INPLASY

INPLASY2025110027

doi: 10.37766/inplasy2025.11.0027

Received: 10 November 2025

Published: 11 November 2025

Corresponding author:
Stuart Phillips

phillis@mcmaster.ca

Author Affiliation:
McMaster University.

GLP-1 Receptor Agonists and Skeletal Muscle Health: Overview of Reviews Examining Muscle Mass, Strength, and Physical Function in Adults with Obesity

Chen, KV; Lowisz, CV; Nunes, EA; Phillips, SM.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025110027

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 November 2025 and was last updated on 11 November 2025.

INTRODUCTION

Review question / Objective Does GLP-1RA induced weight loss affect body composition, skeletal muscle mass, strength, and physical function in adults with overweight/obesity?

Rationale We do not fully understand how Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) induced weight loss affects skeletal muscle mass. Accumulating data shows that use of GLP-1RAs in the treatment of overweight/obesity and Type 2 Diabetes Mellitus causes significant lean mass loss, however the degree to how much of this is skeletal muscle is highly debated. There is mixed evidence suggesting that individuals receiving GLP-1RA therapy experience fat free mass (FFM) losses beyond what is generally expected with non-pharmaceutical weight loss therapy (i.e. 25% FFM). Large clinical trials have assessed weight and body composition changes in response to GLP-1RA therapy, with estimated lean mass reductions ranging from approximately 15% up to 60% as a proportion of total weight loss. Importantly, skeletal muscle comprises only a portion of Dual-Energy X-ray Absorptiometry (DEXA)-derived lean mass. However, there are limited trials that have used gold standard measures of body composition (i.e. magnetic resonance imaging) to quantify muscle or assess muscle quality (i.e. myosteatosis). The highly variable, albeit significant lean mass losses reported have been argued to be in line with the magnitude of weight loss that is achieved rather than an independent effect of the drug, although this has not yet been tested. This has led to concerns about unintended effects of GLP-1RAs on skeletal muscle mass, strength, and physical function, particularly in older adults who are already at risk of age-related muscle decline (sarcopenia). This overview of reviews will provide a comprehensive analysis of the existing data presented in systematic reviews and meta-analyses, on whether GLP-1RA use affects skeletal

muscle mass (or proxies of muscle mass, i.e. lean mass, FFM), strength, and physical function.

Condition being studied To determine how GLP-1RA induced weight loss affects skeletal muscle, strength, and physical function in adults with overweight/obesity.

