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Effects of Glucagon-Like Peptide-1 Receptor Agonist on Bone Mineral Density and Bone Turnover Markers: A Meta-Analysis

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ABSTRACT

Aims: Glucagon-like peptide-1 receptor agonist (GLP-1RA) may promote bone formation, but conversely, they could also weaken bones due to the reduction in mechanical load associated with weight loss. However, the clinical effects in humans have not been clearly demonstrated. This meta-analysis aimed to evaluate whether GLP-1RAs affect BMD and bone turnover markers.

Material and Methods: PubMed, Embase, and Scopus were searched on June 13, 2024. The eligibility criteria were: (1) human studies, (2) receiving a GLP-1RA for more than 4 weeks, (3) an untreated control group or a placebo group, (4) reporting of at least one BMD or bone turnover marker, and (5) an RCT design. The risk of bias was assessed using the Cochrane risk of bias 2 tool. Fixed- or random-effects meta-analysis was performed according to heterogeneity.

Results: Seven studies were included in the meta-analysis. GLP-1RAs did not significantly change BMD in the femoral neck (mean difference [MD], 0.01 g/cm^2; 95% CI, −0.01–0.04 g/cm^2), in the total hip (MD, −0.01 g/cm^2; 95% CI, −0.02–0.01 g/cm^2), and in the lumbar spine (MD, 0 g/cm^2; 95% CI, −0.02–0.02 g/cm^2). C-terminal telopeptide of type 1 collagen (CTX), a bone resorption marker, significantly increased after GLP-1RA treatment (MD, 0.04 μg/L; 95% CI, 0.01–0.07 μg/L). GLP-1RAs did not significantly change bone formation markers such as procollagen type 1 N-terminal propeptide, bone-specific alkaline phosphatase, osteocalcin.

Conclusions: GLP-1RA did not affect BMD and bone formation markers. However, GLP-1RAs led to a significant increase in CTX.

1 | Introduction

Glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by intestinal L-cells, plays a crucial role in regulating glucose homoeostasis and satiety [1]. GLP-1 receptor agonists (GLP-1RAs) are a class of medications that mimic the effects of GLP-1 by binding to its receptor and stimulating insulin secretion, reducing glucagon secretion, slowing gastric emptying, and promoting satiety. GLP-1RAs are primarily used for the treatment of type 2 diabetes mellitus (T2DM) but are also being

investigated for their potential benefits in obesity and cardiovascular disease [2].

Although GLP-1RAs are effective in improving glycaemic control and reducing cardiovascular risk, there is also growing interest in their effects on bone health. Several studies have suggested that GLP-1RAs may have a bone protective effect [3]. In fact, GLP-1RAs induce differentiation of mesenchymal stem cells into osteoblasts rather than adipocytes and stimulate expression of genes associated with osteogenesis [3, 4]. GLP-1 also results in decreasing osteoclast number and serum level of bone resorption markers in old rats with osteoporosis [5]. Furthermore, GLP-1RAs bind to the GLP-1 receptor expressed in thyroid C cells to release calcitonin, a hormone inhibiting bone resorption [3]. As a result, GLP-1RAs amplified bone mineral density (BMD), which is a measure of bone strength and density, in animal models [5–11].

Despite the bone protective effects of GLP-1RAs in vitro and in vivo, their clinical effects in humans have not been clearly demonstrated. Weight loss following GLP-1RA treatment can have unintended consequences on bone health, as reduced mechanical strain on the skeleton may lead to a reduction in BMD [12]. A 10% weight loss generally corresponds to around 1%–2% bone loss [13]. The bone response to weight loss varied among different populations. In a prospective epidemiological study, postmenopausal women within the normal weight range experienced greater bone loss compared with those who were overweight or obese [14]. In patients with T2DM, who typically have elevated BMD compared to other populations, weight loss still decreases BMD and raises the risk of fractures [15–18]. The Look AHEAD study demonstrated that intensive lifestyle intervention for weight loss significantly reduced BMD, leading to a noteworthy 39% increase in the risk of fragility fractures in overweight individuals with T2DM [18].

In a meta-analysis including 28 randomised controlled trials (RCTs), GLP-1RAs displayed insignificant effects on the risk of bone fracture (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.28–2.02) [19]. In a large population-based cohort study (n = 216,816), GLP-1RAs were not associated with a decreased risk of bone fracture (adjusted hazard ratio, 0.99; 95% CI, 0.82–1.19) [20]. However, the evidence is still limited and conflicting. Another meta-analysis including 38 RCTs suggested that GLP-1RAs were correlated with a decline in bone fracture risk (OR, 0.71; 95% CI, 0.56–0.91) [21]. These beneficial effects were dependent on the type of GLP-1RAs and duration of treatment. It is important to note that these meta-analyses reported dissimilar findings, and more research is needed to fully understand the effects of GLP-1RAs on bone health.

