Metabolism 164 (2025) 156113

Contents lists available at ScienceDirect

Metabolism

journal homepage: www.journals.elsevier.com/metabolism

Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: Systematic review and network meta-analysis

Paschalis Karakasis [a,*], Dimitrios Patoulias [b], Nikolaos Fragakis [a], Christos S. Mantzoros [c]

[a] Second Department of Cardiology, Hippokration General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] Second Propedeutic Department of Internal Medicine, Faculty of Medicine, School of Health Sciences Aristotle, University of Thessaloniki, Greece
[c] Beth Israel Deaconess Medical Center and Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
GLP-1 receptor agonist
Obesity
Diabetes
Cardio-renal-metabolic health
Body weight
Fat mass
Lean mass
Body composition
Sarcopenia
Fat free mass

ABSTRACT

Background and aims: While glucagon-like peptide-1 receptor agonists (GLP-1RAs) effectively reduce body weight, their impact on lean mass remains uncertain. This meta-analysis evaluated the effects of GLP-1RAs and GLP-1/GIP receptor dual agonists (GLP-1/GIP-RAs) on body composition, focusing on total weight, fat mass, and lean mass in adults with diabetes and/or overweight/obesity.

Methods: A systematic search of Medline, Embase, and the Cochrane Library was conducted through November 12, 2024. Data were analyzed using random-effects pairwise and network meta-analyses to compare interventions with placebo or active comparators.

Results: Twenty-two randomized controlled trials (2258 participants) were included. GLP-1RAs significantly reduced total body weight (MD -3.55 kg, 95 %-CI [−4.81, −2.29]), fat mass (MD -2.95 kg, 95 %-CI [−4.11, −1.79]), and lean mass (MD -0.86 kg, 95 %-CI [−1.30, −0.42]), with lean mass loss comprising approximately 25 % of the total weight loss. However, the relative lean mass, defined as percentage change from baseline, was unaffected. Liraglutide, at 3.0 mg weekly or 1.8 mg daily, was the only GLP-1RA to achieve significant weight reduction without significantly reducing lean mass. Tirzepatide (15 mg weekly) and semaglutide (2.4 mg weekly) were the most effective for weight and fat mass reduction but were among the least effective in preserving lean mass.

Conclusions: Potent GLP-1 RAs, such as tirzepatide and semaglutide, demonstrate greater overall weight loss but are associated with a significant reduction in lean mass.

1. Introduction

Elevated blood glucose levels and obesity are recognized as independent factors contributing to the onset and advancement of sarcopenia, a complication frequently observed in individuals with type 2 diabetes mellitus (T2D) [1]. Impaired insulin signaling, the buildup of glycation end products, and chronic inflammation may drive muscle degradation in individuals experiencing persistent hyperglycemia and/or obesity [2]. Importantly, muscle loss not only diminishes physical function and quality of life but is also associated with increased rates of all-cause mortality [3,4].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and glucose-dependent insulinotropic polypeptide/GLP-1 receptor dual agonists (GLP-1/GIP-RAs) represent a class of pharmacological agents widely employed in the management of T2D and obesity. These agents are well-recognized for their weight-lowering properties, which affect various body components, including adipose tissue and skeletal muscle [5]. The potential reduction in skeletal muscle is a significant concern for clinicians, particularly when treating patients with sarcopenia, thereby often limiting the use of these medications in such populations [6]. In fact, previous research has indicated a modest yet significant loss in lean mass with glucose-lowering agents that have a more moderate effect on weight, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors [7,8]. Studies have indicated that patients treated with GLP-1RAs exhibited reductions in both fat mass and lean mass compared to those receiving gliclazide [9]. However, recent findings suggest that GLP-1RAs may not decrease muscle mass and may even promote its increase [10]. Furthermore, it has been proposed that activation of GLP-

* Corresponding author at: Second Department of Cardiology, Hippokration General Hospital, Medical School, Aristotle University of Thessaloniki, Konstantinoupoleos 49, 54642 Thessaloniki, Greece.
E-mail address: pkarakaa@auth.gr (P. Karakasis).

https://doi.org/10.1016/j.metabol.2024.156113
Received 21 November 2024; Accepted 20 December 2024
Available online 22 December 2024

1 receptors may play a role in regulating skeletal muscle remodeling and could potentially mitigate the onset of sarcopenia [11].

Given the contradictory evidence, this meta-analysis aimed to fill the knowledge gap regarding the effect of GLP-1RAs on body mass composition and to quantify changes in total body weight, fat mass, and lean mass according to the type and dosage of these medications.

2. Material and methods

The study adhered to the guidelines specified in the Cochrane Handbook for Systematic Reviews [12], and was reported following the PRISMA 2020 standards for systematic reviews and meta-analyses [13], along with the relevant extension statement for NMA [14] (Supplemental Table 1). The study protocol was registered a priori on the Open Science Network (10.17605/OSF.IO/SU5HC), and no amendments were made to the original protocol thereafter.

2.1. Search strategy

A comprehensive literature search was systematically conducted by two independent researchers across multiple databases, including MEDLINE (via PubMed), Embase (via Embase.com), and the Cochrane Central Register of Controlled Trials, covering all records from database inception through November 12, 2024. No limitations were applied concerning date, language, publication status, or year at the initial search stage. The primary search terms included "Glucagon-like peptide-1 receptor agonist", "GLP-1 receptor-based agonist", "body composition", "fat mass" and "lean mass" applied both as free-text keywords and using Medical Subject Headings (MeSH). Additional searches were carried out manually on ClinicalTrials.gov, the Epistemonikos database, and Google Scholar. Furthermore, backward and forward citation tracking was employed using the {citationchaser} R package [15]. Detailed search strategies are provided in Supplemental Tables 2–4.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

Eligible studies included randomized controlled trials (RCTs) that examined the effects of GLP-1RAs and dual agonists on body composition in adults (aged 18 years or older) with baseline diabetes or overweight/obesity.

2.2.2. Exclusion criteria

Studies with the following characteristics were excluded: (i) observational studies, case reports, case series, and narrative reviews; (ii) editorials, letters, commentaries, and expert opinions; (iii) clinical practice guidelines, conference abstracts, protocols, and dissertations; (iv) studies reporting exclusively on body weight without assessing changes in fat or lean mass; and (v) studies for which the full text was not retrievable.

2.3. Outcomes

The endpoints for the meta-analysis were changes in total body weight, fat mass, and lean mass, measured using dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), or computed tomography (CT), comparing GLP-1RAs with placebo or any active comparator.

2.4. Study selection

In the initial phase, two authors independently screened all titles and abstracts from records identified through the prespecified search strategy. To enhance the sensitivity of the study selection process, discrepancies at this stage did not result in exclusions. Subsequently, two investigators independently evaluated the full texts of potentially eligible studies. Any disagreements were resolved through consensus or, if necessary, by consulting a senior author. The screening process in the initial phase was facilitated by the Abstrackr tool [16], while Mendeley was utilized for reference management.

2.5. Data extraction

A data extraction form was developed and underwent a pilot phase using a subset of four studies. Following a series of training and calibration sessions, a standardized form for data extraction was finalized. Data extraction was conducted independently in duplicate, with any discrepancies resolved by consensus or, when necessary, by consulting a senior author. For each study, we extracted information on sample size, relevant clinical and demographic characteristics, and adjusted effect estimates for outcomes of interest, when such adjustments were available. Additionally, corresponding authors from the included studies were contacted to request supplementary information if subgroup-level data were missing or not explicitly provided in the published reports.

2.6. Quality assessment

Two authors independently evaluated the risk of bias in the included studies, considering all predefined domains from the revised Cochrane Collaboration tool (RoB 2): bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result [17]. Trials were classified as having an overall low risk of bias only if all five domains were rated as low risk. Any discrepancies in assessment were resolved through discussion or, if needed, by involving a third author with greater expertise.

2.7. Data analysis

All analyses were conducted using R Statistical Software, version 4.2, utilizing the *meta*, *netmeta*, and *dmetar* packages. Categorical variables are reported as frequencies and percentages (%), while continuous variables are presented as means with standard deviations (SD) for normally distributed data, and as medians with interquartile ranges (IQR) for non-normally distributed data. All outcomes are reported as absolute changes from baseline between the GLP-1RAs and control groups, unless otherwise stated. To estimate the relative effects between intervention and control groups, effect estimates, and their 95 % confidence intervals (CIs) were pooled using random-effects pairwise models, employing the restricted maximum likelihood estimator for between-study variance within a frequentist framework. A two-tailed p-value of <0.05 was considered statistically significant for summary effect estimates. All analyses followed an intention-to-treat approach.

The I^2 statistic was calculated to assess the proportion of total variability due to between-study heterogeneity, indicating the degree of inconsistency across studies. Additionally, heterogeneity was formally assessed using Cochran's Q test. Generally, thresholds of 25 %, 50 %, and 75 % are used to indicate low, moderate, and high heterogeneity, respectively [18]. To evaluate small-study effects and potential publication bias, contour-enhanced funnel plots (plotting effect size against standard error) were used for visual assessment, with Egger's test providing a formal statistical evaluation.

To explore potential effect modification, pre-specified subgroup analyses were conducted based on the primary indication (diabetes or overweight/obesity), the measurement modality used (DXA, MRI, or CT), and the median follow-up duration (below or above 6 months). Meta-regression analyses were undertaken to investigate the potential association of change in total body weight with changes in fat mass and lean mass.

Lastly, leave-one-out meta-analyses were conducted, systematically excluding each study one at a time. This approach was used to evaluate how individual studies affected the overall effect size estimate and to

identify any studies exerting a particularly strong influence on the results.

2.8. Network meta-analysis

Transitivity is a fundamental assumption in network meta-analysis (NMA) [19]. Our assessment of transitivity focused on (i) whether the trials included in the analysis were jointly randomized, and (ii) whether potential effect modifiers were evenly distributed across each treatment comparison in the network. To address the first concern, we examined the similarity of patient populations within the network and consulted with clinical experts to confirm that patients across the trials were eligible to receive any of the interventions considered in the network. For the second issue, we reviewed the dataset of eligible studies for inconsistencies in predefined effect modifiers, such as average patient age, sex, duration of intervention, length of follow-up, and risk of bias. If the distribution of effect modifiers was deemed sufficiently comparable, the studies were considered appropriate for data synthesis.

Network diagrams were created for each outcome to visually examine the interventions directly compared within the included RCTs. Direct effect estimates and 95 % CIs were calculated using random-effects maximum likelihood models. Direct and indirect estimates were then combined using a random-effects frequentist NMA [20]. Global network homogeneity was assessed using Cochran's Q test, while between-study variance was evaluated with τ^2. Statistical inconsistency was examined globally using the design-by-treatment test [21]. Small study effects, including potential publication bias, were assessed visually with comparison-adjusted funnel plots and formally tested using Egger's test.

