INPLASY

Skeletal Effects of GLP-1 Receptor Agonist Therapy in Individuals with Overweight or Obesity: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - This study received no specific funding.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202630076

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 March 2026 and was last updated on 21 March 2026.

INTRODUCTION

Review question / Objective The primary objective is to evaluate the effects of GLP-1 receptor agonist therapy on whole-body and site-specific bone mineral density (lumbar spine, femoral neck, total hip) in adults with overweight or obesity, with subgroup analyses according to BMI category, treatment duration, GLP-1 RA type, and dosing regimen. The secondary objective is to assess changes in bone turnover biomarkers (CTX, ALP, and osteocalcin) and explore potential mechanisms to determine whether GLP-1 RA–induced weight loss and metabolic improvements exert complex effects on bone health.

Rationale Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly used for obesity management; however, their effects on bone mineral density (BMD) remain unclear. Weight loss induced by GLP-1 RAs may reduce mechanical loading on the skeleton, while GLP-1-mediated metabolic pathways may independently influence bone remodeling. Current evidence is limited and inconsistent, with no comprehensive quantitative systematic review evaluating the impact of GLP-1 RAs on whole-body and site-specific BMD or associated bone turnover markers in overweight or obese populations.

Condition being studied Bone mineral density changes and bone turnover in adults with overweight or obesity (BMI >25 kg/m^2) receiving GLP-1 receptor agonist therapy.

METHODS

Search strategy PubMed/MEDLINE: (("glucagon-like peptide-1"[MeSH Terms] OR "GLP-1 receptor agonist"[Title/Abstract] OR "GLP-1RA"[Title/Abstract] OR "exenatide"[Title/Abstract] OR "liraglutide"[Title/Abstract] OR "dulaglutide"[Title/Abstract] OR "semaglutide"[Title/Abstract]) AND ("bone density"[MeSH Terms] OR "bone mineral density"[Title/Abstract] OR "osteoporosis"[MeSH Terms] OR "bone fracture"[Title/Abstract] OR "bone turnover"[Title/Abstract])); Filters:

Randomized Controlled Trial, Humans, English. For Embase: equivalent Emtree terms ('glucagon like peptide 1'/exp, 'bone density'/exp) with title/abstract free-text synonyms, limited to randomized controlled trials, humans, and English. For CENTRAL: MeSH descriptors and free-text terms in title, abstract, and keyword fields, restricted to the Trials register.

Participant or population Adults (BMI >25 kg/m²) with overweight or obesity, including individuals with prediabetes or type 2 diabetes mellitus.

Intervention Treatment with any GLP-1 receptor agonist, including but not limited to exenatide, dulaglutide, semaglutide, or liraglutide.

Comparator Placebo or active comparators, including other antidiabetic therapies (e.g., insulin glargine, pioglitazone).

Study designs to be included Randomized controlled trials (RCTs) with parallel-group design comparing GLP-1 receptor agonists with placebo or other antidiabetic therapies. A minimum follow-up duration of 12 weeks was required. Both double-blind, single-blind, and open-label RCTs were eligible. Cross-over trials, quasi-experimental studies, observational studies, case reports, and conference abstracts were excluded.(1) Adults with BMI >25 kg/m², including individuals with prediabetes, type 2 diabetes mellitus, or obesity; (2) Intervention: treatment with a GLP-1 receptor agonist; (3) Comparator: placebo or other antidiabet.

Eligibility criteria (1) Adults with BMI >25 kg/m², including individuals with prediabetes, type 2 diabetes mellitus, or obesity; (2) Intervention: treatment with a GLP-1 receptor agonist; (3) Comparator: placebo or other antidiabetic therapies; (4) Study design: randomized controlled trial with parallel comparison group; (5) Both groups reported pre- and post-treatment bone mineral density outcomes; (6) Follow-up duration ≥12 weeks; (7) Published as full-length original article in English.

Information sources Primary databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Supplementary source: Google Scholar (first 200 results sorted by relevance screened per query, deduplicated against primary databases). Search period: from inception to March 21, 2026.

Main outcome(s) Primary databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Supplementary source: Google Scholar (first 200 results sorted by relevance screened per query, deduplicated against primary databases). Search period: from inception to March 21, 2026.