The relatively long latency period for bone fracture causes difficulty in analysing causality with drugs [22]. Instead, the effect of GLP-1RAs on bone health can be identified early using BMD or bone turn markers. Bones undergo constant remodelling through resorption and formation, and various biochemical markers are released during this process [23]. The bone resorption markers include C-terminal telopeptide of type 1 collagen (CTX), N-terminal telopeptide of type I collagen (NTX), pyridinoline, and deoxypyridinoline [23]. Bone formation markers include procollagen type 1 N-terminal propeptide (P1NP), C-terminal propeptide (P1CP), bone-specific alkaline phosphatase (bone ALP), and osteocalcin [23]. Therefore, the purpose of this meta-analysis was to evaluate whether GLP-1RAs affect BMD and bone turnover markers.

2 | Materials and Methods

The meta-analysis was registered in INPLASY (registration number: INPLASY202460050) and the study was executed and reported according to the PRISMA statement guidelines [24].

2.1 | Search Strategy

Studies investigating the effects of GLP-1RAs on BMD or bone turnover markers were searched in PubMed, Embase, and Scopus on June 13, 2024. Search queries were determined in consideration of Population, Intervention, Comparison, Outcomes and Study design (PICOS) criteria (Table 1) and are presented in Table S1. For PubMed and Embase, the RCT filter built into the database was used. For Scopus, the RCT filter recommended by librarians at the John W. Scott Health Sciences Library was employed [25].

2.2 | Study Selection

The criteria for selecting the studies were: (1) human studies, (2) included an experimental group receiving a GLP-1RA for more

TABLE 1 | PICOS criteria for inclusion of studies.

PICOS	Criteria
Population	Human
Intervention	GLP-1RA for more than 4 weeks
Comparison	Untreated or receiving a placebo
Outcome	At least one BMD (femoral neck, total hip, lumbar spine), bone resorption (CTX, NTX, pyridinoline, deoxypyridinoline), or bone formation (P1NP, P1CP, bone ALP, osteocalcin) markers
Study design	Randomised controlled trial

Abbreviations: ALP, alkaline phosphatase; CTX, C-terminal telopeptide of type 1 collagen; GLP-1RA, glucagon-like peptide-1 receptor agonist; NTX, N-terminal telopeptide of type I collagen; P1CP, procollagen type 1 C-terminal propeptide; P1NP, procollagen type 1 N-terminal propeptide.

than 4 weeks, (3) incorporated an untreated control group or a group receiving a placebo, (4) reported at least one BMD or bone turnover marker, and (5) RCT design. There were no restrictions on the study period, publication year, or language. Studies that did not meet the criteria of PICOS were excluded. Some studies were excluded because of the type of publication (e.g., review articles, editorials, or conference abstracts).

The selection process was independently conducted by two evaluators. At the first screening, titles and abstracts were screened, and in the second selection, full-text articles were assessed for eligibility. Any discrepancy between the two researchers was resolved through discussion or arbitration with a third researcher.

2.3 | Quality Assessments and Data Extraction

A revised Cochrane risk of bias tool for randomised trials (RoB2) for parallel-groups was used to assess the risk of bias of the selected literature (as all trials were parallel designs) [26]. The degree of bias was judged as "high," "some concerns," and "low" for each category, and the risk of bias was evaluated by summing the results of each category [26].

One researcher (H.J.K.) extracted the data, and two researchers (M.S.G. and S.Y.K.) confirmed it. The following data were extracted from eligible studies: general study information (e.g., author, year of publication, title, study design, study period, number of participants, age/sex/health status of participants), GLP-1RA information (e.g., type of GLP-1RA, dosage), and baseline and endpoint levels of BMD or bone markers. If the difference between the baseline and the end point was stated, the value was extracted. If the data were presented only as graphs, numbers were extracted from the figure using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer).

2.4 | Statistics

Outcomes reported in three or more studies were analysed: BMD in the femoral neck, BMD in the total hip, BMD in the lumbar spine, CTX, P1NP, bone ALP, and osteocalcin. Effect size, a difference in effect between two groups, was presented as mean difference (MD). A combined effect size and its 95% CI were calculated as the weighted average of the study level effect sizes by a generic inverse variance method through Review Manager version 5.4 (The Cochrane collaboration, London, United Kingdom) software. The values entered in the software were the number of participants, the difference between baseline and end point and its standard deviation (SD) in each group, which were calculated as: $\text{mean}_{\text{final}} - \text{mean}_{\text{baseline}}$ and $[(\text{SD}_{\text{baseline}})^2 + (\text{SD}_{\text{final}})^2 - (2 \times R \times \text{SD}_{\text{baseline}} \times \text{SD}_{\text{final}})]^{1/2}$, assuming a correlation coefficient (R) of 0.5 [27].