The ranking probabilities for various GLP-1RAs were assessed using P-scores, which quantify the comparative performance of each treatment. P-scores range from 0 to 1, where a higher score denotes superior overall efficacy of the treatment relative to its competitors. Finally, a partial ordering of treatments was undertaken to evaluate their comparative performance for the combined outcomes of total body weight loss and changes in lean mass [22].

Considering that lean individuals with diabetes are thought to be at increased risk for sarcopenia and frailty, the impact of GLP-1RAs on body composition—particularly on lean body mass—in this population is of concern. Therefore, we conducted a sensitivity analysis that included exclusively patients with diabetes.

3. Results

3.1. Study selection and characteristics

The PRISMA diagram detailing the database search and study selection process is provided in **Supplemental Fig. 1**. After duplicate records were removed, an initial set of 515 identified studies was screened by title and abstract. Of these, 361 studies were excluded. The remaining 128 studies underwent a thorough full-text evaluation, resulting in the inclusion of 22 RCTs that satisfied the eligibility criteria [5,9,23–42].

The baseline characteristics of the included studies are summarized in Table 1. In total, 22 studies involving 2258 participants were analyzed. The proportion of male participants varied between 5 % and 87 %, with mean ages ranging from 34.4 to 63.7 years. The median follow-up duration was 24 weeks (IQR 16–48 weeks). At baseline, the median body mass index (BMI) was 33 kg/m^2 (IQR 31–37), and the median lean mass was 56 kg (IQR 51–59).

The majority of RCTs were assessed as having a low risk of bias, while four studies were rated as having some concerns for bias (Supplemental Fig. 2).

3.2. Pairwise meta-analysis

3.2.1. Total body weight

A total of 18 RCTs, including 1369 individuals, evaluated the effect of GLP-1RAs on total body weight. Participants randomized to those agents had a significantly higher reduction in total body weight compared to placebo or active controls [Mean difference (MD) = −3.55 kg, 95 % confidence interval (CI) = [−4.81, −2.29], $P < 0.001$; $I^2 = 81$ %, heterogeneity $P < 0.01$; Fig. 1]. Non-significant subgroup differences were observed based on the primary indication (diabetes or overweight/obesity, Supplemental Fig. 3A). RCTs with duration above the median follow-up of 6 months reported greater reduction in total body weight compared to those duration of <6 months (P for subgroup difference = 0.03, Supplemental Fig. 3C).

3.2.2. Fat mass

The change in fat mass was reported by 15 RCTs, involving 1387 participants. The use of GLP-1RAs resulted in a significant reduction in fat mass compared to placebo or active comparator (MD = −2.95 kg, 95 % CI = [−4.11, −1.79], $P < 0.001$; $I^2 = 83$ %, heterogeneity $P < 0.01$; Fig. 1). This reduction was not significantly modified by the indication (diabetes or overweight obesity), the imaging modality (DXA, MRI or CT) or the duration of follow-up (Supplemental Fig. 4).

3.2.3. Lean mass

In total 20 RCTs, including 1623 participants, evaluated the absolute change in lean mass. Individual receiving GLP-1RAs had a significantly greater reduction in lean mass compared to placebo or active comparator (MD = −0.86 kg, 95 % CI = [−1.30, −0.42], $P < 0.001$; $I^2 = 54$ %, heterogeneity $P < 0.01$; Fig. 1). No significant differences were observed in the prespecified subgroup analyses (Supplemental Fig. 5).

The relative change in lean mass—defined as the percentage change compared to baseline lean mass—was evaluated in 8 RCTs involving 692 participants. Specifically, the percentage change in lean mass did not differ significantly between individuals receiving GLP-1RAs and those receiving a placebo or active comparator (MD = −0.87 %, 95 % CI = [−2.28, 0.53], $P = 0.224$; $I^2 = 87$ %, heterogeneity $P < 0.01$; Fig. 1). Similarly to the absolute change in lean mass, no significant differences were observed across subgroups (Supplemental Fig. 5).

3.2.4. Meta-regression analysis

Total body weight reduction was significantly associated with changes in fat mass (Fig. 2A), whereas it did not significantly affect the pooled mean difference in lean mass (Fig. 2B).

3.2.5. Sensitivity analyses and publication bias

The sensitivity analysis, utilizing a leave-one-out approach, identified no outliers or influential studies that impacted the pooled effect estimates (Supplemental Figs. 7–10). Additionally, no evidence of small-study effects or publication bias was detected, as indicated by symmetrical, contour-enhanced funnel plots comparing effect size with standard error, along with results from Egger's tests (Supplemental Figs. 11–14).

3.3. Network meta-analysis

A total of 22 RCTs were included in the network meta-analyses, involving 2258 participants. The individual drugs included in the networks were divided in the following categories: (i) GLP-1RAs (liraglutide, semaglutide and exenatide), (ii) GLP-1/GIP-RAs (tirzepatide), (iii) sodium-glucose cotransporter-2 inhibitors (canagliflozin), (iv) dipeptidyl peptidase-4 inhibitors (sitagliptin), (v) biguanides (metformin), (vi) sulfonylureas (gliclazide), (vii) insulins (insulin glargine) and (viii) placebo. All interventions included at least one placebo-controlled trial assessing one or more outcomes, and all networks exhibited robust connectivity.

Table 1
Characteristcs of included randomized controlled trials.

Author, year	Treatment duration (weeks)	Primary indication for GLP-1RAs	Intervention	No. of patients	Age (years)	Men (%)	DM (%)	Baseline BMI (kg/m^2)	Baseline Weight (kg)	Baseline lean mass (kg)
Astrup A, 2012 [40]	20	Obesity	Liraglutide 1.2 mg qd sc	95	47.2 (9.7)	23	6	34.8 (2.6)	96.2 (13.5)	55 (8.9)
			Liraglutide 1.8 mg qd sc	90	45.5 (10.9)	24	2	35 (2.6)	98 (12.5)	51.7 (11.3)
			Liraglutide 2.4 mg qd sc	93	45.0 (11.1)	24	1	35 (2.8)	98.4 (13)	50.6 (11.9)
			Liraglutide 3.0 mg qd sc	93	45.9 (10.7)	25	4	34.8 (2.8)	97.6 (13.7)	53.1 (10.3)
			Placebo	98	45.9 (10.3)	25	4	34.9 (2.8)	97.3 (12.3)	51 (11)
Gibbons C, 2021 [29]	12	T2D	Oral Semaglutide 14 mg po	15	58.2 (13.3)	86.7	100	30.8 (4)	93.9 (27)	NR
			Placebo							
Harder H, 2004 [42]	8	T2D	Liraglutide 0.6 mg qd sc	21	59.9 (11)	52.4	100	36.8 (4.6)	106.9 (2.9)	59.6 (2.5)[b]
			Placebo	12	60.1 (6.7)	8.3	100	36.1 (3.4)	98 (3.8)	49.7 (1.9)[b]
Ghanim H, 2020 [39]	26	T1D	Liraglutide 1.8 mg qd sc	37	47 (2)	47	100	33.3 (1.2)	94.2 (3.1)	52 (2.1)[b]
			Placebo	27	45 (3)	41	100	29.5 (1.3)	83.3 (3.4)	50.1 (2.2)[b]
Neeland IJ, 2017 [36]	49	Overweight/ obesity	Liraglutide 3.0 mg qd sc	73	49.6 (9.8)	8	0	37.2 (6)	101 (17.9)	NR
			Placebo	55	50.9 (8.8)	7	0	38.1 (6.1)	102.3 (17.9)	NR
Ishøy PL, 2017 [34]	13	Obesity	Exenatide 2.0 mg qw sc	20	37.4 (10.7)	55	0	39.5 (3.5)	118.3 (16)	59.9 (11.7)
			Placebo	20	34.4 (10.6)	45	0	38.6 (6.3)	111.7 (18)	57.4 (7.5)
Dubé MC, 2018 [23]	24	T1D	Liraglutide 1.8 mg qd sc	15	35.8 (1.7)	–	100	30.5 (0.9)	89 (3.8)	58.9 (3.4)[b]
			Placebo							
Mensberg P, 2017 [38]	16	T2D	Liraglutide 0.6 mg qd sc	17	56.4 (9)	76	100	32.5 (3.7)	101.0 (14.5)	63.3 (12.2)
			Placebo	16	55.6 (12)	62	100	32.4 (5.2)	96.8 (17.4)	58 (12)
Silver HJ, 2023 [26]	14	Obesity/ prediabetes	Liraglutide 1.8 mg qd sc	44	50.3 (10.8)	32	0	38.6 (6.1)	108.5 (21.6)	53.6 (9.3)
			Sitagliptin po	22			0	39.6 (5.7)	112.1 (23.4)	57.5 (13.9)
			Calorie restriction	22			0	38.4 (5.7)	109.9 (16.9)	56 (9.7)
van Eyk HJ, 2020 [37]	26	T2D	Liraglutide 1.8 mg qd sc	22	55 (11)	36	100	30.4 (3.8)	81.9 (11)	62.2 (9.4)
			Placebo	25	55 (9)	44	100	28.6 (4)	77.8 (12.4)	60 (12.1)
Feng WH, 2019 [9]	24	T2D	Liraglutide 1.8 mg qd sc	29	46.8 (1.8)	72.4	100	28.1 (0.6)	81.1 (2.3)	52 (8.7)[b]
			Metformin 1 g bid po	29	46.3 (2.3)	65.5	100	26.8 (0.7)	74.8 (2.5)	47.6 (9.6)[b]
			Gliclazide 120 mg qd po	27	48.2 (2.5)	70.4	100	27.5 (0.5)	78.13 (2.4)	50.3 (9.4)[b]
Yin TT, 2018 [35]	16	Overweight/ obesity and T2D	Exenatide 10 μg bid sc	19	47.6 (2.5)	63	100	28.1 (0.5)	80.8 (2.4)	52 (2.1)[b]
			Insulin glargine	18	48.3 (2.3)	67	100	27.0 (0.6)	75.1 (1.8)	48.4 (1.3)[b]
Heise T, 2023 [32]	28	T2D	Semaglutide 1 mg qw sc	44	63.7 (5.9)	77.3	100	30.8 (3.8)	92.7 (14)	56.3 (10.3)
			Tirzepatide 15 mg qw sc	45	61.1 (7.1)	68.9	100	31.3 (5)	94.2 (14)	57.7 (9.3)
			Placebo	28	60.4 (7.6)	75.0	100	32.2 (4)	98.7 (14.6)	59.1 (10.3)
Jendle J, 2009 [5]	26 (LEAD-2)	T2D	Liraglutide 0.6 mg qd sc	27	58 (10)	77	100	NR	93 (12)	NR
			Liraglutide 1.2 mg qd sc	31	59 (8)	55	100	NR	86 (15)	NR
			Liraglutide 1.8 mg qd sc	37	58 (9)	51	100	NR	91 (15)	NR
			Glimepiride 4 mg qd po	37	56 (9)	70	100	NR	97 (12)	NR
			Placebo	20	56 (10)	75	100	NR	94 (16)	NR
	52 (LEAD-3)	T2D	Liraglutide 1.2 mg qd	23	55 (11)	52	100	NR	94 (15)	NR

