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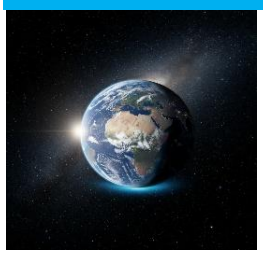

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# How does the use of GLP-1 receptor agonists affect bone mineral density and fracture risk in obese individuals?

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**Abstract**

Glucagon -like peptide-1 receptor agonists (GLP-1RAs) are an important group of drugs widely used in the treatment of type 2 diabetes and obesity. Studies indicate their beneficial effect on glycemic control and weight reduction, as well as potential involvement in bone metabolism modulation. The aim of this review was to evaluate the current knowledge regarding the impact of GLP-1RAs on bone mineral density (BMD) and fracture risk.

A narrative literature review with elements of systematic searching was conducted, covering clinical and observational studies from 2015 to 2025. The available data indicate that GLP-1RAs do not cause a significant decrease in BMD compared to placebo or insulin glargine. Some studies observed a slight increase in bone resorption markers, which did not translate into clinically relevant decreases in BMD. Cohort studies data suggest a potential decreased risk of osteoporosis among GLP-1RA-treated population. Current literature confirms the overall safety of GLP-1RA therapy in the context of bone health, although further long-term studies are necessary to fully clarify their effects on bone microarchitecture and fracture risk.

**Introduction:**

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a relatively recently introduced group of drugs used in the treatment of type 2 diabetes, and obesity (1,2). Studies conducted to date have demonstrated their beneficial effect on the cardiovascular profile in patients diagnosed with type 2 diabetes (DM2) and with increased body weight (3). GLP-1 analogues are also being used with growing frequency for weight reduction in the general population without any medical indication (4).

Weight loss, regardless of the method used, is a factor that can reduce bone mineral density and increase the risk of fractures (23). Studies conducted to date suggest a direct effect of GLP-1 analogues on structural changes in bone tissue through their interaction with osteoblasts and osteoclasts (5,9,10).

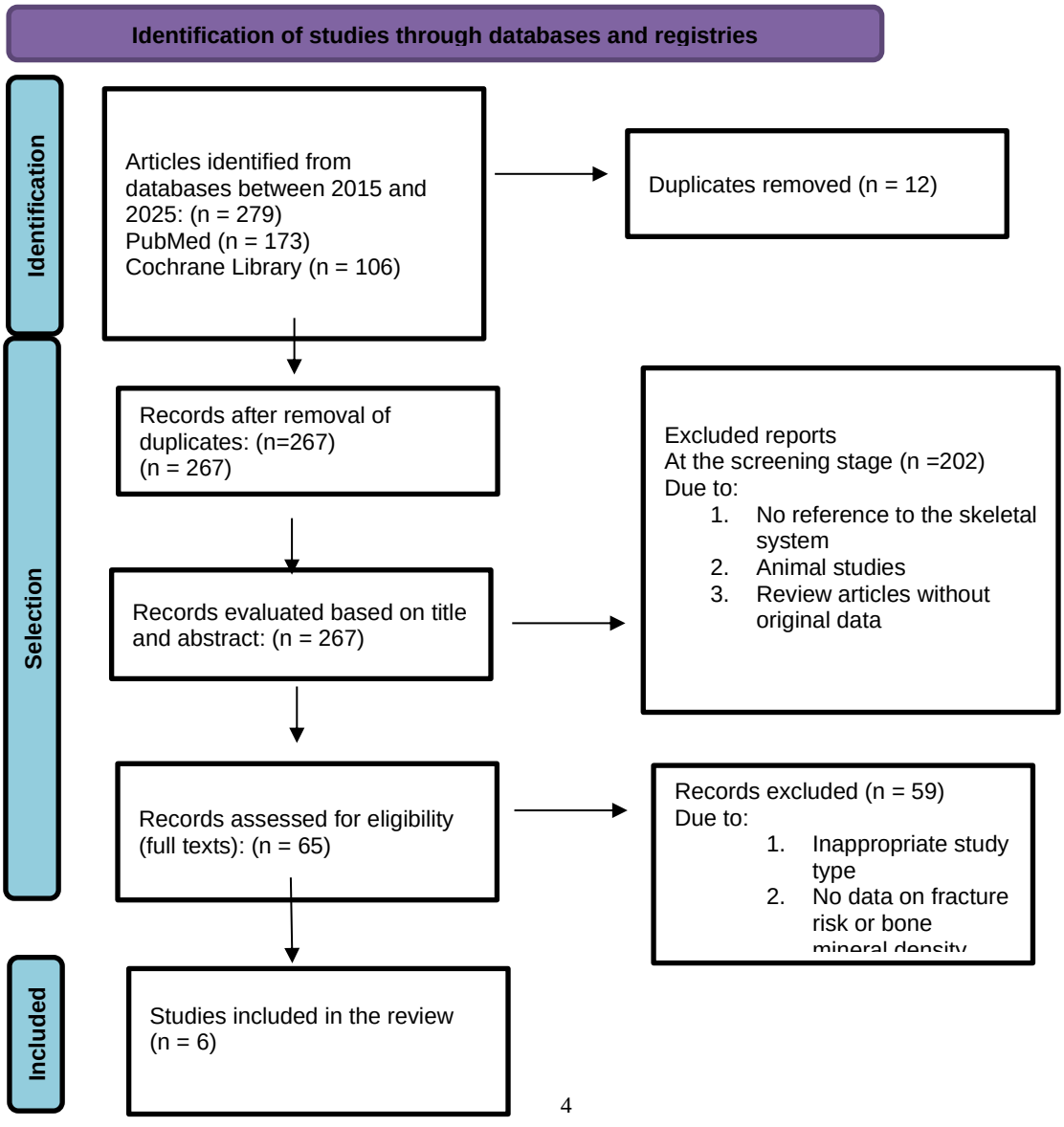
The aim of this study is to review the current knowledge on the effect of GLP-1 receptor agonists on bone metabolism, with particular consideration on changes in bone mineral density (BMD) in patients undergoing GLP-1RA therapy.