A fixed-effect model or a random-effects model was used according to heterogeneity [28]. When Higgins I^2 was > 75% or the p-value of the Cochran's Q test was < 0.05, the random-effects model was utilised, otherwise the fixed-effect model was employed. Forest plots were used to visualise the results of the meta-analysis. Subgroup analysis was conducted according to body mass index (BMI) of participants (≥ 30 and < 30 kg/m^2). In the sensitivity analysis, the robustness of the results was evaluated by excluding studies of different natures. Assessment of publication bias was not conducted because there were fewer than 10 studies in the meta-analysis.

2.5 | Certainty of Evidence

Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [29]. Five domains of GRADE (imprecision, inconsistency, risk of bias, indirectness, and publication bias) were measured and the overall level of evidence was rated as "very low," "low," "moderate," and "high." Imprecision was considered based on whether the 95% CIs of an estimate crossed the clinical decision threshold [30]. Because there was no reference threshold for outcomes exercised in this study, a 30% change from the baseline value was selected as the threshold. Inconsistency was evaluated as serious or very serious when I^2 was 50%–75% or more than 75%, respectively [31]. Risk of bias was gauged based on risk of bias within a study and across studies [32]. Indirectness referred to differences in population, intervention, comparator, and outcome from the review question [33]. Publication bias was not determined due to the small number of studies; thus, the quality of evidence was down-graded by one level.

3 | Results

3.1 | Characteristics of Included Studies

Figure 1 shows the flow chart of the study selection process. Of 259 studies identified, seven studies were eligible for meta-analysis. Characteristics of the included studies are presented in Table 2 [34–40]. Three studies were determined to have a low risk of bias and for the other four there were some concerns (Table S2).

3.2 | Bone Mineral Density

Figure 2 illustrates the effect of GLP-1RA on BMD. The average baseline BMD in the femoral neck, total hip, and lumbar spine were 0.83, 0.97, and 1.03 g/cm^2, respectively. BMD in the femoral neck was reported in five studies (324 participants). Excluding the study by Cai et al., which reported higher BMD in the GLP-1RA group, the remaining studies were not statistically significant. The pooled result showed no significant difference between the GLP-1RA and the control group (random-effect model; MD, 0.01 g/cm^2; 95% CI, −0.01–0.04 g/cm^2; Figure 2A). In the subgroup analysis according to BMI, there was no difference in BMD in the femoral neck between the GLP-1RA and the control group (Figure 2A).

BMD in the total hip was stated in six studies (361 participants). In the study by Cai et al., BMD was higher in the exenatide group, whereas in the study by Hansen et al., BMD was lower in the semaglutide group. The pooled result showed no significant difference between the GLP-1RA and the control group (random-

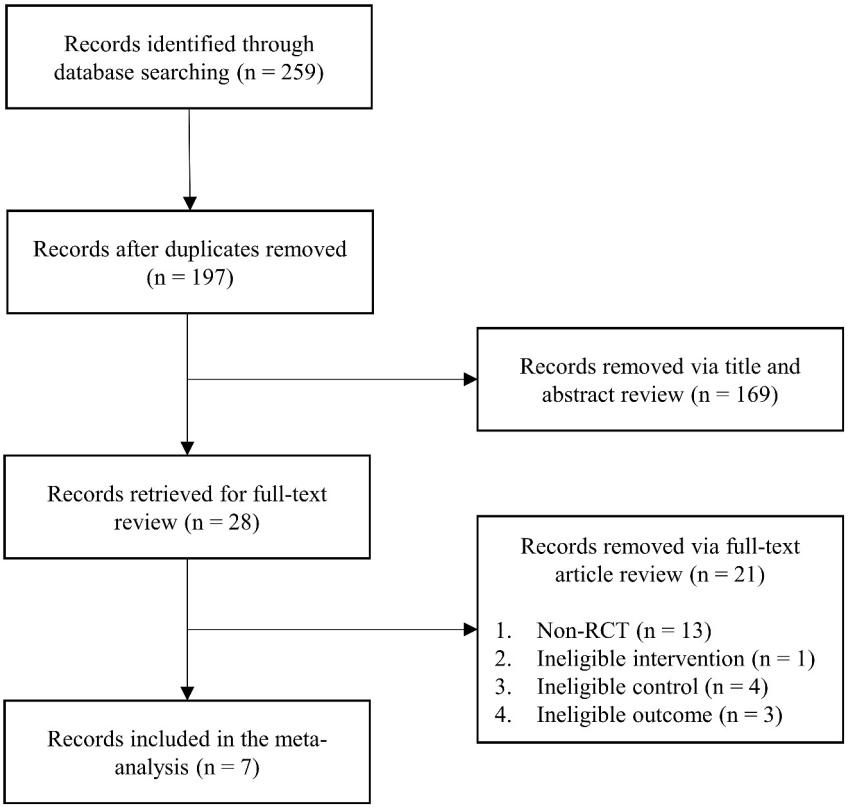

FIGURE 1 | Flow chart of the study selection process. RCT, randomised controlled trial.

effect model; MD, −0.01 g/cm^2; 95% CI, −0.02–0.01 g/cm^2; Figure 2B). In the subgroup analysis according to BMI, there was no difference in BMD in the total hip between the GLP-1RA and the control group (Figure 2B).