(continued on next page)

Table 1 (*continued*)

Author, year	Treatment duration (weeks)	Primary indication for GLP-1RAs	Intervention	No. of patients	Age (years)	Men (%)	DM (%)	Baseline BMI (kg/m^2)	Baseline Weight (kg)	Baseline lean mass (kg)
			Liraglutide 1.8 mg qd	20	54 (9)	50	100	NR	94 (14)	NR
			Glimepiride 8 mg qd	18	54 (13)	33	100	NR	88 (14)	NR
Kadouh H, 2020 [24]	16	Obesity	Liraglutide 3.0 mg qd sc	19	42 (32–51)[a]	5	NR	37.2 (33.6–41)[a]	NR	48.9 (44.1–53.8)[a]
			Placebo	21	37 (26–51)[a]	14	NR	34.6 (33.4–38.9)[a]	NR	48.4 (45.7–52.1)[a]
Lundgren JR, 2021 [25]	48	Obesity	Liraglutide 3.0 mg qd sc	49	44 (12)	36	0	32.6 (2.9)	96.7 (12.5)	60.4 (11.6)
			Placebo	49						
Grannell A, 2021 [27]	16	Obesity	Liraglutide 3.0 qw sc	59	53.7 (9.2)	51	NR	43 (6.2)	123.2 (23.3)	64 (12)
			Standard care	19	56.7 (12.7)	53	NR	43 (5.7)	119.5 (24.1)	65.1 (17.2)
Blundell J, 2017 [28]	12	Obesity	Semaglutide 1.0 mg qw sc	28	42	66	0	33.8	101.3	NR
			Placebo							
McCrimmon RJ, 2020 [31]	52	T2D	Semaglutide 1.0 qw weekly sc	88	57.8 (9.9)	NR	100	32.6 (6.4)	89 (18.2)	51.3 (10.1)
			Canagliflozin 300 mg qd po	90	58.6 (10.1)	NR	100	32.3 (5.5)	87.6 (18.2)	51.3 (10.7)
Wilding JPH, 2021 [30]	68	Overweight/ obesity	Semaglutide 2.4 mg qw sc	95	NR	NR	NR	NR	NR	NR
			Placebo	45	NR	NR	NR	NR	NR	NR
Bunck MC, 2010 [33]	48	T2D	Exenatide 20 μg bid sc	29	58.4 (1.4)[b]	64	100	30.9 (0.7)[b]	90.3 (2.4)[b]	57.8 (2.1)[b]
			Insulin glargine	28	58.3 (1.3)[b]	67	100	30.1 (0.6)[b]	94.1 (2.5)[b]	60.1 (1.7)[b]
Jastreboff AM, 2022 [41]	72	Obesity	Tirzepatide 5, 10 or 15 mg qw sc	255	NR	NR	NR	NR	NR	NR
			Placebo							

Abbreviations: BMI, body mass index; bid, twice daily; kg, kilograms; NR, not reported; po, per os; sc, subutaneous; T1D, type 1 diabetes; T2D, type 2 diabetes; qd, once daily; qw, once weekly.
Reported as mean (SD) unless otherwise indicated.
[a] Reported as median (Q1-Q3).
[b] Reported as mean (SE).

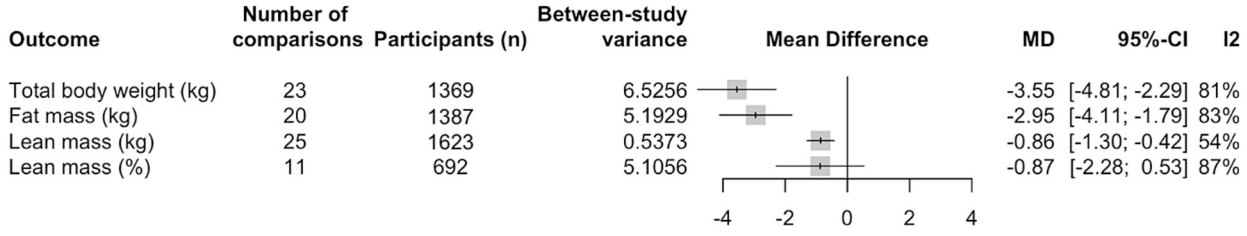


Fig. 1. Forest plots of pairwise meta-analyses on the effects of GLP-1RAs on total body weight (kg), fat mass (kg), lean mass (kg), and percentage change in lean mass (%) compared to placebo or active comparator.
Abbreviations: 95 %-CI, 95 % confidence interval; kg, kilograms; MD, mean difference.

3.3.1. *Total body weight*

The change in total body weight was evaluated in 17 RCTs, involving 1127 participants. Tirzepatide at 15 mg sc (subcutaneously) weekly resulted in a greater reduction in total body weight compared to placebo (MD -10.81 kg, 95 % CI [−13.55, −8.07], Fig. 3). The network plot and the league table of network estimates are presented in Fig. 4. Supplemental Fig. 15 presents network estimates for comparisons among all possible reference groups.

3.3.2. *Fat mass*

The change in fat mass was assessed across 14 RCTs encompassing 1145 participants. A weekly dose of 15 mg sc tirzepatide led to a significantly greater reduction in fat mass compared to placebo (MD −8.75 kg, 95 % CI [−11.33, −6.17], Fig. 3). The network plot and league table of network estimates are provided in Fig. 5. Additionally, Supplemental Fig. 16 depicts network estimates for all possible reference group comparisons.

3.3.3. *Lean mass*

Lean mass changes were evaluated across 19 RCTs involving 1381 participants. Among the GLP-1RAs examined, only semaglutide at 2.4 mg sc weekly, tirzepatide at 15 mg sc weekly, liraglutide at 3.0 mg sc daily, and semaglutide at 1.0 mg sc weekly resulted in a statistically significant reduction in lean mass relative to placebo (Fig. 4). Fig. 6 presents the network plot and league table of network estimates, while Supplemental Fig. 17 provides network estimates for all possible reference group comparisons.

3.3.4. *Ranking of GLP-1RAs*

Fig. 2 and Supplemental Figs. 18–20 present P-score values and

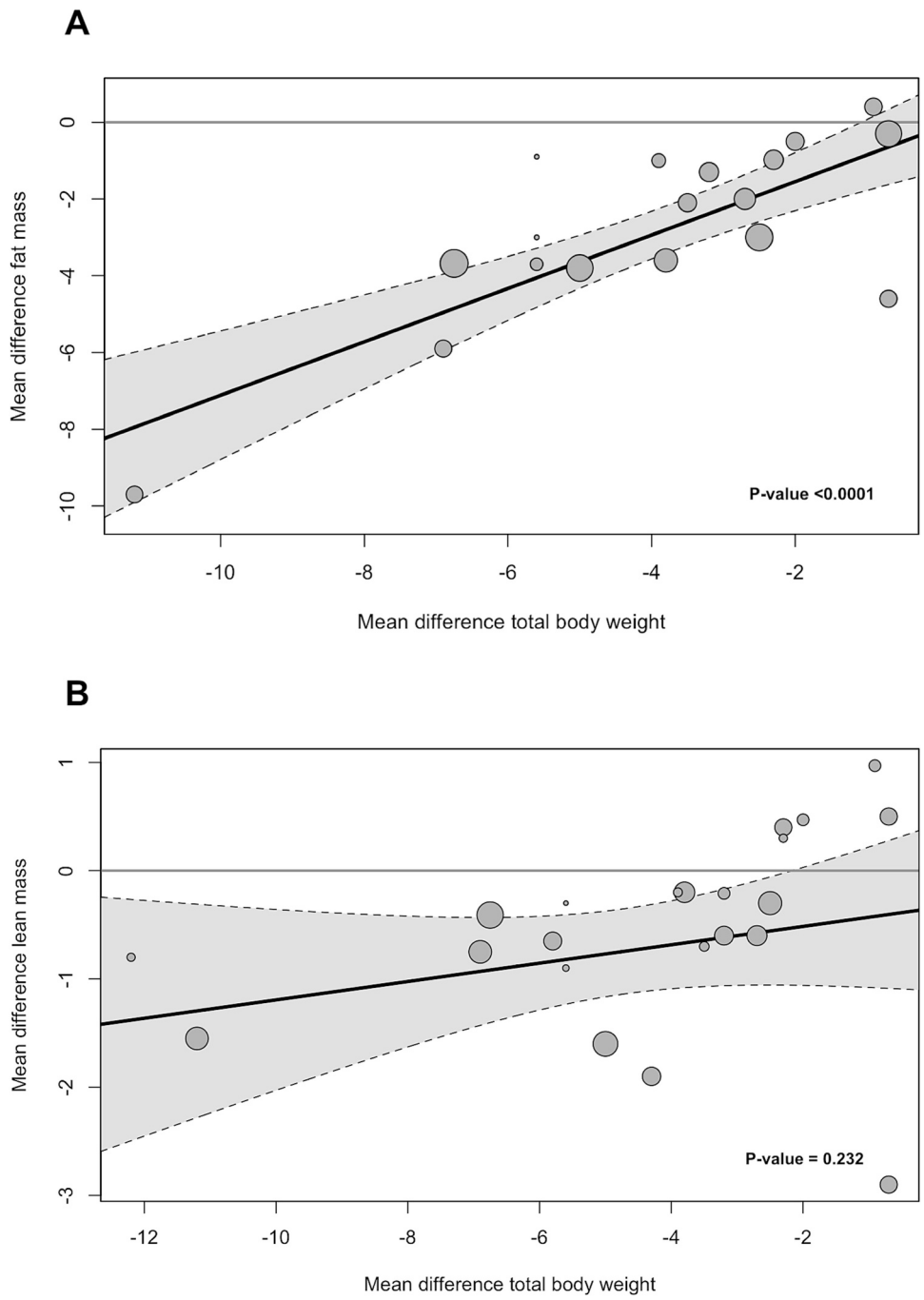


Fig. 2. Meta-regression analysis demonstrating the association of total body weight reduction with changes in fat mass (β = 0.7, 95 %-CI 0.45 to 0.94; A) and lean mass (β = 0.09, 95 %-CI -0.05 to 0.22; B).

ranking probabilities for the prespecified endpoints. At a weekly dose of 15 mg sc, tirzepatide was the most effective agent for reducing total body weight and fat mass yet ranked among the least effective in preserving lean mass. Among GLP-1RAs, only liraglutide—administered either at 1.8 mg sc daily or 3.0 mg sc weekly—achieved significant weight reduction without their impact on lean mass reaching statistical significance. Based on the partial order of treatments analysis, liraglutide at 3.0 mg sc weekly ranked as the best therapy for the combined endpoints of total body weight reduction and change in lean mass (Fig. 7).