**Methodology:**

For the purposes of this study, a detailed review of the scientific literature available in the PubMed and Cochrane Library databases was conducted. The search process involved the use of precisely selected keywords, such as glucagon-like peptide 1 (GLP-1), liraglutide, semaglutide, bone mineral density, and obesity.

The inclusion criteria covered publications published between 2015 and 2025 that referred to the effect of GLP-1 analogues on bone mineral density in people with obesity. Only articles that met the quality standards for methodological reliability and data currency were included.

The review is narrative in nature with elements of systematic literature search, and the study selection process is presented in accordance with the PRISMA 2020 guidelines.



**Mechanisms of action of GLP-1RAs:**

Current GLP-1RAs are synthetic proteins with partial or complete amino acid sequence identity to endogenous GLP-1. They are distinguished by greater resistance to degradation by DPP-4, prolonged half-life, and enhanced receptor activation, which allows them to reproduce the effects of natural GLP-1. (1,2)

Among the currently available GLP-1 receptor agonists, we can distinguish between short-acting preparations (exenatide, lixisenatide) and extended-release preparations (liraglutide, semaglutide, dulaglutide). Short-acting GLP-1 analogues have a stronger effect on gastric emptying and postprandial glycemia, while extended-release preparations have a greater effect on morning blood glucose and are characterized by a more stable therapeutic effect (8).

These drugs work by mimicking the function of the natural gut hormone GLP-1, which is released by epithelial cells in the small intestine and colon in response to food intake (1,2).

The action of GLP-1 agonists results from the activation of the GLP-1 receptor, which is a G protein-coupled receptor. This receptor can be found, among others, in pancreatic beta cells, neurons of the central nervous system, bone marrow stromal cells, and osteoblasts (5,9).

GLP-1 receptor activation leads to the initiation of a series of signaling cascades, which ultimately lead to cAMP–PKA pathway activation (10), the ultimate effect of which is an elevation of intracellular $Ca^{2+}$ concentration (7), which promotes increased ATP production (7) and subsequent increased insulin secretion (6,7), suppression of glucagon secretion (6,7), and modulation of gastrointestinal function (8).

In addition, GLP-1RAs can activate alternative signaling pathways, including PI3K/Akt and MAPK/ERK, which play key roles in the regulation of cell survival, proliferation, and response to oxidative stress (5,12). It has also been shown that GLP-1RAs can exert an anti-inflammatory effect by suppressing proinflammatory cytokine production and modulating the activation of NF-κB transcription factors (12,13).

At the time of writing, the main application of GLP-1RA remains the treatment of type 2 diabetes. However, a growing number of studies indicate the positive effect of these drugs in obesity therapy (4), the treatment of metabolic dysfunction associated fatty liver disease (MAFLD) (11) and reduction of cardiovascular event risk in patients with or without diagnosed diabetes (3).

Other potential therapeutic applications of GLP-1 analogues include neuroprotective effects and the treatment of neurodegenerative diseases such as Alzheimer's disease (13).

**The effect of GLP-1RA on bone tissue:**

Preclinical studies to date, including animal models and in vitro cell analyses, indicate that GLP-1 and its agonists may affect bone tissue metabolism indirectly and directly (5,9). The GLP-1 receptor (GLP-1R) has been detected in bone marrow stromal cells and osteoblasts, which is the basis for the direct influence of GLP-1RA on osteogenesis (9,2). Stimulation of the GLP-1 receptor promotes mesenchymal stem cell differentiation towards osteoblasts. Increased expression of osteogenic markers such as RUNX2, osteocalcin, and alkaline phosphatase has been demonstrated, with simultaneous inhibition of adipogenesis. This mechanism may be related to the activation of signaling pathways PKA/ β -catenin, and PI3K/Akt (9).