BMD in the lumbar spine was observed in five studies (324 participants). Similar to the results for the total hip, the study by Cai et al. showed a tendency for higher BMD in the GLP-1 RA group, while the study by Hansen et al. found significantly lower BMD in the semaglutide group. The pooled result showed no significant difference between the GLP-1RA and the control group (random-effect model; MD, 0 g/cm^2; 95% CI, −0.02–0.02 g/cm^2; Figure 2C). In the subgroup analysis according to BMI, there was no difference in BMD in the lumbar spine between the GLP-1RA and the control group (Figure 2C).

Although the overall analysis was not significant, the sensitivity analysis, excluding some studies, showed that BMD was statistically lower in the GLP-1RA group, driven by the Hansen's study, which had a narrower confidence interval (Figure S1–S3). When studies involving patients with T2DM were excluded, BMD in the total hip was significantly lower in the GLP-1RA group (Figure S1). Additionally, when short-acting GLP-1RA studies were excluded, BMD in the lumbar spine was significantly lower in the GLP-1RA group (Figure S2).

3.3 | Bone Resorption Markers

Figure 3 describes the effect of GLP-1RA on CTX, which was informed in six studies (378 participants). The average baseline CTX concentration was 0.31 μg/L. GLP-1RAs significantly increased CTX by 0.04 μg/L (random-effect model; MD, 0.04 μg/L; 95% CI, 0.01–0.07 μg/L). However, in the subgroup analysis, the number of studies included in each subgroup was small. While the direction was consistent with the overall analysis, it did not show a statistically significant difference. Alternatively, despite excluding certain studies in the sensitivity analysis, the pooled results continued to show marginal or statistical significance (Figure S1–S3).

3.4 | Bone Formation Markers

Figure 4 displays the effect of GLP-1RA on P1NP, bone ALP, and osteocalcin. The average baseline P1NP, bone ALP, and osteocalcin concentrations were 48.2, 16.9, and 15.5 μg/L, respectively. P1NP was described in six studies (378 participants) and was not significantly different between GLP-1RA and the control group (random-effect model; MD, −0.36 μg/L; 95% CI, −4.48–3.76 μg/L; Figure 4A). In the subgroup analysis according to BMI, there was no difference in P1NP between the GLP-1RA and the control group (Figure 4A). The difference between GLP-1RA and the control group remained non-significant even in sensitivity analysis (Figure S1–S3). Bone ALP and osteocalcin were reported in three studies (137 participants). These bone formation markers were not significantly different between GLP-1RA and the control group (all fixed-effect model; MD, −1.24 μg/L; 95% CI, −3.02–0.53 μg/L; Figure 4B and MD, −0.08 μg/L; 95% CI, −1.80–1.65 μg/L; Figure 4C). Subgroup analysis and sensitivity analysis were not performed because the number of studies included was small. In

TABLE 2 | Characteristics of the included studies.

References	Study period	Intervention	Sample size	Age (years)[a]	Male (%)	BMI (kg/m^2)[a]	Health status
Cai et al. [34]	52 weeks	E (2 mg/ week)	E: 19	E: 62.9 ± 1.7	53	E: 27.1 ± 0.9	T2DM
		D (1.5 mg/ week)	D: 19	D: 57.4 ± 1.8		D: 25.3 ± 0.7	
			P: 17	P: 62.0 ± 1.2		P: 27.0 ± 0.8	
Eriksson et al. [35]	12–16 weeks	E (2 mg/ week)	E: 20	E: 37.1 ± 10.6	47	E: 39.2 ± 3.8	Schizophrenia treated with minimum one antipsychotic drug and obese (BMI ≥ 30 kg/m^2)
			P: 20	P: 34.5 ± 10.1		P: 38.4 ± 6.1	
Hansen et al. [36]	52 weeks	S (1 mg/ week)	S: 32	S: 62.7 ± 5.6	14	S: 27.9 ± 4.8	Increased fracture risk
			P: 32	P: 63.6 ± 5.4		P: 27.6 ± 4.3	
Hygum et al. [37]	26 weeks	L (1.8 mg/day)	L: 30	L: 62 (59–65)	50	L: 33.0 (30.9–35.1)	T2DM
			P: 30	P: 64 (61–67)		P: 31.3 (29.2–33.4)	
Iepsen et al. [38]	52 weeks	L (1.2 mg/day)	L: 18	L: 46 ± 2	0	L: 31.4 ± 0.8	Healthy obese (BMI 30–40 kg/m^2) glucose-tolerant individuals that completed weight loss phase
			C: 19	C: 45 ± 2		C: 29.0 ± 0.5	
Johansen et al. [39]	26 weeks	E (10 μg three times daily)	E: 52	E: 50.1 ± 14.2	72	E: 29.0 ± 4.8	T1DM and BMI > 22 kg/m^2
			P: 53	P: 50.4 ± 14.0		P: 27.7 ± 4.1	
Maagensen et al. [40]	16 weeks	L (1.8 mg/day)	L: 35	L: 43.9 ± 10.4	68	L: 33.3 ± 4.9	Schizophrenia or psychosis treated with clozapine or olanzapine, with prediabetes and BMI > 27 kg/m^2
			P: 37	P: 42.4 ± 9.8		P: 33.7 ± 6.7	

