



GLP-1 Receptor Agonists and Muscle Mass: A Narrative Review of What Body Composition Data Do and Do Not Show

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Abstract

Body composition analyses of incretin-based weight treatments have produced an alarming headline: 39 to 40 per cent of the weight lost in two semaglutide programmes was lean mass. Three findings complicate it. First, the proportion of lean mass relative to total body mass increased despite the absolute loss, so composition improved rather than deteriorated. Second, the estimate is unstable: across six studies of 1,541 adults, lean mass accounted for anywhere between almost none and 40 per cent of weight lost, with the same drug class and the same measurement method. Third, lean mass on a scan is not muscle, since the compartment includes body water and non-muscle organs, so a fall in it does not by itself establish loss of muscle or sarcopenia. Where function was measured rather than inferred, a prospective cohort of 106 patients found handgrip strength rose by 4.5 kg over 12 months and sarcopenic obesity fell from 49 to 33 per cent. This review sets out what these data support and what they do not.

Keywords: GLP-1 receptor agonists; Lean mass; Body composition; Muscle function; Sarcopenic obesity

Introduction

Incretin-based treatments produce weight reduction of a magnitude previously reached only by surgery, with semaglutide giving mean loss of about 15 per cent over 68 weeks and tirzepatide 15 to 21 per cent over 72 weeks [1,2,3,28,34]. Attention has since turned from how much weight is lost to what tissue it comes from [4,5].

The concern is specific and reasonable. Skeletal muscle is the principal site of insulin-mediated glucose disposal and a determinant of physical function, and loss of it during weight reduction is not a neutral outcome, particularly in older people [31,32]. Strategies for preserving muscle during weight reduction have been reviewed separately [23]. [6,7,8].

This review examines what body composition studies of these agents have measured, how consistent the estimates are, what the measurement actually captures, and what happened where function rather than composition was assessed.

Material and Methods

Search strategy: PubMed and the archives of the major obesity, endocrinology and body composition journals were searched for studies reporting body composition during incretin-based treatment. Search terms combined semaglutide, tirzepatide and GLP-1 receptor agonist with lean mass, fat-free mass, body composition, muscle and dual-energy absorptiometry. Reference lists of the systematic review [9] and the principal trial analyses [10,11] were screened by hand for primary sources.

Eligibility: Studies were included if they reported measured body composition or muscle function during treatment with these agents. Studies reporting weight change alone are cited for context and identified as such.

Data extraction and handling: Design, population, measurement method, the compartment reported and the estimate were extracted as published. Whether an estimate

describes absolute lean mass, lean mass as a share of weight lost, or lean mass as a proportion of total body mass is stated in each case, because these three quantities can move in different directions in the same dataset. This review reports measured outcomes and makes no dietary, protein, caloric or exercise recommendations. 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 and was not registered as a systematic review.

Results

The headline figure: Body composition analyses from two semaglutide programmes reported that 39 to 40 per cent of the weight lost was lean mass (Figure 1) [10,12]. Across recent trials of both agents, lean soft tissue loss has been reported to comprise 26 to 40 per cent of weight lost [13].

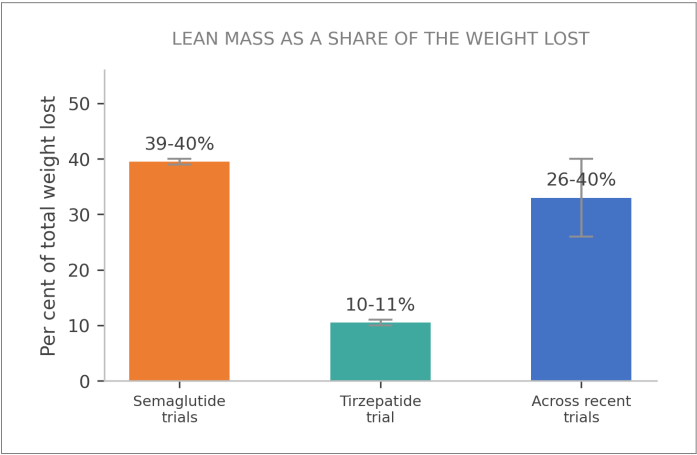


Figure 1: Lean mass as a share of the weight lost [10,11,12,13]

The tirzepatide comparison: Body composition analysis of the principal tirzepatide obesity trial reported that fat mass fell by 33 to 36 per cent while lean mass fell by 10 to 11 per cent (Figure 6) [11,12]. A real-world comparison using paired body composition measurements from electronic records reported greater lean body mass decline with tirzepatide than with semaglutide, alongside its greater total weight reduction [14,15].