3.3.5. Network consistency and heterogeneity

All fitted models demonstrated good convergence, and no statistical evidence of inconsistency was found across NMA estimates. No violations of transitivity assumptions were identified. The contribution of direct evidence to each network estimate is detailed in Supplemental Figs. 21–23, while comparisons of direct versus indirect evidence for each network are presented in Supplemental Figs. 24–26.

3.3.6. Small study effects and publication bias

No evidence of small-study effects (including publication bias) was detected, as indicated by symmetrical, contour-enhanced funnel plots and by results from Egger's tests, suggesting minimal risk of bias in the network pooled estimates.

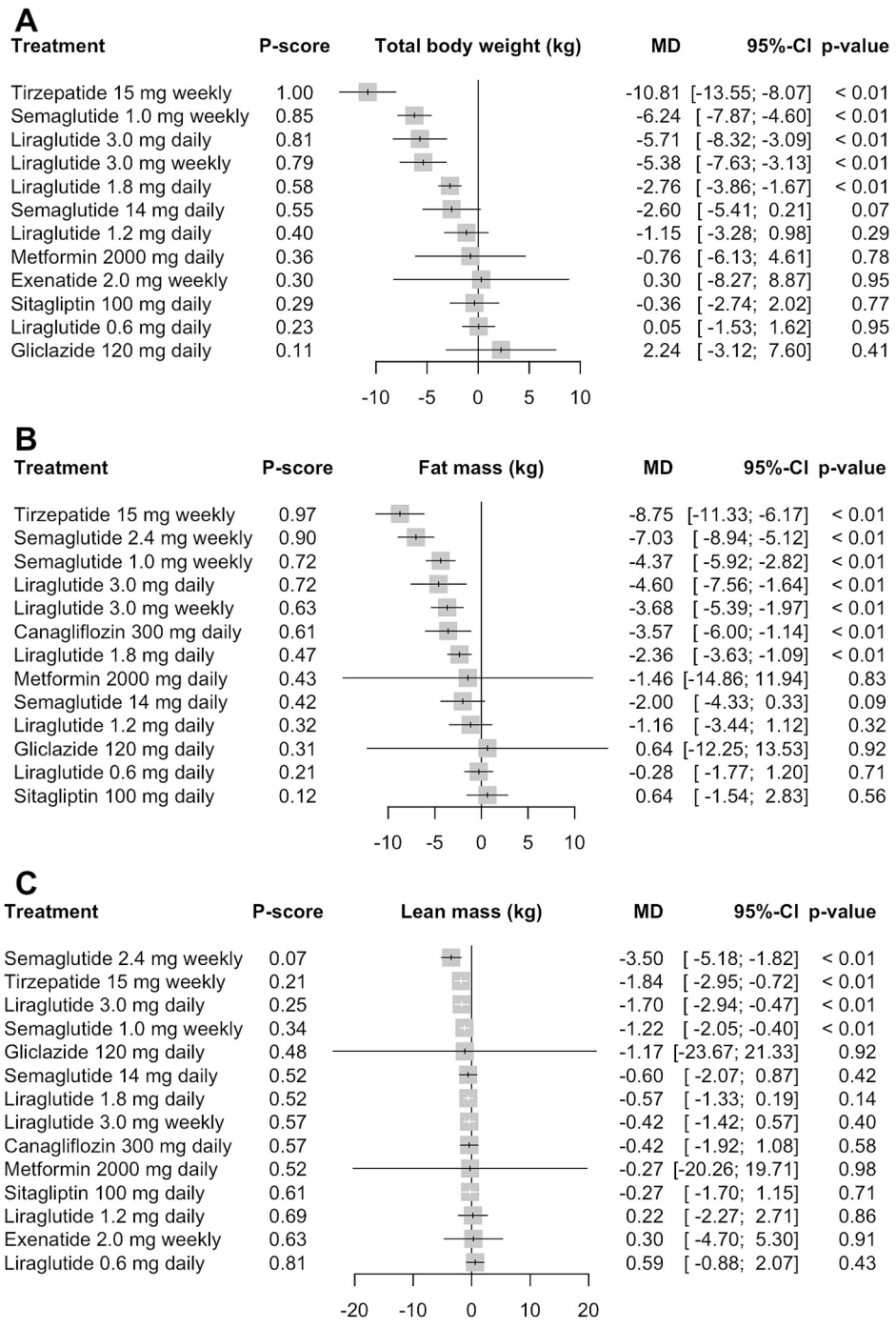


Fig. 3. Forest plots of random-effects network meta-analyses on change in total body weight (A), fat mass (B), and lean mass (C) compared to placebo. Abbreviations: 95 %-CI, 95 % confidence interval; kg, kilograms; MD, mean difference.

3.3.7. Sensitivity analysis

In the sensitivity analysis, which included exclusively individuals with baseline diabetes, tirzepatide at 15 mg sc weekly resulted in the most pronounced reduction in total body weight, fat mass, and lean mass. In contrast, the other GLP-1RAs had a non-significant effect on lean mass compared to placebo (Supplemental Fig. 30). The network estimates are presented in Supplemental Tables 5–7.

4. Discussion

This is the first meta-analysis to examine the impact of GLP-1RAs on body composition across their commercially available doses. Our findings indicate that GLP-1RAs produce a substantial absolute reduction in total body weight, fat mass, and lean mass, with lean mass contributing approximately 25 % to the total weight loss. However, these agents do not significantly alter the percentage of lean mass when assessed in relation to concomitant changes in total body weight. We were not able to analyze the impact on muscle function.

Mechanistic insights from preclinical studies show that liraglutide may protect against obesity-induced muscle atrophy by activating the silent information regulator type 1 pathway, which plays a pivotal role in enhancing insulin sensitivity, reducing lipid accumulation, and mitigating muscle degradation [43]. Additionally, liraglutide exerts anti-atrophy effects by suppressing the expression of muscle atrophy

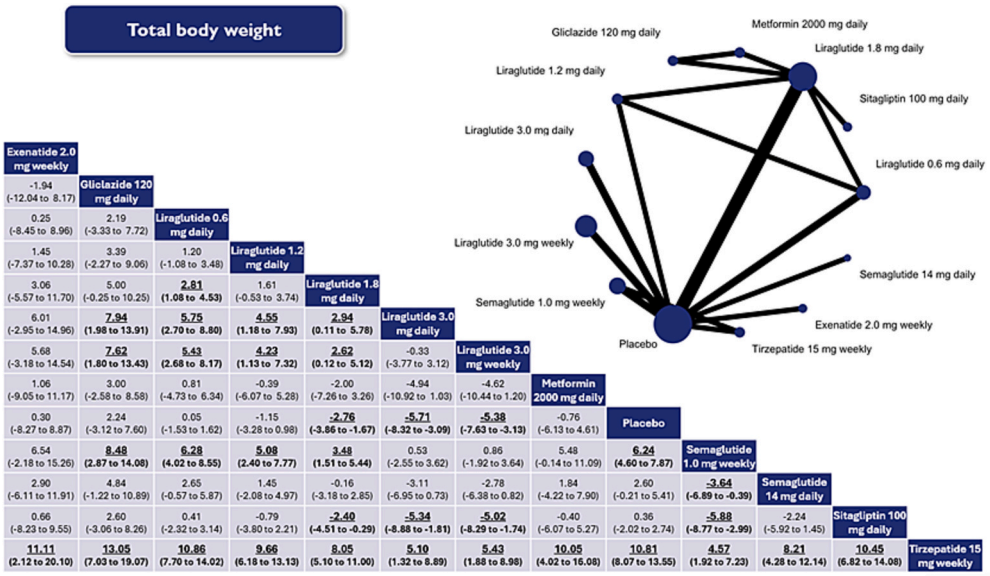


Fig. 4. Network plot (top right) displaying the efficacy of different GLP-1RAs and their doses in reducing total body weight (kg) in patients with diabetes or obesity. In the plot, each node represents a different therapy, while the edges indicate direct comparisons made between these strategies in the included RCTs. Line width is proportional to the number of trials comparing each pair of treatments. Node size is proportional to the number of randomized participants. The accompanying league table (bottom left) presents GLP-1RAs and co-agonists in alphabetical order, showing network estimates (MD, mean differences) and 95 % confidence intervals (CIs) for pairwise comparisons between the column- and row-defining treatments. MD <0 indicates a benefit for the column-defining therapy. Estimates with a two-tailed *p*-value <0.05 were considered statistically significant and are presented in bold.