Abbreviations: BMI, body mass index; C, control; D, dulaglutide; E, exenatide; L, liraglutide; P, placebo; S, semaglutide; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
[a]Data shown as mean ± SD or mean (95% confidence interval).

summary, GLP-1RA did not exert a significant impact on bone formation markers, including P1NP, bone ALP, and osteocalcin.

3.5 | Certainty of Evidence

The results of GRADE evaluation are exhibited in Table 3. The certainty of evidence was low for BMD in the femoral neck, BMD in the total hip, and P1NP because of inconsistency and the small number of studies. The certainty of evidence was moderate for BMD in the lumbar spine, CTX, bone ALP, and osteocalcin because of the small number of studies.

4 | Discussion

We conducted a quantitative meta-analysis of RCTs which assessed the effects of GLP-1RAs on BMD and bone turnover markers. As a result of this meta-analysis, GLP-1RAs significantly increased the bone resorption marker CTX, whereas it did not induce significant changes in BMD (in the femoral neck, total hip, and lumbar spine) or bone formation markers (P1NP, bone ALP, and osteocalcin).

Antidiabetic drugs can potentially impact fractures or BMD [41, 42]. Metformin has shown positive or neutral effects on fractures and BMD [43]. Thiazolidinediones activate peroxisome proliferator-activated receptor gamma, leading mesenchymal stem cells to differentiate into adipocytes rather than osteoblasts [44], thereby increasing the risk of fractures [45, 46]. The sodium glucose co-transporter-2 inhibitor canagliflozin has been associated with bone loss and an increased risk of fractures [47]. However, there is currently insufficient clinical evidence regarding the effects of GLP-1RA on bone health.

In contrast to the observed elevation in BMD in animals with GLP-1RA, the alteration in BMD in this study did not reach statistical significance, consistent with findings from other human studies [48, 49]. Significantly increased BMD was exclusively reported in the study by Cai et al. [34]. Caution is warranted in interpreting BMD in this meta-analysis, as two studies (Cai et al. [34] and Hygum et al. [37]) were conducted in patients with T2DM. BMD alone does not comprehensively capture bone quality and fracture risk in individuals with T2DM, who exhibit an elevated risk of fractures even with normal or high BMD [50, 51]. This paradoxical phenomenon is attributed to the direct inhibition of osteoclastogenesis by elevated glucose, and the