How unstable the estimate is: A systematic review of six studies including 1,541 adults with overweight or obesity found weight reduction driven primarily by fat mass loss, with lean mass remaining stable in some studies and falling by up to 40 per cent of total weight reduction in others (Figure 2). Notable decreases were particularly evident in the larger trials [9].

Table 1: Three ways of expressing the same change and the direction of each [9,10,12,13]

Table 2: Composition and function in a prospective cohort of 106 patients [19]

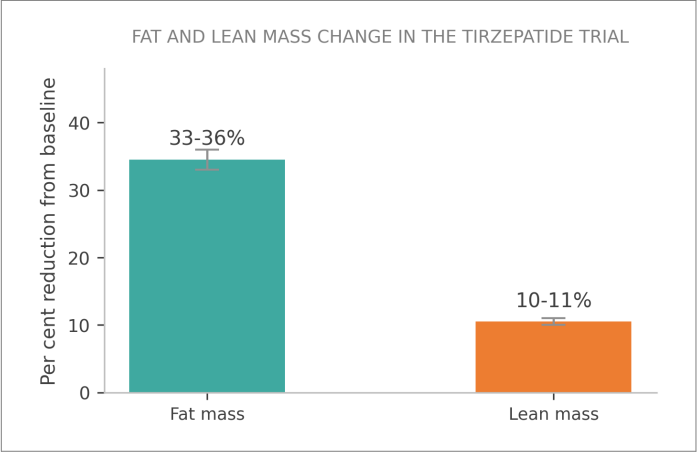


Figure 6: Fat and lean mass change in the tirzepatide trial [11,12]

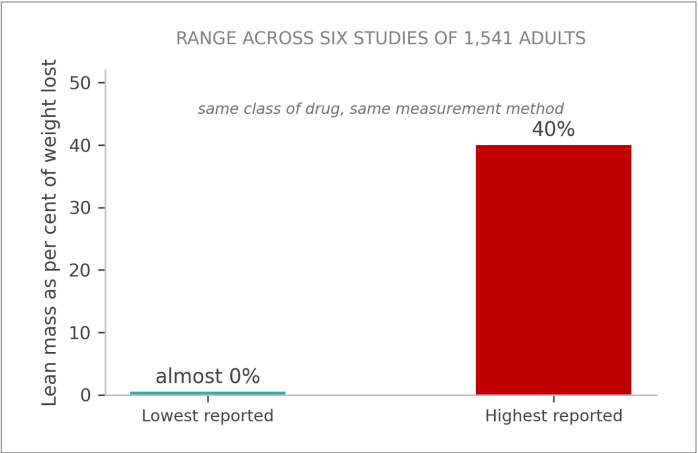


Figure 2: Range of reported lean mass loss across six studies of 1,541 adults [9]

The direction the headline omits: In the same systematic review, and in the two semaglutide programmes, the proportion of lean mass relative to total body mass increased despite the absolute reduction, which the investigators interpreted as an overall improvement in body composition [9,10,12]. A meta-analysis of 18 randomised studies covering oral and subcutaneous semaglutide and older agents in the class reported significant reductions in fat-free mass, and it examined absolute rather than proportional change [16].

Quantity reported	Direction	Interpretation
Absolute lean mass	Falls	Tissue is lost [9,10]
Lean mass as share of weight lost	26% to 40%	Substantial fraction [12,13]
Lean mass as proportion of body mass	Rises	Composition improves [9,10]
Fat mass	Falls more	Predominant loss [9,11]

What the measurement captures: Lean body mass as estimated by these methods should not be equated with skeletal muscle mass, since the compartment also incorporates body water and non-muscle organs. A reduction in lean mass therefore does not by itself establish clinically meaningful sarcopenia (Figure 5) [14,17]. Rapid weight loss is accompanied by changes in hydration and in the mass of metabolically active organs, both of which register in this compartment [17,18].

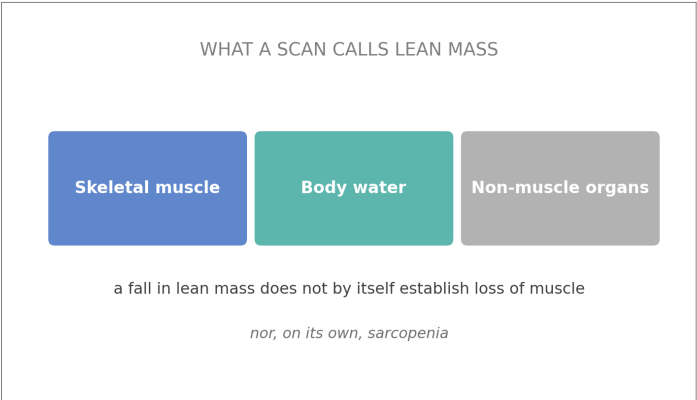


Figure 5: What a scan measures as lean mass [14,17]

Where function was measured: A prospective study enrolled 115 patients with obesity, of whom 106 completed, with mean body mass index 46.3 kg/m2 and 68.9 per cent female. Weight fell by 10 per cent at seven months and 13 per cent at 12 months, with 59 per cent achieving at least 10 per cent reduction. Fat mass fell by 14 and 18 per cent at the same time points (Figure 3). Lean mass declined initially, by 3 kg at seven months, then stabilised [19].

