Lean mass; Body composition; Protein intake; Resistance training

Introduction

Incretin-based therapies now produce weight loss approaching the magnitude achieved by surgery, and with that has come concern about the effect on muscle quantity and function [1,2]. Loss of lean tissue accompanies any substantial weight loss, but the size of these reductions has brought the question into clinical view [1,3].

The mechanism by which intake falls is central. These agents reduce appetite and slow gastric emptying, so total energy intake declines and protein intake usually declines with it, at a point when protein requirements for preserving lean tissue are unchanged or higher [3,4].

This review examines how much lean mass is lost, how consistent that figure is, whether the loss translates into impaired function, and what the evidence supports for protecting lean tissue during treatment.

Objective

This review sets out to establish four things from the published literature. First, what proportion of weight lost is lean tissue and how far studies agree. Second, whether absolute lean loss is the same thing as deteriorating body composition. Third, what has been measured about muscle function rather than mass. And fourth, what protein intake and resistance training have been shown to achieve alongside treatment.

Literature Review

The pooled figure and its range: Systematic review and network meta-analysis reports that these agents produce substantial absolute reductions in total body weight, fat mass and lean mass, with lean mass contributing approximately 25 per cent of total weight loss [5]. A review of the registration trials describes considerable heterogeneity: in some studies lean mass reductions range between 40 and 60 per cent of total weight lost, while others show approximately 15 per cent or less (Figure 2) [1]. Other reviews place the figure at 20 to 30 per cent [6,7].

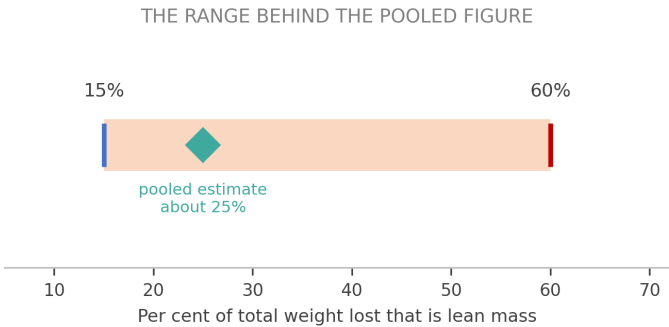


Figure 2: The range behind the pooled figure [1,5,6]

What individual trials reported: In a semaglutide trial, lean mass fell by 6.92 kg or 13.2 per cent against a weight reduction of 15.3 kg or 14.9 per cent, giving a fraction of weight lost from lean mass of 45.2 per cent. In a tirzepatide trial at the highest dose, lean mass fell by 5.67 kg or 10.9 per cent against a weight reduction of 22.1 kg or 20.9 per cent, a fraction of 25.7 per cent. In a semaglutide substudy in type 2 diabetes, lean mass fell by 2.3 kg or 4.5 per cent against a weight reduction of 5.3 kg or 6.0 per cent, a fraction of 43.4 per cent (Figure 1) [1].

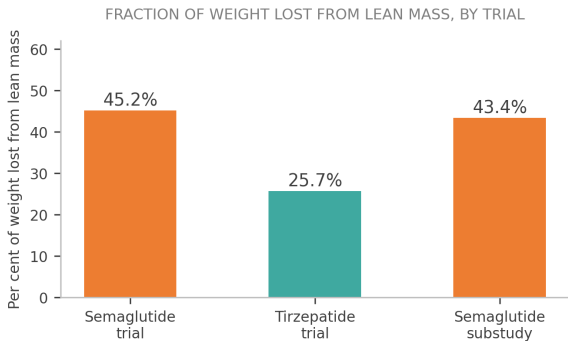


Figure 1: Fraction of weight lost from lean mass, by trial [1]

The distinction that the fraction conceals: In that same substudy, although 43.4 per cent of the weight lost was lean tissue, lean mass as a proportion of the whole, lean plus fat, actually increased (Figure 3) [1]. The network meta-analysis reports the same pattern more generally: these agents do not significantly alter the percentage of lean mass when assessed in relation to concomitant changes in total body weight [5]. Absolute loss of lean tissue and deterioration in body composition are therefore separate findings that the headline fraction runs together (Table 1).