METHODS

Search strategy Pubmed:
("Glucagon-Like Peptide 1 Receptor Agonists"[Mesh] OR "glp-1 receptor agonist*"[tiab] OR “liraglutide”[tiab] OR “semaglutide”[tiab] OR “exenatide”[tiab] OR “dulaglutide”[tiab] OR “albiglutide”[tiab] OR “tirzepatide”[tiab] OR “incretin mimetics”[tiab] OR “incretin analog”[tiab] OR “GIP/GLP-1 agonist”[tiab] OR “GLP-1 analog” [tiab]) AND ("Body Composition"[Mesh] OR "Muscle, Skeletal"[Mesh] OR "Muscle Strength"[Mesh] OR "Physical Functional Performance"[Mesh] OR “body composition”[tiab] OR “skeletal muscle”[tiab] OR “lean mass”[tiab] OR “fat-free mass”[tiab] OR “muscle mass”[tiab] OR “muscle strength”[tiab] OR “5RM”[tiab] OR “1RM”[tiab] OR “1 repetition max”[tiab] OR “physical function”[tiab] OR “gait speed”[tiab] OR “handgrip”[tiab] OR "six minute walk"[tiab] OR "6-minute walk"[tiab] OR “SPPB”[tiab] OR “6mwt” [tiab] OR “TUG”[tiab] OR “timed up and go”[tiab] OR “chair stand test”[tiab] OR “stair climb test” [tiab] OR “short physical performance battery” [tiab]) AND ("systematic review"[tiab] OR "systematic reviews"[tiab] OR "meta-analysis"[pt] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab])
Embase:
1. exp Glucagon-Like Peptide 1 Receptor Agonists/ OR (glp-1 receptor agonist* or GLP1 receptor agonist*).ti,ab,kw. OR liraglutide.ti,ab,kw. OR semaglutide.ti,ab,kw. OR exenatide.ti,ab,kw. OR dulaglutide.ti,ab,kw. OR albiglutide.ti,ab,kw. OR tirzepatide.ti,ab,kw.
2. exp Body Composition/ OR exp Skeletal Muscle/ OR exp Muscle Strength/ OR exp Physical Performance/ OR body composition.ti,ab,kw. OR skeletal muscle.ti,ab,kw. OR lean mass.ti,ab,kw. OR fat free mass.ti,ab,kw. OR muscle mass.ti,ab,kw. OR muscle strength.ti,ab,kw. OR physical function.ti,ab,kw. OR gait speed.ti,ab,kw. OR handgrip.ti,ab,kw. OR SPPB.ti,ab,kw. OR six minute walk.ti,ab,kw. OR 6 minute walk.ti,ab,kw.
3. exp Systematic Review/ OR exp Meta-Analysis/ OR systematic review.ti,ab,kw. OR systematic reviews.ti,ab,kw. OR meta-analysis.ti,ab,kw. OR meta-analyses.ti,ab,kw.
4. Combine 1 and 2 and 3
Web of Science Core Collection:
TS=("glp-1 receptor agonist*" OR "glucagon-like peptide 1 receptor agonist*" OR "glucagon-like receptor-1 agonist*" OR "incretin mimetic*" OR "incretin analog*" OR "GIP/GLP-1 agonist*" OR "GLP-1 analog*" OR liraglutide OR semaglutide OR exenatide OR dulaglutide OR albiglutide OR tirzepatide) AND TS=(obesity OR obese OR "type 2 diabetes" OR T2D) AND TS=("body composition" OR "skeletal muscle" OR "lean mass" OR "fat free mass" OR muscle OR "muscle mass" OR "muscle strength" OR "physical function" OR "gait speed" OR handgrip OR SPPB OR "short physical performance battery" OR "six minute walk" OR "6 minute walk" OR 6MWT OR TUG OR "timed up and go" OR "chair stand test" OR "stair climb test" OR "5RM" OR "5 repetition max" OR "1RM" OR "1 repetition max") AND TS=("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta-analyses") Refined by: DOCUMENT TYPES = Review, Languages: English, Timespan: All years, Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI
CIHNL (EBSCO):
(MH "Glucagon Like Peptide 1 Receptor Agonists+" OR "glucagon-like peptide 1" OR "glucagon-like peptide 1 receptor agonist*" OR "glp-1 receptor agonist*" OR "glp 1 receptor agonist*" OR "incretin mimetic*" OR "incretin analog*" OR "GIP/GLP-1 agonist*" OR "glp-1 analog*" OR liraglutide OR semaglutide OR exenatide OR dulaglutide OR albiglutide OR tirzepatide) AND (MH "Body Composition+" OR MH "Muscle Strength+" OR MH "Musculoskeletal System+" OR MH "Physical Fitness+" OR "body composition" OR "skeletal muscle*" OR "lean mass*" OR "fat free mass*" OR "muscle*" OR "muscle mass*" OR "muscle strength*" OR "physical function*" OR ("gait" N3 "speed") OR handgrip OR SPPB OR "short physical performance battery" OR ("six minute walk" OR "6 minute walk" OR 6MWT) OR ("timed up and go" OR TUG) OR ("chair stand" N3 test) OR ("stair climb" N3 test) OR ("1 repetition max" OR "1RM" OR "5 repetition max" OR "5RM")) AND (MH "Systematic Review+" OR MH "Meta Analysis+" OR "systematic review*" OR "meta-analys*" OR "meta-analyses")
Google Scholar:
allintitle:("glucagon-like peptide" OR "glp-1" OR liraglutide OR semaglutide OR exenatide OR dulaglutide OR albiglutide OR tirzepatide) ("systematic review" OR "meta-analysis") ("body composition" OR "skeletal muscle" OR "lean mass" OR "muscle mass" OR "muscle strength" OR strength OR "physical function" OR "gait speed" OR handgrip OR SPPB OR six minute walk OR 6 minute walk).

Participant or population Adults (≥18 years) with overweight/obesity (BMI ≥25 kg/m²) with/without type 2 diabetes mellitus (T2DM).

Intervention GLP-1 receptor agonists (e.g., liraglutide, semaglutide, exenatide, dulaglutide). Dual agonists (e.g., tirzepatide) and triple agonists (e.g., retatrutide) were included if assessed within reviews primarily focused on GLP-1RAs.