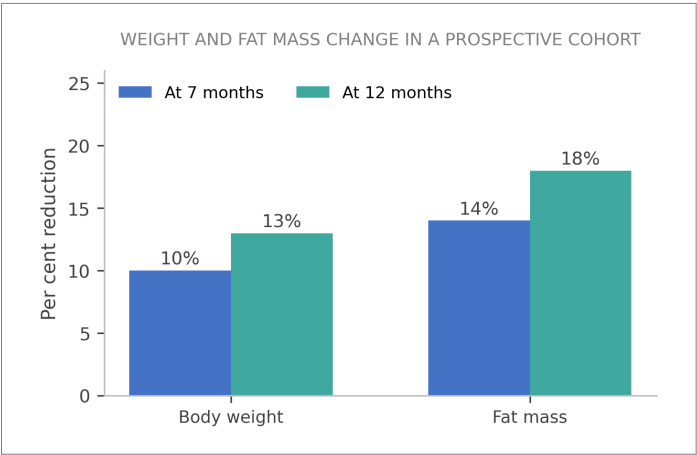


Figure 3: Weight and fat mass change in a prospective cohort [19]

Function improved in the same cohort: Handgrip strength increased significantly, by 4.5 kg at 12 months, and the prevalence of sarcopenic obesity fell from 49 per cent at baseline to 33 per cent at 12 months (Figure 4). Resting energy expenditure normalised to lean mass increased significantly between seven and 12 months [19].

Outcome	Reported change	Time point
Body weight	-10%, then -13%	7 and 12 months
Fat mass	-14%, then -18%	7 and 12 months
Lean mass	-3 kg, then stable	7 and 12 months
Handgrip strength	+4.5 kg	12 months
Sarcopenic obesity	49% to 33%	Baseline to 12 months

Table 3: What body composition data do and do not establish

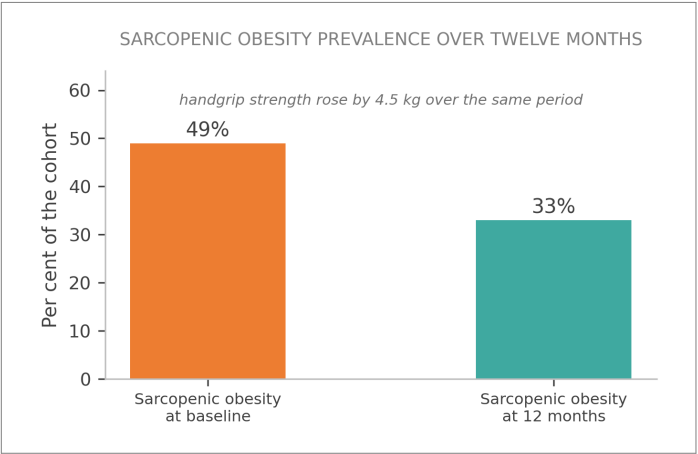


Figure 4: Sarcopenic obesity prevalence over twelve months [19]

Subgroup differences: In the same cohort, women showed greater weight and fat mass loss, while patients with type 2 diabetes or previous exposure to an agent in this class showed attenuated responses, and those with a history of bariatric surgery showed the most pronounced changes in body composition parameters [19]. Trials examining whether an agent added to semaglutide can preserve lean mass are under way and report composition endpoints directly [20]. Reviews covering this class alongside sodium-glucose cotransporter 2 inhibitors reach similar conclusions about lean mass [25,26], and the effects of these agents on appetite and energy intake supply the mechanism by which the loss occurs [27].

Question	What the data support
Is lean mass lost?	Yes, in absolute terms [9,10]
Is that the same as muscle loss?	Not established by these measurements [14,17]
Does composition worsen?	No; lean proportion rose [9,10]
Is the estimate consistent?	No; from near zero to 40% [9]
Does function decline?	Not where it was measured [19]

The comparison that is missing: Weight reduction by any route reduces fat-free mass. Systematic review of significant weight loss across methods reported the same phenomenon long before these agents existed, and studies of dietary restriction in older adults describe accompanying changes in strength and bone [21,22]. The relevant question is therefore not whether lean mass falls but whether it falls more than it would for the same weight change achieved another way, and no study reviewed here makes that comparison directly [23,24].