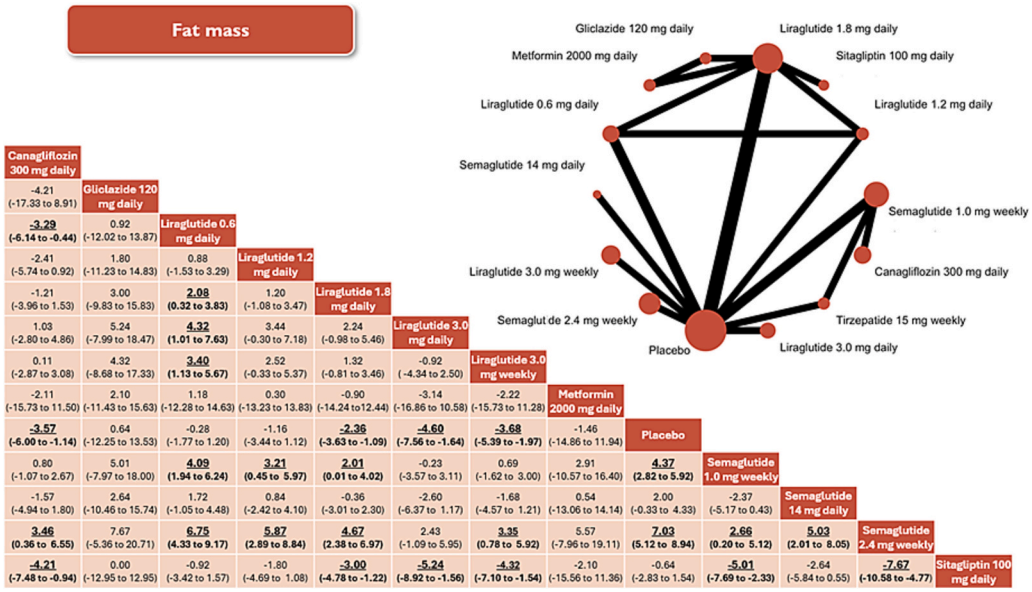
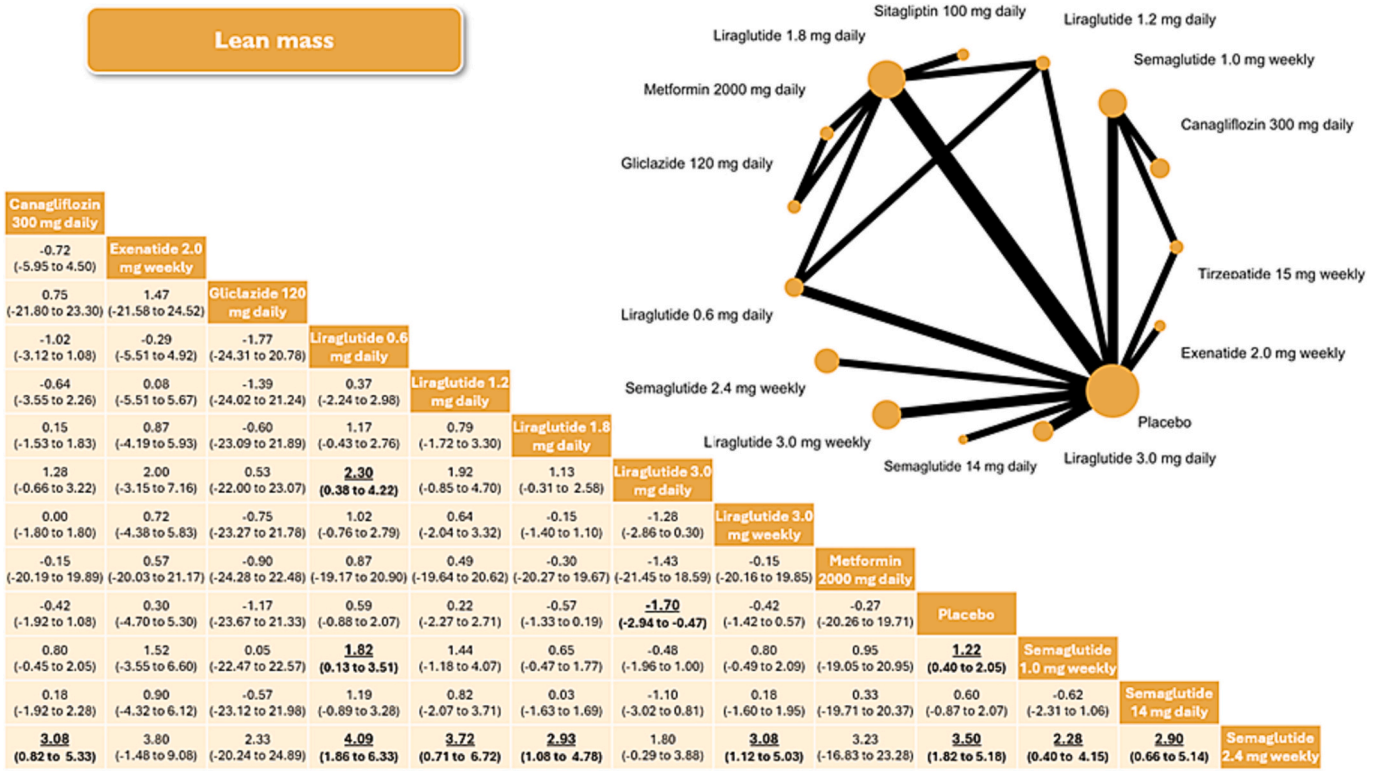


Fig. 5. Network plot and league table presenting estimates from the random-effects network meta-analysis for the association between different GLP-1RAs and the change in fat mass (kg).

genes (atrogenes) and promoting the expression of myogenic differentiation factors, thereby supporting muscle regeneration and structural integrity [44]. Its actions involve a complex network of cyclic adenosine monophosphate -dependent signaling pathways, including protein kinase A, phosphoinositide 3-kinase/protein kinase B, p38 mitogen-activated protein kinase, and extracellular signal-regulated kinase, which collectively enhance myogenesis and prevent structural muscle loss [44]. These mechanistic effects, along with the demonstrated reduction in muscle fat and improvement in adverse muscle composition observed in RCTs [45], need to be confirmed by future studies and need to be taken under consideration when considering medications leading to significant weight loss without disproportionally compromising lean muscle mass. Further randomized studies are needed to validate and expand these findings in terms of both muscle mass and muscle function.

Loss of muscle mass during significant weight reduction can have profound implications for metabolic health and future weight management [46]. Muscle tissue plays a central role in glucose utilization and energy expenditure; its reduction can exacerbate insulin resistance, hinder glycemic control, and lower metabolic rate, potentially increasing the risk of type 2 diabetes and cardiovascular diseases [46]. Additionally, diminished muscle mass may contribute to sarcopenic obesity, where a combination of low muscle and high fat mass exacerbates metabolic dysfunction [46]. The loss of muscle strength and function can also impair physical performance and quality of life.



Canagliflozin 300 mg daily	Exenatide 2.0 mg weekly	Gliclazide 120 mg daily	Liraglutide 0.6 mg daily	Liraglutide 1.2 mg daily	Liraglutide 1.8 mg daily	Liraglutide 3.0 mg daily	Liraglutide 3.0 mg weekly	Metformin 2000 mg daily	Placebo	Semaglutide 1.0 mg weekly	Semaglutide 14 mg daily	Semaglutide 2.4 mg weekly
-0.72 (-5.95 to 4.50)												
0.75 (-21.80 to 23.30)	1.47 (-21.58 to 24.52)											
-1.02 (-3.12 to 1.08)	-0.29 (-5.51 to 4.92)	-1.77 (-24.31 to 20.78)										
-0.64 (-3.55 to 2.26)	0.08 (-5.51 to 5.67)	-1.39 (-24.02 to 21.24)	0.37 (-2.24 to 2.98)									
0.15 (-1.53 to 1.83)	0.87 (-4.19 to 5.93)	-0.60 (-23.09 to 21.89)	1.17 (-0.43 to 2.76)	0.79 (-1.72 to 3.30)								
1.28 (-0.66 to 3.22)	2.00 (-3.15 to 7.16)	0.53 (-22.00 to 23.07)	**2.30 (0.38 to 4.22)**	1.92 (-0.85 to 4.70)	1.13 (-0.31 to 2.58)							
0.00 (-1.80 to 1.80)	0.72 (-4.38 to 5.83)	-0.75 (-23.27 to 21.78)	1.02 (-0.76 to 2.79)	0.64 (-2.04 to 3.32)	-0.15 (-1.40 to 1.10)	-1.28 (-2.86 to 0.30)						
-0.15 (-20.19 to 19.89)	0.57 (-20.03 to 21.17)	-0.90 (-24.28 to 22.48)	0.87 (-19.17 to 20.90)	0.49 (-19.64 to 20.62)	-0.30 (-20.27 to 19.67)	-1.43 (-21.45 to 18.59)	-0.15 (-20.16 to 19.85)					
-0.42 (-1.92 to 1.08)	0.30 (-4.70 to 5.30)	-1.17 (-23.67 to 21.33)	0.59 (-0.88 to 2.07)	0.22 (-2.27 to 2.71)	-0.57 (-1.33 to 0.19)	**-1.70 (-2.94 to -0.47)**	-0.42 (-1.42 to 0.57)	-0.27 (-20.26 to 19.71)				
0.80 (-0.45 to 2.05)	1.52 (-3.55 to 6.60)	0.05 (-22.47 to 22.57)	**1.82 (0.13 to 3.51)**	1.44 (-1.18 to 4.07)	0.65 (-0.47 to 1.77)	-0.48 (-1.96 to 1.00)	0.80 (-0.49 to 2.09)	0.95 (-19.05 to 20.95)	**1.22 (0.40 to 2.05)**			
0.18 (-1.92 to 2.28)	0.90 (-4.32 to 6.12)	-0.57 (-23.12 to 21.98)	1.19 (-0.89 to 3.28)	0.82 (-2.07 to 3.71)	0.03 (-1.63 to 1.69)	-1.10 (-3.02 to 0.81)	0.18 (-1.60 to 1.95)	0.33 (-19.71 to 20.37)	0.60 (-0.87 to 2.07)	-0.62 (-2.31 to 1.06)		
3.08 (0.82 to 5.33)	3.80 (-1.48 to 9.08)	2.33 (-20.24 to 24.89)	**4.09 (1.86 to 6.33)**	**3.72 (0.71 to 6.72)**	**2.93 (1.08 to 4.78)**	1.80 (-0.29 to 3.88)	**3.08 (1.12 to 5.03)**	3.23 (-16.83 to 23.28)	**3.50 (1.82 to 5.18)**	**2.28 (0.40 to 4.15)**	**2.90 (0.66 to 5.14)**	

Fig. 6. Network plot and league table presenting estimates from the random-effects network meta-analysis for the association between different GLP-1RAs and the change in lean mass (kg).

Moreover, reduced muscle mass is associated with weight regain due to its impact on basal metabolic rate, creating a cycle of weight loss and gain that further deteriorates body composition [46]. Strategies that focus on preserving or even enhancing lean mass, such as resistance training, adequate protein intake, and emerging pharmacotherapies targeting muscle preservation, are critical in mitigating these risks [46].

The use of GLP-1RAs is widely recognized for its ability to delay gastric emptying and enhance feelings of fullness, ultimately reducing energy intake [47]. These agonists increase satiety and lower caloric consumption, promoting weight loss that primarily targets fat mass; however, lean mass may also be affected, especially during substantial weight loss, where the preservation of lean mass becomes essential [28]. Reports of sporadic skeletal muscle loss among patients treated with GLP-1RAs have raised concerns about the risk of sarcopenia [48,49]. Sarcopenia, characterized by a decline in muscle mass and physical function, may develop as a primary condition or as a secondary outcome of other underlying disorders, potentially resulting in adverse prognosis for patients [50,51].

In the present meta-analysis, the users of GLP-1RAs had only a modest reduction in absolute lean mass, with no significant effect on the percentage of lean mass. The impact of these agents on skeletal muscle mass is complex and influenced by multiple factors. Although a decrease in lean mass has been observed among patients taking these agonists, emerging evidence suggests that GLP-1RAs may, in fact, enhance skeletal muscle function. Diabetes itself is an independent risk factor for skeletal muscle loss, and GLP-1RAs, by exerting antidiabetic effects, may mitigate glucotoxicity in skeletal muscle [52]. Additionally, these agonists may reduce ectopic fat deposits that compromise skeletal muscle quantity and quality [53]. Further, GLP-1RAs can enhance vascular blood flow and stimulate glucose uptake in skeletal muscle via the AMP-activated protein kinase pathway, thereby promoting muscle synthesis and inhibiting muscle degradation [54,55].