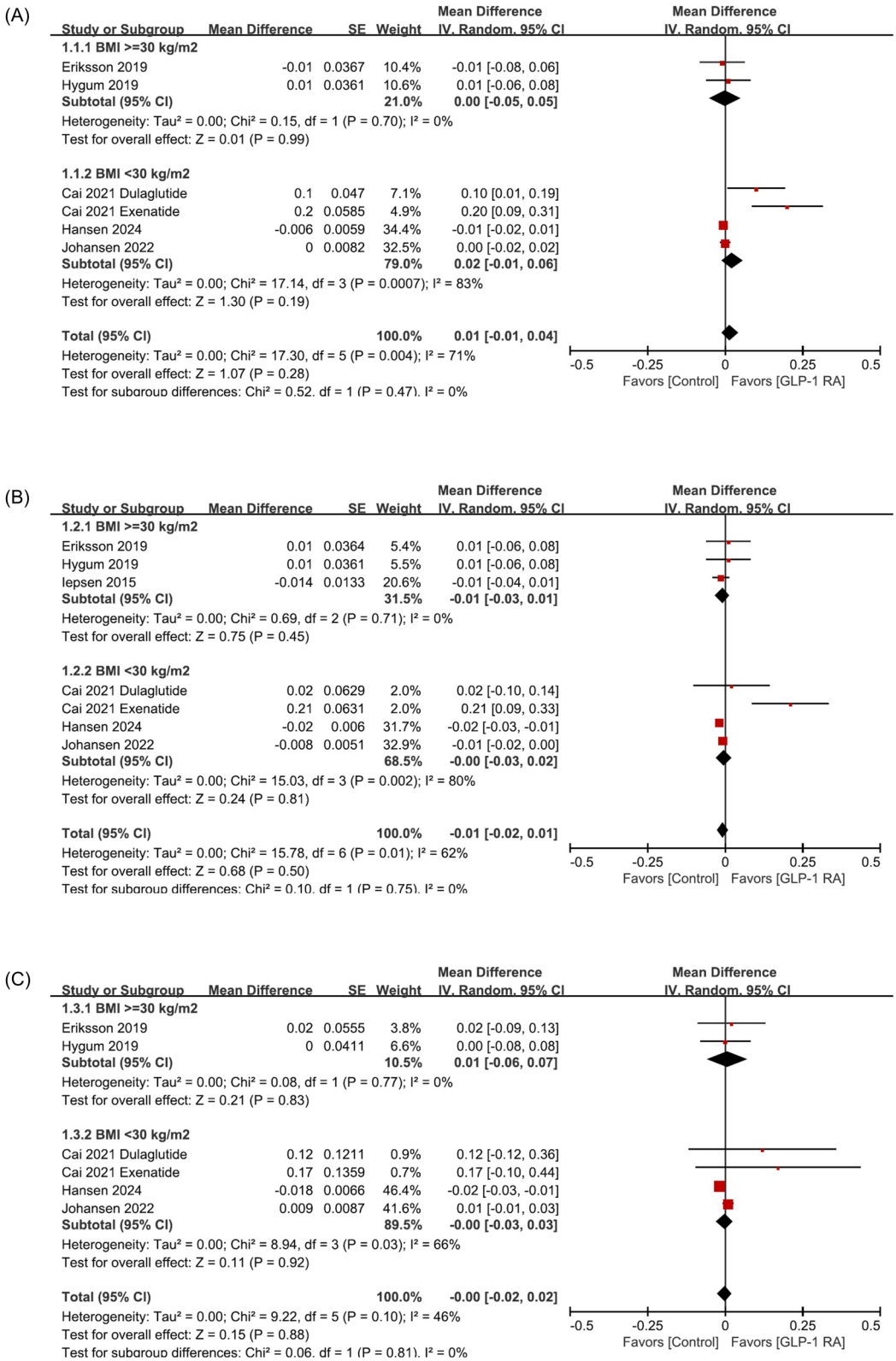

FIGURE 2 | The effect of GLP-1RA on BMD (A) in the femoral neck, (B) in the total hip, (C) and in the lumbar spine. BMI, Body mass index.

accumulation of advanced glycation end-products forming collagen cross-links, subsequently diminishing bone strength [41]. Assessing bone turnover markers or bone microstructure can complement the limitations of BMD by offering insights into the quality of the bone [15, 51]. In contrast, a recent study administering semaglutide to adults at increased risk of fractures reported a decrease in cortical bone BMD due to lower mechanical loading following weight loss [36]. It is important to interpret these findings cautiously, considering the difference in administering semaglutide compared with other studies.

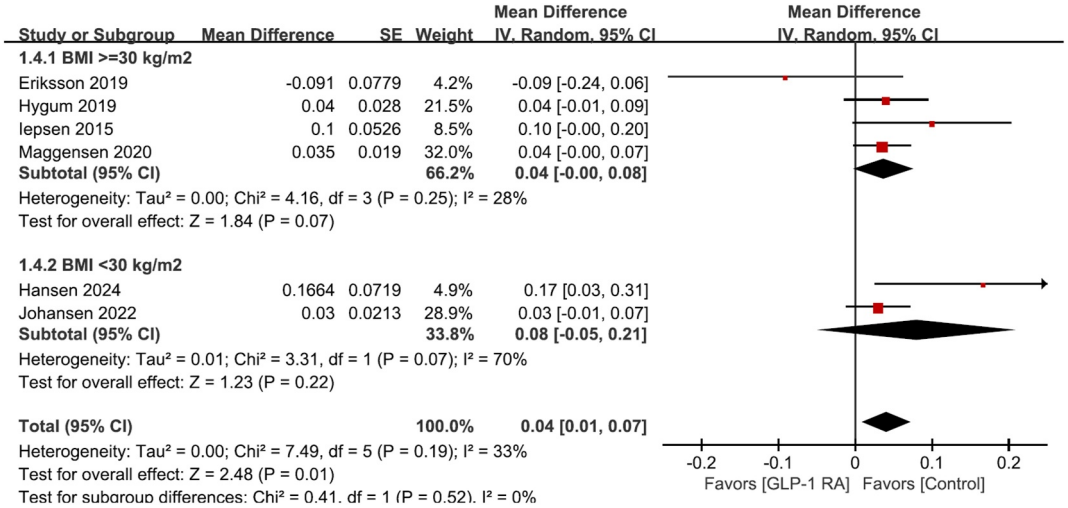

FIGURE 3 | The effect of GLP-1RA on CTX.