It has also been shown that GLP-1 receptor agonists can inhibit osteoclastogenesis, among other things by increasing the ratio of osteoprotegerin (OPG) to receptor activator of nuclear factor κB ligand (RANKL), which leads to a decrease in osteoclast activity (5,2). In animal models, the anti-resorptive effect has also been associated with increased calcitonin secretion in response to GLP-1R stimulation in thyroid C cells, which further limits bone resorption processes (5).

The indirect effect of GLP-1RA on bone metabolism includes modulation of adipokines and anti-inflammatory effect. GLP-1 agonists reduce the expression of proinflammatory cytokines, including IL-6 and TNF-α, and suppress pathway activation of NF-κB, reducing oxidative stress in bone cells (12). In addition, they positively modulate the metabolic profile, including glycemic control and insulin resistance, which also affects osteoblast activity (1).

An important factor in the context of the effect of GLP-1 analogues on bone tissue is the fact that GLP-1RAs can induce significant body weight reduction, which may ultimately have an antagonistic effect on their potentially beneficial impact on bone tissue structure. Weight loss, regardless of the method of intervention, is associated with a reduction in mechanical loading on bone and an increase in markers of resorption such as CTX-1, which translates into a decrease in BMD, especially in the femoral neck and lumbar spine (23).

**Results:**

Six clinical trials meeting the selection criteria were included in the analysis, including four randomized controlled trials, one observational study, and one retrospective cohort study. The studies included adult populations with obesity or type 2 diabetes, and the observation period ranged from 24 to 52 weeks [14–19].

Available clinical data indicate that GLP-1 receptor agonist therapy (GLP-1RA) does not have a negative effect on bone mineral density (BMD). Four randomized clinical trials showed no significant reduction in bone mineral density (BMD) as assessed by DXA compared to control groups receiving placebo or insulin glargine [14–17]. Stable BMD values were observed in the lumbar spine, femoral neck, and total bone mass measurements [14–16].

One study showed that liraglutide may reduce BMD during intensive weight loss induced by a very low-calorie diet (VLCD), which is confirmed by a simultaneous increase in bone formation marker levels - P1NP [17]. This result suggests the possibility of using GLP-1RA as a form of protection in conditions of increased risk of bone mass loss. Nevertheless, these findings warrant further direct and comprehensive investigation.

Bone metabolism markers presented a variable profile across studies. Several studies observed a slight increase in CTX concentration, yet in no case was this change associated with a clinically significant decrease in BMD [14–16]. The concentration of bone formation markers, such as P1NP, bALP, and osteocalcin, remained stable, indicating a balance between formation and resorption processes during GLP-1RA therapy [14-19].

An important factor interfering with the interpretation of the effect of GLP-1RAs on bone tissue status remains the fact of weight reduction. It has been documented that Significant weight loss has been shown to reduce bone mineral density, independent of the method by which the weight reduction is achieved [23]. This suggests that the observed densitometric changes may result from energy deficit and reduction of mechanical loading, rather than from the direct action of the GLP-1RAs.

Data from a large retrospective cohort study showed that the use of GLP-1 receptor agonists may be associated with a reduced risk of osteoporosis compared with patients not receiving this group of drugs [20]. The mechanism behind this phenomenon remains unclear, but it is believed to involve modulation of the balance between osteoblastogenesis and osteoclastogenesis, including regulation of the osteoprotegerin (OPG) to the RANKL ligand

ratio, which is a key pathway controlling bone resorption. In addition, GLP-1 agonists have an anti-inflammatory effect, which may reduce proinflammatory cytokine-induced osteoclast activation, such as TNF-α or IL-6 (12). An indirect effect resulting from improvement of metabolic parameters, including weight loss, improved glycemic control, and increased insulin sensitivity, which have a beneficial systemic effect on balancing bone tissue metabolic processes. Although these observations are promising, they need to be confirmed in randomized clinical trials directly focused on assessing bone health in patients using GLP-1Ras (21).