The application of GLP-1RAs in muscular disorders has been investigated using animal models. In rodent models, liraglutide and semaglutide demonstrated a reduction in obesity-induced muscle atrophy via the GLP-1/Sirtuin (SIRT1) pathway [43]. Additionally, multiple studies have examined the effects of dulaglutide on skeletal muscle atrophy and inflammation in rodents, proposing it as a potential treatment for muscle injury associated with sarcopenic obesity [56,57]. Recent preclinical studies also suggest that GLP-1RAs may positively influence muscle lipid distribution, muscle fiber content, and muscle fiber size [44,58]. Some studies further indicate that GLP1-RAs could facilitate skeletal muscle remodeling by altering muscle fiber type, composition, and energy substrate utilization [11]. However, it is important to note that these findings, primarily derived from preclinical models, require validation through studies in humans.

Advanced imaging techniques, such as MRI, offer a promising alternative to address the inherent variability observed in DXA-based studies and provide granular evidence of muscle composition changes associated with GLP-1RAs. In this regard, a subgroup analysis from the SURPASS-3 MRI study recently demonstrated that the dual incretin receptor agonist tirzepatide reduced muscle fat infiltration by 4.4 % in subjects with T2D compared to controls after 52 weeks of treatment [59]. Similarly, an MRI-based substudy by Pandey et al. evaluated muscle quality in 128 obese women without baseline diabetes. This study found that, compared to placebo, liraglutide reduced thigh muscle fat by 7.8 % from baseline and improved muscle composition, with a notable reduction in the incidence of adverse muscle composition—defined as high muscle fat and low muscle mass—relative to controls [45].

Future research should focus on assessing lean mass loss with greater precision, employing state-of-the-art techniques such as advanced imaging modalities (e.g., MRI, CT, and DXA with enhanced algorithms) to provide detailed insights into the composition of lean mass. While many current studies report aggregate lean mass changes, the inability to distinguish between muscle and bone loss limits our understanding of the metabolic and structural impacts of weight reduction. Addressing this limitation is particularly crucial for improving treatment strategies

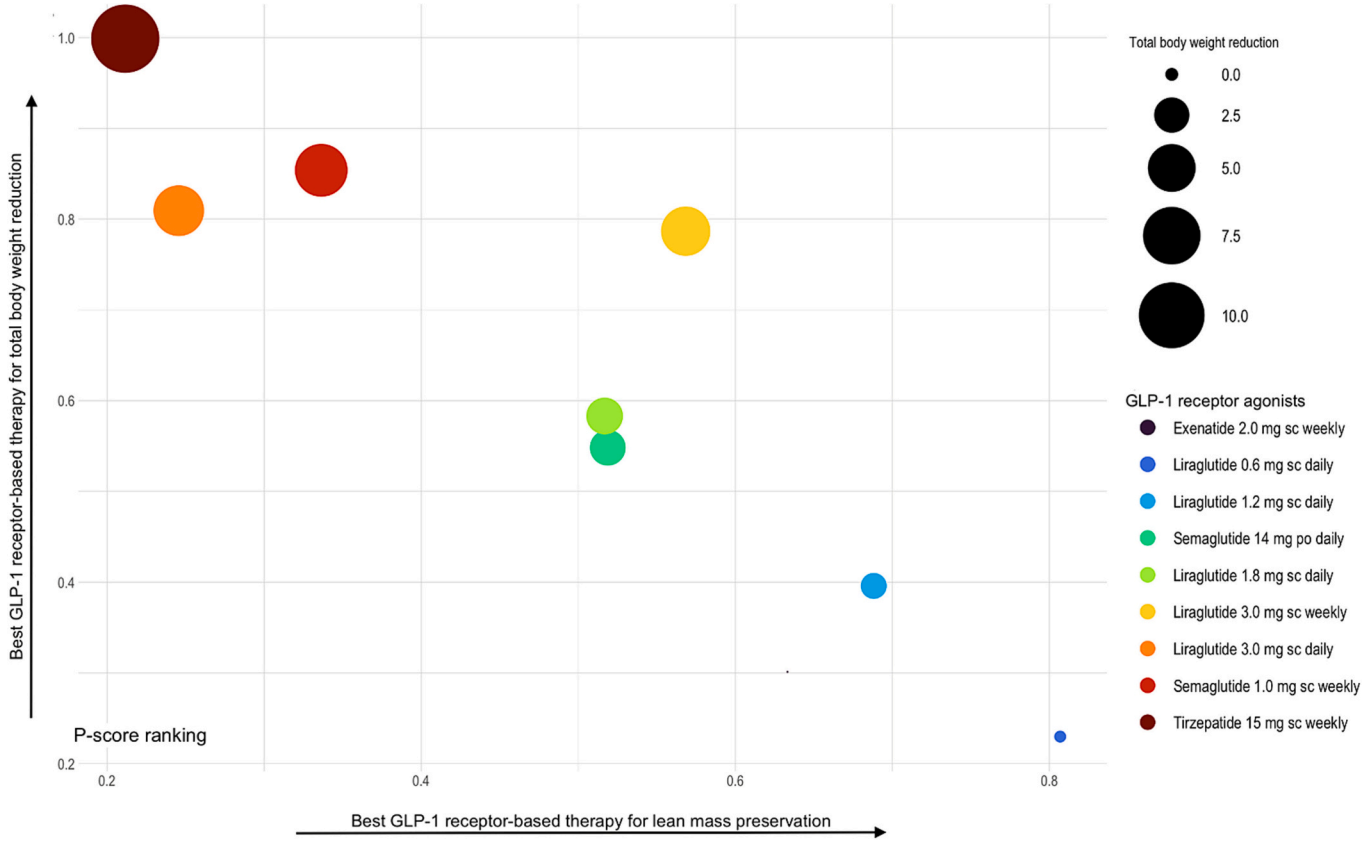


Fig. 7. Cluster ranking plot of P-scores for total body weight reduction and changes in lean mass. The plot is based on partial order of treatments analysis of P-scores. Treatments in the upper right corner are more effective (ie, increased total weight loss) and safer (ie, lower reduction in lean mass) compared with the other treatments.
Abbreviations: po, per os; sc, subcutaneously.

that preserve both skeletal muscle and bone integrity during weight loss. Accurate differentiation between muscle and bone loss would enable researchers to identify targeted interventions, to mitigate muscle atrophy and bone mineral density decline, respectively.

This differentiation is especially critical for specific populations, such as postmenopausal women, who are already at an elevated risk of osteoporosis and fractures due to hormonal changes that accelerate bone loss [60]. In this group, substantial bone loss during weight reduction could exacerbate fracture risk, undermining the benefits of obesity treatments. Similarly, older adults and individuals with sarcopenia or sarcopenic obesity may experience compounded functional decline if both muscle and bone mass are significantly reduced. Future studies should therefore not only prioritize the detailed evaluation of lean mass loss and muscle function but also explore the interplay between muscle and bone health in these high-risk populations. This nuanced understanding will be key to optimizing treatment protocols and ensuring that weight-loss strategies do not compromise long-term musculoskeletal health.

Emerging myostatin and activin inhibitors represent a promising new class of medications that could complement GLP-1RAs to mitigate lean muscle loss during weight reduction [61,62]. By targeting pathways involved in muscle degradation, these agents have the potential to enhance "quality weight loss," focusing on fat reduction while preserving muscle and bone mass, thereby improving overall metabolic and physical health outcomes [61,62]. However, more research is needed to explore their efficacy, safety, and long-term impact, particularly when used alongside GLP-1RAs. Future studies should aim to validate these combinations across diverse populations and clinical settings, ensuring their benefits are broadly applicable.

4.1. *Clinical implications and future research*

Sarcopenia, characterized by the progressive decline in muscle mass and strength, is among the most prevalent conditions associated with aging, affecting over 10 % of the global population, or approximately 70.3 million individuals worldwide [63]. Individuals aged 65 years and older with sarcopenia are at increased risk of disability, reduced quality of life, and premature mortality, imposing significant personal and socioeconomic challenges [64]. Sarcopenic obesity, a clinical condition defined by excess adiposity combined with reduced skeletal muscle mass and/or function, has gained widespread recognition [65]. It is estimated that approximately 11 % of older adults globally are affected by sarcopenic obesity, with prevalence rates rising sharply beyond the age of 70 [66]. This condition is a critical prognostic indicator for disability and survival, significantly elevating the risk of obesity- and age-associated diseases [67,68]. Importantly, sarcopenic obesity is highly prevalent among individuals with T2D and is significantly associated with severe adverse outcomes, thereby further complicating the prognosis of these patients [69]. Consequently, achieving effective weight reduction while simultaneously preserving lean mass has emerged as a critical yet challenging objective for this vulnerable population.

To this end, determining the optimal dose of therapy with GLP-1RAs to balance weight loss, fat mass reduction, and lean mass preservation is of paramount importance. To date, no RCT has directly compared the various doses of these commercially available agents, leaving the optimal dosing strategy unclear. Notably, the present meta-analysis bridges this critical gap in knowledge. Although the available data appear limited, an emerging pattern suggests that the greater the efficacy of GLP-1RAs in inducing weight loss, the greater the associated loss of muscle mass. This phenomenon appears to be a class effect; however,

dual GLP-1RAs, along with semaglutide, seem to result in more pronounced weight loss compared to other agents. A recent study involving individuals with obesity found that tirzepatide treatment alone does not impair physical function; however, it is less effective compared to a combination of resistance training and aerobic exercise [70] an area that needs to be studied in more detail in the future. Therefore, treatment with GLP-1RAs could be complemented by the implementation of high protein diets and exercise programs to minimize muscle mass reduction and enhance physical status and cardiorespiratory fitness in individuals across the spectrum of cardio-renal-metabolic diseases [25,71]. This approach is expected to be most effective among younger individuals and remains to be studied in the future.

Finally, studies assessing the correlation between lean mass changes after GLP-1RAs treatment and changes in physical function indices are eagerly awaited [72]. To date, similar to detailed studies on the magnitude of weight loss, solid evidence on its functional significance is lacking, aside from findings from small studies in specific populations. For example, a secondary analysis from the SLIM LIVER study [73], which involved individuals with HIV receiving low-dose semaglutide for metabolic dysfunction-associated steatotic liver disorder, showed decreased psoas muscle volume but no significant change in physical function, suggesting that functionality was maintained. Similarly, another study involving patients with T2D reported that treatment with semaglutide preserved hand grip strength over a 6-month follow-up period [74].