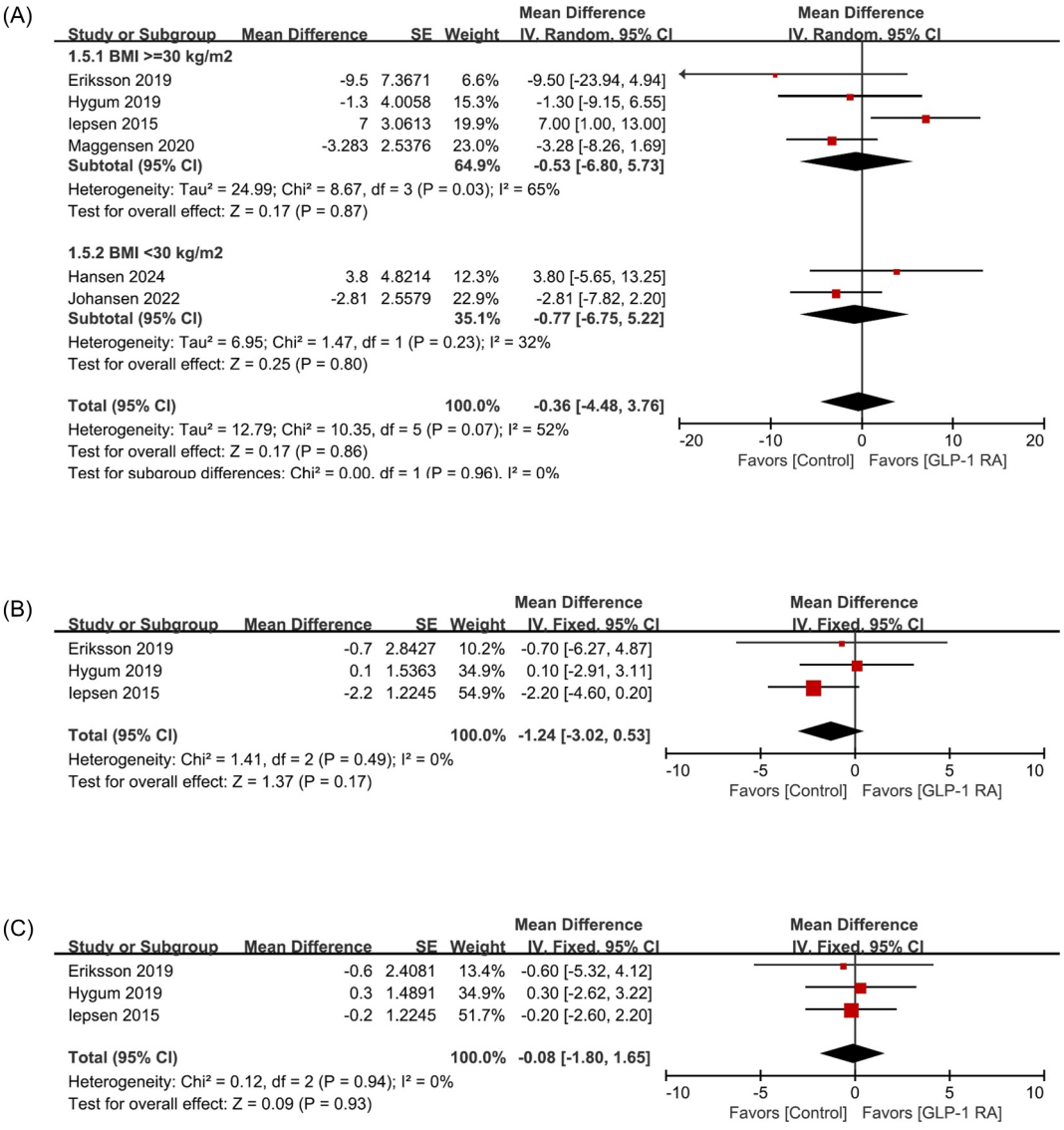

FIGURE 4 | The effect of GLP-1RA on (A) P1NP, (B) bone ALP, and (C) osteocalcin.

TABLE 3 | Certainty of evidence.

Number of studies	Risk of bias	Imprecision	Inconsistency	Indirectness	Other considerations	Certainty
Outcome: BMD in the femoral neck						
5 RCTs	Not serious	Not serious	Serious[a]	Not serious	Small number of studies	⨁⨁◯◯ Low
Outcome: BMD in the total hip						
6 RCTs	Not serious	Not serious	Serious[a]	Not serious	Small number of studies	⨁⨁◯◯ Low
Outcome: BMD in the lumbar spine						
5 RCTs	Not serious	Not serious	Not serious	Not serious	Small number of studies	⨁⨁⨁◯ Moderate
Outcome: CTX						
6 RCTs	Not serious	Not serious	Not serious	Not serious	Small number of studies	⨁⨁⨁◯ Moderate
Outcome: P1NP						
6 RCTs	Not serious	Not serious	Serious[a]	Not serious	Small number of studies	⨁⨁◯◯ Low
Outcome: Bone ALP						
3 RCTs	Not serious	Not serious	Not serious	Not serious	Small number of studies	⨁⨁⨁◯ Moderate
Outcome: Osteocalcin						
3 RCTs	Not serious	Not serious	Not serious	Not serious	Small number of studies	⨁⨁⨁◯ Moderate

Abbreviations: ALP, alkaline phosphatase; BMD, bone mineral density; CTX, C-terminal telopeptide of type 1 collagen; P1NP, procollagen type 1 N-terminal propeptide.
[a]Moderate heterogeneity ($I^2 > 50\%, \leq 75\%$).