Comparator Placebo, diet or lifestyle interventions alone, or other pharmacological comparators (if included in the review).

Study designs to be included Systematic reviews or meta-analyses of RCTs (parallel or crossover).

Eligibility criteria Systematic reviews and meta-analyses including adults ≥18 years on GLP-1RAs.

Information sources Embase, PubMed, the Web of Science core collection, CINHL (EBSCO), and Google Scholar.

Main outcome(s) Body weight, BMI, body composition (fat mass, lean mass, % fat free mass), skeletal muscle mass (whole-body or regional), strength (e.g., handgrip, leg press, 1-RM), physical function (e.g., gait speed, SPPB, 6MWT).

Additional outcome(s) None.

Data management All data are stored or managed on the PI and CO-I's personal computers. Extracted data are curated and shared on cloud-based databases.

Quality assessment / Risk of bias analysis Consensus Analysis Strategy for Overviews of Reviews
All reviews will be scored using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) tool (Shea et al. BMC Med Res Methodol.2007;7:10). This 11-item tool assesses the degree to which review methods avoided bias. The methodological quality is rated as high (score 8-11), moderate (score 4-7) or low (score 0-3).
To organize the evidence, authors will systematically synthesize the extracted data of each review. This results in standardized effectiveness statements (i.e., sufficient evidence, some evidence, insufficient evidence, insufficient evidence to determine) about the treatment effect of the interventions in the individual systematic reviews.
The quality of the evidence (QoE) supporting each bottom-line statement will be rated by using a method based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for primary evidence (1 - very low; 2 - low; 3 - moderate; 4 - high). This method considers study design (meta-analysis: yes or no) and AMSTAR rating of the included systematic reviews.

Strategy of data synthesis Summary of results across included systematic reviews will be separated by outcome domain (muscle mass, strength, and physical function) and comparator type (placebo, diet or lifestyle interventions alone, or other pharmacological comparators) alongside the methodological quality of the review, number of trials included in the relevant analysis and sample size. The overall effectiveness of each intervention will be based on the total number of participants affected positively across the relevant systematic reviews.

Subgroup analysis f an adequate amount of systematic reviews are available, then we will apply the aforementioned data synthesis strategy on two sub-groups of our total sample size, based on age: young adults (18 - 59 years old), and older adults (≥60 yrs). We will also perform sub-group analysis of our total sample size, based on participants who have (OW/OB+T2DM) and do not have T2DM (OW/OB-T2DM).

Sensitivity analysis None planned.

Language restriction English.

Country(ies) involved Canada.

Other relevant information
Exclusion Criteria:
- Pediatric populations (<18 years). Populations with other primary conditions (e.g., cancer, HIV, organ failure) unless OW/OB subgroup results are reported separately. Animal models.
- Non-GLP-1 pharmacological agents (e.g., orlistat, SGLT2 inhibitors, DPP-4 inhibitors) unless used as comparators. Lifestyle or surgical interventions without a GLP-1RA arm. Studies without a comparator (e.g., single-arm extensions, narrative descriptions only).
- Reviews reporting only glycemic control, cardiometabolic risk factors, or safety outcomes without body composition, muscle, strength, or functional outcomes.
- Narrative reviews, expert opinions, editorials, scoping reviews, overviews without systematic methodology, or single RCTs/observational studies. Conference abstracts, dissertations, grey literature, non-peer-reviewed reports.

- Non-English publications.

Keywords Obesity; GLP-1RA; Anti-Obesity Medication; Weight Loss; Body Composition; Skeletal Muscle; Lean Mass; Strength; Physical Function.

Dissemination plans Presentations at academic meetings and publication in a scientific journal.

Contributions of each author

Author 1 - Kelly Chen - All phases: idea inception, search, data screening, data synthesis, writing, and editing.
Email: chenk267@mcmaster.ca
Author 2 - Caroline Lowisz - All phases: idea inception, search, data screening, data synthesis, writing, and editing.
Email: lowiszc@mcmaster.ca
Author 3 - Everson Nunes - All phases: idea inception, search, data screening, data synthesis, writing, and editing.
Email: nunese1@mcmaster.ca
Author 4 - Stuart Phillips - All phases: idea inception, search, data screening, data synthesis, writing, and editing.
Email: phillis@mcmaster.ca