4.2. Strengths and limitations

Despite the rigorous execution of the present study, it is essential to acknowledge several potential limitations. Firstly, variations in methodologies for assessing body composition were evident across studies, ranging from DXA to MRI and CT. While lean mass was analyzed due to its consistent reporting in the primary studies compared to other indices of non-fat mass, analyses of its individual components were not conducted due to the unavailability of such data. Secondly, while sarcopenia encompasses not only a reduction in lean mass but also a decline in muscle function, this latter aspect was not evaluated due to insufficient data. Consequently, further randomized studies are needed to examine the clinical significance of our findings and their implications for the functional status of these patients. Thirdly, certain studies may have been limited by small sample sizes, and the inclusion of individuals with diabetes and/or overweight/obesity may restrict the generalizability of the findings to broader populations. Therefore, further randomized studies are needed to determine whether the non-significant effect on lean mass is genuine or a result of insufficient statistical power. Regarding liraglutide, which ranked as the best treatment in the cluster ranking analysis, it should be noted that it was the most studied GLP-1RA among the included RCTs, potentially limiting the statistical concerns related to its non-significant effect on lean mass. Additionally, lifestyle factors, dietary habits, and concurrent medical conditions that could influence the effects of GLP-1RAs were not fully accounted for, possibly introducing biases into the results. Given the median duration of 6 months across the available studies, the extended, long-term effects of GLP-1RAs remain insufficiently elucidated and warrant comprehensive investigation in future RCTs. Lastly, due to the scarcity of available evidence, no comparisons could be made between GLP-1RAs and other approved weight-lowering medications, such as orlistat, phentermine, naltrexone/bupropion, and topiramate.

5. Conclusions

GLP-1RAs result in substantial reductions in total body weight, fat mass, and lean mass. Approximately 25 % of the total weight loss is attributed to lean mass, with no significant effect on the percentage of lean mass relative to total body weight. Among the different doses, only liraglutide at 1.8 mg sc daily or 3.0 mg sc weekly showed a significant reduction in total body weight without significantly affecting lean mass. Future RCTs should further assess the long-term robustness of these findings and explore their impact on prognosis and functional capacity in this patient population.

Protocol

The protocol for this study is available at https://osf.io/su5hc/.

CRediT authorship contribution statement

Paschalis Karakasis: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **Dimitrios Patoulias:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Nikolaos Fragakis:** Writing – review & editing. **Christos S. Mantzoros:** Writing – review & editing, Supervision, Conceptualization.

Consent

Not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors for its design or conduction.

Declaration of competing interest

CSM reports grants through his institution from Merck, Esperion, Abbott, Massachusetts Life Sciences Center and Boehringer Ingelheim, has received personal consulting fees and support with research reagents from Ansh Inc., collaborative research support from LabCorp Inc., reports personal consulting fees from Olympus, Genfit, Lumos, Novo Nordisk, Amgen, Corcept, Intercept, 89 Bio, Madrigal, Aligos, Esperion and Regeneron, reports educational activity meals through his institution or national conferences from Esperion, Merck, Boehringer Ingelheim and travel support and fees from UpToDate, TMIOA, Elsevier, and the Cardio Metabolic Health Conference. None is related to this paper. CSM recused himself from handling this paper. The rest authors declare no conflicts of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2024.156113.

Data availability

The data generated in this research will be shared on reasonable request to the corresponding author.

References

[1] Veronese N, Pizzol D, Demurtas J, Soysal P, Smith L, Sieber C, et al. Association between sarcopenia and diabetes: a systematic review and meta-analysis of observational studies. Eur Geriatr Med 2019;10:685–96. https://doi.org/10.1007/s41999-019-00216-x.

[2] Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. Nat Rev Endocrinol 2021;17:534–48. https://doi.org/10.1038/s41574-021-00512-2.

[3] Song E, Hwang SY, Park MJ, Jang A, Kim KJ, Yu JH, et al. Additive impact of diabetes and sarcopenia on all-cause and cardiovascular mortality: a longitudinal

nationwide population-based study. Metabolism 2023;148:155678. https://doi.org/10.1016/j.metabol.2023.155678.
[4] Liu M, Zhang Z, Zhou C, Ye Z, He P, Zhang Y, et al. Predicted fat mass and lean mass in relation to all-cause and cause-specific mortality. J Cachexia Sarcopenia Muscle 2022;13:1064–75. https://doi.org/10.1002/jcsm.12921.
[5] Jendle J, Nauck MA, Matthews DR, Frid A, Hermansen K, Düring M, et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab 2009;11:1163–72. https://doi.org/10.1111/j.1463-1326.2009.01158.x.
[6] Linge J, Birkenfeld AL, Neeland IJ. Muscle mass and glucagon-like Peptide-1 receptor agonists: adaptive or maladaptive response to weight loss? Circulation 2024;150:1288–98. https://doi.org/10.1161/CIRCULATIONAHA.124.067676.
[7] Pan R, Zhang Y, Wang R, Xu Y, Ji H, Zhao Y. Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. PLoS One 2022;17:e0279889. https://doi.org/10.1371/journal.pone.0279889.
[8] Xia C, Han Y, Yin C, Geng R, Liu Z, Du Y, et al. Relationship between sodium-glucose cotransporter-2 inhibitors and muscle atrophy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023;14:1220516. https://doi.org/10.3389/fendo.2023.1220516.
[9] Feng W-H, Bi Y, Li P, Yin T-T, Gao C-X, Shen S-M, et al. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial. J Diabetes Investig 2019;10:399–407. https://doi.org/10.1111/jdi.12888.
[10] Perna S, Guido D, Bologna C, Solerte SB, Guerriero F, Isu A, et al. Liraglutide and obesity in elderly: efficacy in fat loss and safety in order to prevent sarcopenia. A perspective case series study. Aging Clin Exp Res 2016;28:1251–7. https://doi.org/10.1007/s40520-015-0525-y.
[11] Wu L, Zhou M, Li T, Dong N, Yi L, Zhang Q, et al. GLP-1 regulates exercise endurance and skeletal muscle remodeling via GLP-1R/AMPK pathway. Biochim Biophys Acta, Mol Cell Res 2022;1869:119300. https://doi.org/10.1016/j.bbamcr.2022.119300.
[12] Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training n.d. https://training.cochrane.org/handbook/current (accessed January 17, 2023).
[13] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, The PRISMA, et al. Statement: an updated guideline for reporting systematic reviews. BMJ 2020;2021:372. https://doi.org/10.1136/BMJ.N71.
[14] Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777–84. https://doi.org/10.7326/M14-2385.
[15] Haddaway NR, Grainger MJ, Gray CT. citationchaser: an R package and Shiny app for forward and backward citations chasing in academic searching. 2021. https://doi.org/10.5281/ZENODO.4543513.
[16] Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based Practice Center: Abstrackr. In: IHI'12 - proc 2nd ACM SIGHIT int heal informatics symp; 2012. p. 819–23. https://doi.org/10.1145/2110363.2110464.
[17] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019:366. https://doi.org/10.1136/BMJ.L4898.
[18] Chapter 10: Analysing data and undertaking meta-analyses | Cochrane Training n.d. https://training.cochrane.org/handbook/current/chapter-10#section-10-10 (accessed January 8, 2024).
[19] Chapter 11: Undertaking network meta-analyses | Cochrane Training n.d. https://training.cochrane.org/handbook/current/chapter-11 (accessed February 9, 2024).
[20] Seitidis G, Nikolakopoulos S, Hennessy E, Tanner-Smith E, Mavridis D. Network meta-analysis techniques for synthesizing prevention science evidence. Prev Sci 2022;23:415–24. https://doi.org/10.1007/S11121-021-01289-6/FIGURES/2.
[21] Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98–110. https://doi.org/10.1002/JRSM.1044.
[22] Rücker G, Schwarzer G. Resolve conflicting rankings of outcomes in network meta-analysis: partial ordering of treatments. Res Synth Methods 2017;8:526–36. https://doi.org/10.1002/jrsm.1270.
[23] Dubé M-C, D'Amours M, Weisnagel SJ. Beyond glycaemic control: a cross-over, double-blinded, 24-week intervention with liraglutide in type 1 diabetes. Diabetes Obes Metab 2018;20:178–84. https://doi.org/10.1111/dom.13063.
[24] Kadouh H, Chedid V, Halawi H, Burton DD, Clark MM, Khemani D, et al. GLP-1 analog modulates appetite, taste preference, gut hormones, and regional body fat stores in adults with obesity. J Clin Endocrinol Metab 2020;105:1552–63. https://doi.org/10.1210/clinem/dgz140.
[25] Lundgren JR, Janus C, Jensen SBK, Juhl CR, Olsen LM, Christensen RM, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med 2021;384:1719–30. https://doi.org/10.1056/NEJMoa2028198.
[26] Silver HJ, Olson D, Mayfield D, Wright P, Nian H, Mashayekhi M, et al. Effect of the glucagon-like peptide-1 receptor agonist liraglutide, compared to caloric restriction, on appetite, dietary intake, body fat distribution and cardiometabolic biomarkers: a randomized trial in adults with obesity and prediabetes. Diabetes Obes Metab 2023;25:2340–50. https://doi.org/10.1111/dom.15113.
[27] Grannell A, Martin WP, Dehestani B, Al-Najim W, Murphy JC, le Roux CW. Liraglutide does not adversely impact fat-free mass loss. Obesity (Silver Spring) 2021;29:529–34. https://doi.org/10.1002/oby.23098.
[28] Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19:1242–51. https://doi.org/10.1111/dom.12932.
[29] Gibbons C, Blundell J, Tetens Hoff S, Dahl K, Bauer R, Baekdal T. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. Diabetes Obes Metab 2021;23:581–8. https://doi.org/10.1111/dom.14255.
[30] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989–1002. https://doi.org/10.1056/NEJMoa2032183.
[31] McCrimmon RJ, Catarig A-M, Frias JP, Lausvig NL, le Roux CW, Thielke D, et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia 2020;63:473–85. https://doi.org/10.1007/s00125-019-05065-8.
[32] Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, et al. Tirzepatide reduces appetite, energy intake, and fat mass in people with type 2 diabetes. Diabetes Care 2023;46:998–1004. https://doi.org/10.2337/dc22-1710.
[33] Bunck MC, Diamant M, Eliasson B, Cornér A, Shaginian RM, Heine RJ, et al. Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition. Diabetes Care 2010;33:1734–7. https://doi.org/10.2337/dc09-2361.
[34] Ishøy PL, Knop FK, Broberg BV, Bak N, Andersen UB, Jørgensen NR, et al. Effect of GLP-1 receptor agonist treatment on body weight in obese antipsychotic-treated patients with schizophrenia: a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:162–71. https://doi.org/10.1111/dom.12795.
[35] Yin T-T, Bi Y, Li P, Shen S-M, Wang W-M, Jiang C, et al. Effects of exenatide versus insulin glargine on body composition in overweight and obese T2DM patients: a randomized controlled trial. Nutr Metab (Lond) 2018;15:67. https://doi.org/10.1186/s12986-018-0295-6.
[36] Neeland IJ, Marso SP, Ayers CR, Lewis B, Oslica R, Francis W, et al. Effects of liraglutide on visceral and ectopic fat in adults with overweight and obesity at high cardiovascular risk: a randomised, double-blind, placebo-controlled, clinical trial. Lancet Diabetes Endocrinol 2021;9:595–605. https://doi.org/10.1016/S2213-8587(21)00179-0.
[37] van Eyk HJ, Paiman EHM, Bizino MB, IJzermans SL, Kleiburg F, Boers TGW, et al. Liraglutide decreases energy expenditure and does not affect the fat fraction of supraclavicular brown adipose tissue in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2020;30:616–24. doi:https://doi.org/10.1016/j.numecd.2019.12.005.
[38] Mensberg P, Nyby S, Jørgensen PG, Storgaard H, Jensen MT, Sivertsen J, et al. Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. Diabetes Obes Metab 2017;19:172–80. https://doi.org/10.1111/dom.12797.
[39] Ghanim H, Batra M, Green K, Abuaysheh S, Hejna J, Makdissi A, et al. Liraglutide treatment in overweight and obese patients with type 1 diabetes: a 26-week randomized controlled trial; mechanisms of weight loss. Diabetes Obes Metab 2020;22:1742–52. https://doi.org/10.1111/dom.14090.
[40] Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean MEJ, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes 2012;36:843–54. https://doi.org/10.1038/ijo.2011.158.
[41] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16. https://doi.org/10.1056/NEJMoa2206038.
[42] Harder H, Nielsen L, Tu DTT, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 2004;27:1915–21. https://doi.org/10.2337/diacare.27.8.1915.
[43] Xiang J, Qin L, Zhong J, Xia N, Liang Y. GLP-1RA liraglutide and semaglutide improves obesity-induced muscle atrophy via SIRT1 pathway. Diabetes Metab Syndr Obes 2023;16:2433–46. https://doi.org/10.2147/DMSO.S425642.
[44] Gurjar AA, Kushwaha S, Chattopadhyay S, Das N, Pal S, China SP, et al. Long acting GLP-1 analog liraglutide ameliorates skeletal muscle atrophy in rodents. Metabolism 2020;103:154044. https://doi.org/10.1016/j.metabol.2019.154044.
[45] Pandey A, Patel KV, Segar MW, Ayers C, Linge J, Leinhard OD, et al. Effect of liraglutide on thigh muscle fat and muscle composition in adults with overweight or obesity: results from a randomized clinical trial. J Cachexia Sarcopenia Muscle 2024;15:1072–83. https://doi.org/10.1002/jcsm.13445.
[46] Stefanakis K, Kokkorakis M, Mantzoros CS. The impact of weight loss on fat-free mass, muscle, bone and hematopoiesis health: implications for emerging pharmacotherapies aiming at fat reduction and lean mass preservation. Metabolism 2024;161:156057. https://doi.org/10.1016/j.metabol.2024.156057.
[47] Yao H, Zhang A, Li D, Wu Y, Wang C-Z, Wan J-Y, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ 2024;384:e076410. https://doi.org/10.1136/bmj-2023-076410.
[48] Prado CM, Phillips SM, Gonzalez MC, Heymsfield SB. Muscle matters: the effects of medically induced weight loss on skeletal muscle. Lancet Diabetes Endocrinol 2024;12:785–7. https://doi.org/10.1016/S2213-8587(24)00272-9.
[49] Huang H-H, Wang Y-J, Jiang H-Y, Yu HW, Chen Y-Q, Chiou A, et al. Sarcopenia-related changes in serum GLP-1 level affect myogenic differentiation. J Cachexia Sarcopenia Muscle 2024;15:1708–21. https://doi.org/10.1002/jcsm.13524.