Additional outcome(s) Secondary outcomes: Changes in bone turnover biomarkers, including C-terminal telopeptide of type I collagen (CTX, a bone resorption marker), alkaline phosphatase (ALP, a bone formation marker), and osteocalcin (a bone formation marker).

Data management Literature search results from all databases were imported into EndNote X20 reference management software. Duplicate records were identified and removed using both automated deduplication and manual verification. Two independent reviewers screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Extracted data were entered into a standardized data extraction form in Microsoft Excel. Any discrepancies between reviewers were resolved through consensus discussion, with arbitration by a third reviewer when necessary. The final dataset was imported into Review Manager (RevMan) version 5.4 for quantitative synthesis.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of all included studies were assessed using the Cochrane Risk of Bias tool, Version 2.0 (RoB 2), designed for individually randomized parallel-group trials. Five domains were evaluated: (D1) bias arising from the randomization process; (D2) bias due to deviations from intended interventions; (D3) bias due to missing outcome data; (D4) bias in measurement of the outcome; and (D5) bias in selection of the reported result. Each domain was judged as low risk, some concerns, or high risk of bias. An overall risk-of-bias judgment was assigned for each study. Two reviewers independently performed the assessments, and discrepancies were resolved by consensus. Results were visualized using traffic light plots and weighted summary bar charts generated with robvis. The certainty of evidence for each outcome was additionally assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Strategy of data synthesis Quantitative meta-analysis was performed using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). The treatment effect for continuous outcomes

(changes in bone mineral density and bone turnover biomarkers) was calculated using the Mean Difference (MD) with 95% confidence intervals (CI). A random-effects model (DerSimonian–Laird method) was prospectively applied to account for anticipated clinical heterogeneity arising from differences in obesity severity, GLP-1 receptor agonist type, dosing frequency, and treatment duration. Statistical heterogeneity was quantified using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. When only regional DXA data were available, an anatomical weighting approach adapted from Warming et al. (Osteoporos Int, 2002) was applied to estimate whole-body BMD changes using the formula: $\Delta BMD\_wb = (0.40 \times \Delta BMD\_LS) + (0.35 \times \Delta BMD\_TH) + (0.25 \times \Delta BMD\_FN)$. Where quantitative synthesis was not feasible, findings were summarized descriptively. Assessment of publication bias was not performed as the number of included studies per outcome was fewer than 10. All statistical tests were two-sided with a significance level of $p < 0.05$.

Subgroup analysis Predefined subgroup analyses were conducted using whole-body BMD as the primary stratification outcome. Studies were categorized according to: (1) baseline BMI: overweight ($27 < BMI < 30$ kg/m^2) versus obese (BMI ≥30 kg/m^2); (2) intervention duration: short-term (<52 weeks) versus long-term (≥52 weeks); (3) GLP-1 RA pharmacologic classification: exenatide versus non-exenatide agents (semaglutide, liraglutide, dulaglutide); and (4) dosing frequency: long-acting formulations (once weekly) versus short-acting formulations (twice daily).

Sensitivity analysis Formal sensitivity analysis (e.g., leave-one-out analysis) was not conducted owing to the limited number of included studies per pooled outcome ($n \leq 7$), which was considered insufficient to yield stable and interpretable results from iterative exclusion procedures. This is acknowledged as a study limitation, and future reviews with a larger evidence base should incorporate such analyses to assess the robustness of pooled estimates.

Language restriction English only. Only studies published as full-length original articles in English were included.

Country(ies) involved Taiwan (primary institution). Collaborative affiliations may include international co-authors pending manuscript finalization.

Other relevant information This systematic review and meta-analysis was conducted in adherence to the PRISMA 2020 guidelines. The certainty of evidence was assessed using the GRADE framework. HbA1c was extracted when available to characterize the metabolic status of study participants but was not required as a mandatory inclusion criterion. For trials with multiple treatment arms, GLP-1 receptor agonist groups were combined into a single intervention group according to pharmacologic classification, while non-GLP-1 groups were pooled as the comparator group. Means and standard deviations were calculated using sample size-weighted methods.

Keywords Obesity; Glucagon-like peptide-1 receptor agonists; Exenatide; Bone mineral density; Bone turnover marker.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed international journal indexed in SCI/SCIE. Results will also be disseminated through academic conferences and professional meetings in the fields of endocrinology, metabolism, and bone health. The complete dataset and analysis files will be made available from the corresponding author upon reasonable request.

Contributions of each author

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