Why the agents produce it: These drugs reduce energy intake by suppressing appetite rather than by any direct effect on muscle, so the loss of lean tissue is the expected consequence of a substantial energy deficit rather than a distinct pharmacological action [27,28]. That framing matters, because a deficit-driven loss is in principle modifiable by the same factors that modify it in other settings, whereas a direct myotoxic effect would not be [25,26,29].

Discussion

The figure that circulates is that 39 to 40 per cent of weight lost on semaglutide is lean mass [10,12]. It is accurately reported and it is incomplete in three ways, each of which is present in the same publications.

The first is directional. Lean mass fell in absolute terms while rising as a proportion of total body mass, because fat was lost faster [9,10]. Those two statements are both true and describe opposite impressions. A person who loses 15 per cent of body weight of which 40 per cent is lean tissue ends up with a higher proportion of lean tissue than they started with. Reporting the fraction without the proportion produces alarm that the data do not support.

The second is stability. Across six studies of 1,541 adults, lean mass accounted for almost none of the weight lost in some and up to 40 per cent in others, using the same drug class and the same measurement technique [9]. An estimate with that range is not a property of the drug; it reflects differences in population, duration, rate of loss and analytic method. Quoting 40 per cent as though it were the value is a selection from a distribution.

The third is what is being measured. Lean body mass on absorptiometry includes body water and non-muscle organs alongside skeletal muscle, and rapid weight loss shifts both [14,17,18]. A decline in this compartment is consistent with muscle loss and is also consistent with reduced hydration and reduced organ mass. Treating it as a synonym for muscle, and muscle loss as a synonym for sarcopenia, involves two inferential steps that the measurement does not license.

Against all this sits the observation that matters most and is least often quoted. In the prospective cohort where function was assessed rather than inferred, handgrip strength rose by 4.5 kg and sarcopenic obesity fell from 49 to 33 per cent over 12 months [19]. That is a single cohort of 106 patients without a control group, and it cannot settle the question. But it is direct evidence about the outcome the composition data are being used as a proxy for, and it points the opposite way.

The debate has been conducted directly in the literature, with commentaries arguing both that the lean mass change is an adaptive accompaniment of fat loss and that it warrants active attention [29,30]. Neither position is settled by the data reviewed here, and the honest summary is that the composition measurements establish a change in a compartment whose clinical meaning has not been determined.

What would settle it is specific. A trial with muscle function as its primary endpoint, measured by strength and physical performance rather than inferred from a scan, and with an active comparator achieving similar weight loss, would answer the question these analyses are being asked to answer [19,20]. Trials of agents intended to preserve lean mass alongside treatment are under way and report composition endpoints, which is a step towards it rather than the answer [20].

Study limitations

The limitations belong to the underlying literature. Body composition analyses are predominantly exploratory or secondary endpoints of trials designed around weight, so they are not powered for these comparisons and were not the basis of randomisation [10,11]. Dual-energy absorptiometry estimates lean soft tissue rather than measuring muscle, and its estimates are affected by hydration status, which changes during rapid weight loss [17,18]. Definitions differ between studies, with lean mass, fat-free mass and lean soft tissue used inconsistently [9,16]. The prospective functional cohort has 106 completers, no control group and a mean body mass index of 46.3, so it describes a specific population [19]. The real-world comparison between agents is drawn from routinely collected records with unmatched confounding [15]. No trial has been designed with muscle function as its primary endpoint, and trials of agents intended to preserve lean mass are ongoing rather than reported [20]. And weight loss by any means, including dietary restriction and surgery, reduces lean mass, so the relevant comparison is against other routes to the same weight change rather than against no treatment [21,22,24]. Whether weight-loss-induced muscle loss is clinically relevant has been debated directly [29,30], and protein intake and resistance training have been examined as modifying factors in other populations [33].

Conclusion

Incretin-based weight treatment does reduce lean mass in absolute terms, and in two semaglutide programmes that reduction was 39 to 40 per cent of the weight lost. Three things belong beside that figure. The proportion of lean mass to total body mass rose, so body composition improved. The estimate ranges from almost nothing to 40 per cent across six studies of the same drug class, so it is not a stable property. And lean mass on a scan contains water and organs as well as muscle, so its decline does not establish muscle loss, let alone sarcopenia. Where function was measured directly, grip strength improved and sarcopenic obesity became less common. The composition data are worth taking seriously and are not, on their own, evidence of harm.

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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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