[50] Srikanthan P, Karlamangla AS. Muscle mass index as a predictor of longevity in older adults. Am J Med 2014;127:547–53. https://doi.org/10.1016/j.amjmed.2014.02.007.
[51] Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet (London, England) 2019;393:2636–46. https://doi.org/10.1016/S0140-6736(19)31138-9.
[52] Alabadi B, Civera M, De la Rosa A, Martinez-Hervas S, Gomez-Cabrera MC, Real JT. Low muscle mass is associated with poorer glycemic control and higher oxidative stress in older patients with type 2 diabetes. Nutrients 2023:15. https://doi.org/10.3390/nu15143167.
[53] Akoumianakis I, Zagaliotis A, Konstantaraki M, Filippatos TD. GLP-1 analogs and regional adiposity: a systematic review and meta-analysis. Obes Rev an Off J Int Assoc Study Obes 2023;24:e13574. https://doi.org/10.1111/obr.13574.
[54] Andreozzi F, Raciti GA, Nigro C, Mannino GC, Procopio T, Davalli AM, et al. The GLP-1 receptor agonists exenatide and liraglutide activate glucose transport by an AMPK-dependent mechanism. J Transl Med 2016;14:229. https://doi.org/10.1186/s12967-016-0985-7.
[55] Abdulla H, Phillips B, Smith K, Wilkinson D, Atherton PJ, Idris I. Physiological mechanisms of action of incretin and insulin in regulating skeletal muscle metabolism. Curr Diabetes Rev 2014;10:327–35. https://doi.org/10.2174/1573399810666141017153749.
[56] Deng F, Wu W, Fan X, Zhong X, Wang N, Wang Y, et al. Dulaglutide protects mice against diabetic sarcopenia-mediated muscle injury by inhibiting inflammation and regulating the differentiation of myoblasts. Int J Endocrinol 2023;2023:9926462. https://doi.org/10.1155/2023/9926462.
[57] Khin PP, Hong Y, Yeon M, Lee DH, Lee JH, Jun H-S. Dulaglutide improves muscle function by attenuating inflammation through OPA-1-TLR-9 signaling in aged mice. Aging (Albany NY) 2021;13:21962–74. https://doi.org/10.18632/aging.203546.
[58] Xu F, Cao H, Chen Z, Gu H, Guo W, Lin B, et al. Short-term GLP-1 receptor agonist exenatide ameliorates intramyocellular lipid deposition without weight loss in ob/ob mice. Int J Obes 2020;44:937–47. https://doi.org/10.1038/s41366-019-0513-y.
[59] Tirzepatide reduces muscle fat infiltration relative to insulin deglucec in people with type 2 diabetes (SURPASS-3 MRI) - Media Centre | EASD n.d. https://www.easd.org/media-centre/home.html#!resources/tirzepatide-reduces-muscle-fat-infiltration-relative-to-insulin-deglucec-in-people-with-type-2-diabetes-surpass-3-mri-4365ef0b-0df4-4ee2-8da6-1a382d23899e (accessed November 15, 2024).
[60] Walker MD, Shane E. Postmenopausal osteoporosis. N Engl J Med 2023;389:1979–91. https://doi.org/10.1056/NEJMcp2307353.
[61] Rodgers BD, Ward CW. Myostatin/activin receptor ligands in muscle and the development status of attenuating drugs. Endocr Rev 2022;43:329–65. https://doi.org/10.1210/endrev/bnab030.
[62] Lee S-J, Bhasin S, Klickstein L, Krishnan V, Rooks D. Challenges and future prospects of targeting myostatin/activin a signaling to treat diseases of muscle loss and metabolic dysfunction. J Gerontol A Biol Sci Med Sci 2023;78:32–7. https://doi.org/10.1093/gerona/glad033.
[63] Jaacks LM, Vandevijvere S, Pan A, McGowan CJ, Wallace C, Imamura F, et al. The obesity transition: stages of the global epidemic. Lancet Diabetes Endocrinol 2019;7:231–40. https://doi.org/10.1016/S2213-8587(19)30026-9.
[64] Axelrod CL, Dantas WS, Kirwan JP. Sarcopenic obesity: emerging mechanisms and therapeutic potential. Metabolism 2023;146:155639. https://doi.org/10.1016/j.metabol.2023.155639.
[65] Gortan Cappellari G, Guillet C, Poggiogalle E, Ballesteros Pomar MD, Batsis JA, Boirie Y, et al. Sarcopenic obesity research perspectives outlined by the sarcopenic obesity global leadership initiative (SOGLI) - proceedings from the SOGLI consortium meeting in Rome November 2022. Clin Nutr 2023;42:687–99. https://doi.org/10.1016/j.clnu.2023.02.018.
[66] Gao Q, Mei F, Shang Y, Hu K, Chen F, Zhao L, et al. Global prevalence of sarcopenic obesity in older adults: a systematic review and meta-analysis. Clin Nutr 2021;40:4633–41. https://doi.org/10.1016/j.clnu.2021.06.009.
[67] Benz E, Pinel A, Guillet C, Capel F, Pereira B, De Antonio M, et al. Sarcopenia and sarcopenic obesity and mortality among older people. JAMA Netw Open 2024;7:e243604. https://doi.org/10.1001/jamanetworkopen.2024.3604.
[68] Roh E, Choi KM. Health consequences of Sarcopenic obesity: a narrative review. Front Endocrinol (Lausanne) 2020;11:332. https://doi.org/10.3389/fendo.2020.00332.
[69] Zhou Y-Y, Wang J-F, Yao Q, Jian Q-F, Luo Z-P. Prevalence of sarcopenic obesity in patients with diabetes and adverse outcomes: a systematic review and meta-analysis. Clin Nutr ESPEN 2023;58:128–35. https://doi.org/10.1016/j.clnesp.2023.09.920.
[70] Bagherzadeh-Rahmani B, Marzetti E, Karami E, Campbell BI, Fakourian A, Haghighi AH, et al. Tirzepatide and exercise training in obesity. Clin Hemorheol Microcirc 2024;87:465–80. https://doi.org/10.3233/CH-242134.
[71] Sandsdal RM, Juhl CR, Jensen SBK, Lundgren JR, Janus C, Blond MB, et al. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. Cardiovasc Diabetol 2023;22:41. https://doi.org/10.1186/s12933-023-01765-z.
[72] Cortes TM, Vasquez L, Serra MC, Robbins R, Stepanenko A, Brown K, et al. Effect of semaglutide on physical function, body composition, and biomarkers of aging in older adults with overweight and insulin resistance: protocol for an open-labeled randomized controlled trial. JMIR Res Protoc 2024;13:e62667. https://doi.org/10.2196/62667.
[73] Ditzenberger GL, Lake JE, Kitch DW, Kantor A, Muthupillai R, Moser C, et al. Effects of semaglutide on muscle structure and function in the SLIM LIVER study. Clin Infect Dis an Off Publ Infect Dis Soc Am 2024. https://doi.org/10.1093/cid/ciae384.
[74] Volpe S, Lisco G, Racaniello D, Fanelli M, Colaianni V, Vozza A, et al. Once-weekly semaglutide induces an early improvement in body composition in patients with type 2 diabetes: a 26-week prospective Real-life study. Nutrients 2022:14. https://doi.org/10.3390/nu14122414.