GLP-1RAs promote the expression of genes related to bone formation in animals. GLP-1RA augmented mRNA levels of ALP and osteocalcin [6, 52]. In fact, exendin-4 increased P1NP and osteocalcin in a dose-dependent manner in ovariectomised rats [5]. The enhancement of P1NP was not significant at 1 μg/kg/day exendin-4, but was significant in 3 and 10 μg/kg/day [5]. A significant surge in osteocalcin was observed only in 10 g/kg/day exendin-4 [5]. However, the GLP-1RA effect of promoting bone formation seems to be insufficient in humans. Only the study by Iepsen et al. [38] indicated that 52 weeks of liraglutide exposure increased P1NP concentrations by 16% in healthy obese women. No increase in bone formation markers was observed in other studies [35, 37, 38, 40], and other bone formation markers such as bone ALP and osteocalcin also did not escalate in Iepsen's study [38]. It may be a result of differences among species or it may not appear at the doses administered to humans.

The increase in CTX is the opposite outcome of previous animal studies. Exendin-4, one of the GLP-1RAs, decreased the concentration of CTX in an animal osteoporosis model [5]. Liraglutide diminished the amount of CTX in ovariectomised rats and rats with glucocorticoid-induced osteoporosis [53, 54]. One possible explanation is that weight loss by GLP-1RA enhanced CTX in human studies. Diet-induced weight loss has elevated CTX concentrations [55]. For example, Hinton et al. concluded that an average weight loss of 19% after a very low-energy diet significantly amplified CTX from 0.72 to 0.93 μg/L during a 3-month weight loss period in individuals with obesity [55]. Uusi-Rasi et al. presented data that CTX intensified as the degree of weight loss from a very low-energy diet improved in obese premenopausal women [56]. The induction of CTX was the largest at 3 months and declined towards the baseline at 12 months [56]. In the study conducted by Hygum et al. [37] with individuals diagnosed with T2DM, there is a possibility that bone turnover occurred as osteoclastogenesis, previously suppressed by elevated glucose, became activated.

The reasons why BMD did not change despite the increase in CTX may be as follows. First, bone reabsorption and bone formation are coupled [57]. Bone reabsorption was augmented by GLP-1RA, but the bone formation process was not reduced, thus BMD would have been sustained. Second, it is difficult to explain BMD only in association with CTX. In a previous study, the correlation between the change in serum CTX and the change in the spine BMD was moderate ($r = 0.47$) and not statistically significant [58]. Third, CTX increased with statistical significance, but the absolute value was 0.03 μg/L, which is smaller than CTX changes with drugs that affect bone metabolism such as bisphosphonate and denosumab [59–63]. Lastly, human thyroid cells have low GLP-1 receptor expression, unlike rodent models, and calcitonin release by GLP-1RA does not occur. Therefore, there is no indirect BMD improvement effect through calcitonin after GLP-1RA treatment in humans. However, even if the increase in CTX caused by GLP-1RA is not reflected in BMD, it may still affect bone health, necessitating further research.

This meta-analysis has some limitations. First, the type of GLP-1RA, the study period, and the health status of participants varied across studies. Some analyses were significant in heterogeneity. Heterogeneity may potentially influence the effects of GLP-1RAs on bone health. Notably, a recent study involving adults at high risk of fractures found that the semaglutide group showed lower BMD in the lumbar spine and total hip compared with the placebo group [36]. Second, a limited number of studies imposed restrictions on subgroup analysis or meta-regression, preventing the adjustment for the effects of confounding factors such as age, sex, and underlying medical conditions. Particularly, considering the higher BMD and decreased bone turnover in patients with T2DM compared to the general population, the lack of subgroup analysis in T2DM patients is a limitation in evaluating the impact of GLP-1RA. Third, the number of studies included in the analysis was less than 10, so publication bias could not be evaluated.

Fourth, the absence of studies examining changes related to prolonged use exceeding 52 weeks or the effects upon discontinuation of GLP-1RA rendered it impossible to conduct a comprehensive analysis. Lastly, the direct comparison results with other antidiabetic medications are not available.

5 | Conclusion

This study confirmed that GLP-1RA does not cause significant changes in BMD and bone formation markers. However, GLP-1RAs led to a significant increase in CTX. Further research is required to investigate the clinical impact of the increase in bone resorption markers induced by GLP-1RA.

Author Contributions

Conceptualization, M.G.K.; methodology, M.G.K. and H.-J.K.; validation, S.-A.C., M.-S.G., S.-Y.K., J.-H.K. and J.-Y.H.; formal analysis, H.-J.K.; investigation, H.-J.K.; resources, M.G.K.; writing–original draft preparation, H.-J.K.; writing–review and editing, M.G.K. and J.H.K.; supervision, M.G.K.; project administration, M.G.K. All authors have read and agreed to the published version of the manuscript.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3843.

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Supporting Information

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