Table 1: Lean mass change in registration trial data, as tabulated [1]

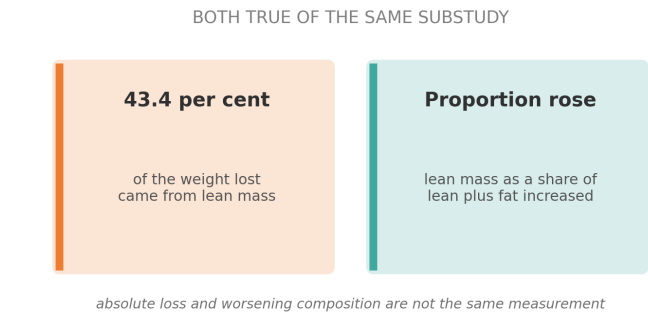


Figure 3: Both true of the same substudy [1,5]

Study	Weight change	Lean change	Fraction lean
Semaglutide trial	-15.3 kg	-6.92 kg	45.2%
Tirzepatide trial	-22.1 kg	-5.67 kg	25.7%
Semaglutide substudy	-5.3 kg	-2.3 kg	43.4%

Where the pattern is most marked: An analysis using electronic health record linked body composition data examined 670,422 first-episode users, 456,742 on semaglutide and 213,680 on tirzepatide, of whom 7,965 had paired measurements before and after initiation over twelve months. Tirzepatide was associated with greater relative lean body mass loss at every time point, with excess losses of 1.1, 1.5, 1.3 and 2 per cent at 3, 6, 9 and 12 months. A depletive pattern, defined as more than 20 per cent total body weight loss with more than 5 per cent lean loss, was more frequent with tirzepatide than semaglutide at 10.3 against 6.7 per cent ($p < 0.001$) (Figure 4) [8].

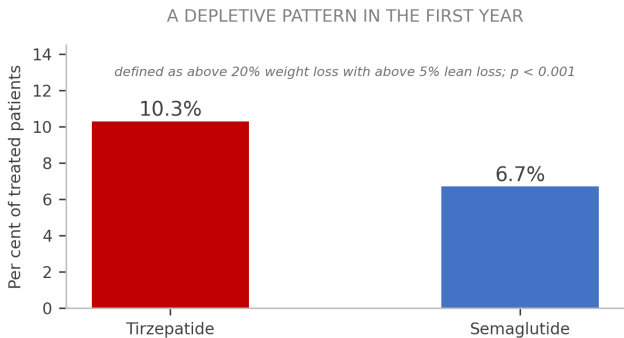


Figure 4: A depletive pattern in the first year of therapy [8]

What happened to function: A cohort study of semaglutide 2.4 mg reported total fat mass decreasing by 14 per cent at seven months and 18 per cent at twelve, with lean mass initially declining by 3 kg at seven months and stabilising thereafter. Handgrip strength improved significantly by 4.5 kg at twelve months, and the prevalence of sarcopenic obesity fell from 49 per cent at baseline to 33 per cent at twelve months (Figure 5) [9]. Resting energy expenditure normalised to lean mass increased significantly between seven and twelve months [9].

Table 2: Summary of reported findings on mass and function



Figure 5: Function in a cohort that also lost lean mass [9]

How far function is measured at all: Reviews state that the extent to which these changes translate into impaired muscle function or increased vulnerability to frailty remains unclear, and describe current studies as constrained by methodological heterogeneity, small sample sizes and limited assessment of functional outcomes [7,10]. Preservation of lean and skeletal muscle mass is described as a critical yet underexplored aspect of incretin-based weight loss [7].

What has been tried for preservation: A case series described three patients with body mass index between 32.9 and 51.9 who prioritised lean tissue preservation during treatment. They undertook intentional exercise or structured physical activity on four to seven days weekly, including resistance training on three to five days, with protein intakes of 0.7 to 1.7 grams per kilogram of body mass or 1.6 to 2.3 grams per kilogram of fat-free mass. Changes in weight, fat mass and lean soft tissue were minus 33.0, minus 53.4 and minus 6.9 per cent in the first patient; minus 26.8, minus 61.6 and plus 2.5 per cent in the second; and minus 13.2, minus 46.9 and plus 5.8 per cent in the third [11].

The scale of the two effects: Meta-analytic estimates over comparable intervention durations put the effect of resistance training on lean soft tissue mass at plus 1.61 kg and the effect of incretin therapy at minus 0.86 kg (Figure 6) [12]. The two are of similar magnitude and opposite sign, which is the basis for the hypothesis that training mitigates the loss, currently being tested prospectively [12] (Table 2).

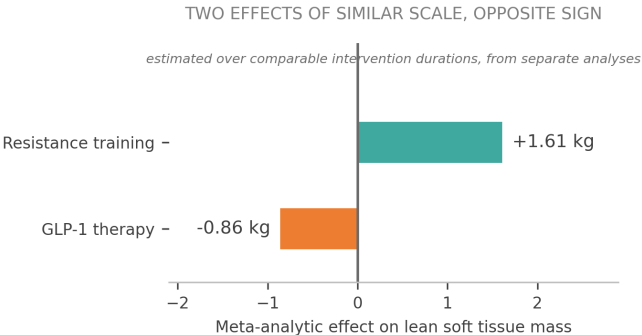


Figure 6: Two effects of similar scale and opposite sign [12]

Table 3: What is and is not established about lean mass on these therapies

Measure	What has been reported
Lean fraction of weight lost	About 25%, range 15 to 60% [1,5]

Proportion lean of total mass	Not significantly altered [1,5]
Depletive pattern, first year	10.3% and 6.7% by agent [8]
Handgrip strength	Improved by 4.5 kg at 12 months [9]
Sarcopenic obesity	49% to 33% at 12 months [9]

What preserves muscle during any weight loss: The question predates these agents. Systematic review has examined the separate and combined effects of energy restriction and exercise on fat-free mass [15], and a whey protein, leucine and vitamin D enriched supplement was shown to preserve muscle mass during intentional weight loss in older adults with obesity [16]. Meta-analysis of protein intake after weight loss in older adults reports effects on body composition [17], and protein intake to support muscle mass and function has been synthesised more broadly [27], as has protein supplementation alongside resistance training [28]. A randomised trial compared aerobic, resistance and combined exercise in dieting older adults with obesity [29].

How the question is framed by others: Commentary has asked directly whether weight-loss-induced muscle mass loss is clinically relevant [25], and whether the muscle response to these agents is adaptive or maladaptive [26]. Reviews have considered whether resistance exercise can optimise body composition and physical function alongside incretin-based pharmacotherapy [20]. The effect of antidiabetic drugs on muscle mass more generally has been reviewed [21,22], and semaglutide specifically assessed for its effect on lean mass across trials [24], including an early real-life prospective study [23].

Definitions and what counts as harm: Sarcopenia definitions and position statements set the thresholds against which any of these changes would be judged [18,19], and sarcopenic obesity has been reviewed as a distinct entity with its own treatment strategies [34]. Comparison with other routes to substantial weight loss is instructive: intensive lifestyle intervention [31], metabolic surgery [32] and combined approaches [30] all produce lean tissue loss alongside fat loss, and improvement in comorbidity is graded by the amount of weight lost rather than by its composition [33]. Pharmacological preservation has been tested directly, with one agent producing an increase in lean body mass alongside fat reduction [13]. Preserving healthy muscle during weight loss has been reviewed as a general problem [14] (Table 3).

Eligibility: Studies were included if they reported body composition or muscle function during treatment, or examined interventions intended to preserve lean tissue. Case series and registered protocols are included where they describe the current state of the preservation literature and are identified as such.

Question	What the evidence supports
Is lean mass lost?	Yes, about 25% of weight lost [5]
Is that figure consistent?	No; 15 to 60% across trials [1]

Does composition worsen?	Proportion lean not significantly altered [1,5]
Does function decline?	Rarely measured; improved where it was [7,9]
Does training preserve it?	Rationale strong, direct evidence thin [11,12]

Method

Search strategy: PubMed and the archives of the major obesity, endocrinology and body composition journals were searched for studies of lean mass during incretin-based weight loss. Search terms combined GLP-1 receptor agonist, semaglutide and tirzepatide with lean mass, body composition, protein intake, resistance training and muscle function. Reference lists of the registration trial review [1] and the network meta-analysis [5] were screened by hand for primary sources.

Data extraction and handling: Population, agent, duration, the method of body composition assessment and the reported change were extracted as published. Whether a figure describes absolute lean mass or lean mass as a proportion of total mass is stated in every case, because those two measures move in opposite directions in at least one of the studies reviewed and are frequently reported interchangeably. This review reports published findings and does not constitute dietary, protein intake, exercise or prescribing guidance for any individual, all of which are matters for the treating clinician. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis of published literature and was not registered as a systematic review.

Concluding Remarks

The commonly quoted figure of roughly a quarter is a reasonable central estimate and a poor summary. Across the registration trials the fraction of weight lost as lean tissue runs from about 15 to 60 per cent, and the three trials tabulated here give 45.2, 25.7 and 43.4 per cent [1,5]. A patient counselled using the pooled figure may be described an experience quite unlike the one they will have.

More importantly, the fraction measures something narrower than it appears to. In the substudy where 43.4 per cent of weight lost was lean tissue, lean mass as a proportion of lean plus fat increased, and the network meta-analysis finds no significant change in that proportion generally [1,5]. Someone losing lean tissue while their body composition improves is not in the situation the phrase muscle loss conveys.

Function is the measure that would settle it, and it is the one least often taken. Reviews describe assessment of functional outcomes as limited and the translation into impaired function or frailty as unclear [7,10]. Where it has been measured, it moved favourably: handgrip strength rose by 4.5 kg over twelve months

and sarcopenic obesity fell from 49 to 33 per cent in the same cohort that lost 3 kg of lean mass [9].

That should not be read as reassurance for everyone. The digital phenotyping analysis identified a depletive pattern in 10.3 per cent of tirzepatide and 6.7 per cent of semaglutide users within the first year [8]. Roughly one in ten and one in fifteen is not a rare event, and the average across a trial population will not describe them. Identifying who falls into that group before it happens is the useful clinical question and is not answered by the studies reviewed here.

On preservation, the honest position is that the rationale is stronger than the evidence. Resistance training has a meta-analytic effect of plus 1.61 kg on lean soft tissue against minus 0.86 kg for the therapy, so the two are of comparable magnitude [12]. The direct evidence that combining them preserves lean tissue during treatment consists largely of a three-patient case series in which two of three gained lean tissue [11]. Three patients who chose to train and monitor their protein are not a trial.

The practical difficulty the title names is nonetheless real and specific. These agents work by reducing intake, so protein intake falls alongside energy intake at the point when the requirement for preserving lean tissue is unchanged. That is a structural feature of the treatment rather than a failure of adherence, and it is the reason protein and training are discussed together in this literature [3,4,11].

Three limitations belong with these conclusions. Body composition is assessed by different methods across studies, including dual-energy absorptiometry and bioimpedance, which are not interchangeable and contribute to the reported heterogeneity [7,12]. The large observational analysis relies on measurements taken in routine care rather than by protocol, so paired assessments were available for 7,965 of 670,422 users and those with measurements may differ systematically from those without [8]. And the preservation evidence is a case series and a registered protocol rather than a completed trial, so the effect of combining protein and training with these agents is currently inferred rather than demonstrated [11,12].

A comparison worth making explicitly is with other routes to the same weight loss. Intensive lifestyle intervention, metabolic surgery and combined approaches all produce lean tissue loss alongside fat loss [30,31,32], and improvement in comorbidity is graded by how much weight is lost rather than by its composition [33]. The concern raised about these agents is therefore about magnitude and speed rather than about a mechanism unique to them [1,26].

There is a measurement point that would improve this literature at modest cost. Body composition is assessed by absorptiometry in some studies and bioimpedance in others, and the two are not interchangeable [7,12]. Reporting lean mass in absolute terms and as a proportion of total mass, with the

assessment method stated, would remove a substantial part of the apparent disagreement described here without requiring any new study [1,5].

Finally, on who should be watched rather than what should be measured. The depletive pattern occurred in about one in ten tirzepatide users in the first year [8], and sarcopenic obesity was present in 49 per cent of one cohort at baseline [9]. Those starting with low muscle mass, older patients, and those losing weight fastest are the groups in whom the average result is least likely to apply, and none of the studies reviewed here was designed to identify them prospectively [8,18,34].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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