Table 1. Summary of clinical studies on GLP-1 receptor agonists and bone health

| Author (Year) | Study type | Population | Intervention / comparison | Duration | Bone assessment | Key outcomes |
|---|---|---|---|---|---|---|
| Jensen SBK et al., 2024 | RCT | Adults with obesity | Liraglutide vs exercise vs combo | 52 weeks | BMD, CTX, P1NP | Liraglutide lowered BMD; exercise mitigated loss |
| Akyay OZ et al., 2023 | RCT | Postmenopausal T2DM | Exenatide vs insulin glargine | 24 weeks | BMD, CTX, P1NP, OPG/RANKL | Maintained BMD; improved OPG/RANKL |
| Cai TT et al., 2021 | RCT | Adults with T2DM | GLP-1RA vs glargine | 52 weeks | BMD, CTX, P1NP | No BMD loss; slight decline with glargine |
| Iepsen EW et al., 2015 | RCT | Women after VLCD | Liraglutide vs placebo | 52 weeks | Total BMD, CTX, P1NP | Prevented bone loss; ↑P1NP |
| Chen M et al., 2025 | Retrospective | Older T2DM | GLP-1RA users vs non-users | >12 months | Osteoporosis incidence | Lower osteoporosis risk (HR=0.69) |
| Li X et al., 2024 | Interventional | T2DM + obesity | GLP-1RA vs control | ≥24 weeks | BMD, CTX, P1NP | No BMD change; ↑CTX |

## Discussion:

Available studies suggest that treatment with GLP-1 receptor agonists does not adversely affect bone mineral density; the observed changes in BMD appear to result mainly from weight loss rather than the direct action of the drug. It is worth noting that the population of patients with obesity and type 2 diabetes is characterized by a chronic inflammatory state, insulin resistance, and bone quality disorders, which significantly hinders the unambiguous interpretation of the results obtained [5,16].

Basic research has demonstrated the potential beneficial effects of GLP-1RA on osteoblasts and suppression of osteoclastogenesis through modulation of the PKA/CREB, PI3K/Akt, and OPG/RANKL pathways, but this effect has not been conclusively confirmed clinically [5,21]. Observational data suggest a lower risk of osteoporosis in people using GLP-

1RAs, which may be due to improvement of metabolic parameters and reduction of inflammation [19].

Available meta-analyses do not confirm an increased risk of fractures during GLP-1RA treatment [20,22], but the lack of long-term clinical studies makes it difficult to fully assess the safety of these drugs in the context of an increased risk of fractures. Further analyses are needed on bone microarchitecture and the impact of the type and duration of therapy on bone remodeling.

**Conclusions:**

Available clinical data indicate that GLP-1 receptor agonist therapy (GLP-1RA) is not associated with a significant adverse effect on bone mineral density in patients with obesity and type 2 diabetes. Four randomized trials showed no reduction in BMD compared with placebo or insulin glargine, and the results were consistent regardless of the location of the bone structures studied [14–17].

Despite minor changes in bone resorption markers, there is no evidence of an imbalance between bone formation and resorption during GLP-1RA treatment. Stable P1NP, bALP, and osteocalcin values suggest that this therapy does not interfere with the fundamental processes of bone remodeling [14–17].

Weight loss, a common consequence of GLP-1RA use, remains an important factor modifying bone tissue metabolism. The data obtained indicate that weight loss may partially mask the potentially beneficial effects of these drugs on bone metabolism parameters, especially in populations undergoing intensive nutritional interventions [19].

Population data suggest the possibility of a long-term protective effect of GLP-1RA on the skeletal system. In cohort analyses, the use of GLP-1 receptor agonists was associated with a reduced risk of osteoporosis diagnosis compared to other hypoglycemic therapies [19]. However, these relationships need to be confirmed in prospective studies with long follow-up periods.

The available literature, which includes systematic reviews and meta-analyses covering larger populations, seems to confirm the neutral safety profile of GLP-1RA regarding BMD and the absence of an increased risk of fractures [20–22]. These results are consistent with

observations from clinical trials and highlight the multifactorial nature of changes in bone metabolism in people with metabolic disorders.

In summary, GLP-1RA therapy can be considered safe in terms of its effect on bone metabolism in populations with obesity and type 2 diabetes. However, there is a lack of studies evaluating the effect of GLP-1RA on bone microarchitecture and long-term effects. These studies are necessary for a full assessment of the safety of therapy in terms of bone health, especially in populations with metabolic burdens.

## Author Contribution

For full transparency, all submitted manuscripts must include an Author Contribution Statement specifying the work of each author. For research articles with multiple authors, a short paragraph must be provided stating their individual contributions.

"Conceptualization, Jakub Zalewski and Alicja Cyrzan.; methodology, Alicja Cyrzan.; software, Maciej Wojewódzki.; validation, Adam Zysk, Mateusz Ząbek and Bartosz Fronczak.; formal analysis, Beata Flis and Martyna Iwanowska.; investigation, Jakub Zalewski and Adrian Goss.; resources, Adam Zysk, Mateusz Ząbek, Alicja Cyrzan, Bartosz Fronczak.; data curation, Małgorzata Styczyńska and Maciej Wojewódzki.; writing—original draft preparation, Jakub Zalewski.; writing—review and editing, Małgorzata Styczyńska, Adrian Goss, Beata Flis.; visualization, Maciej Wojewódzki.; supervision, Jakub Zalewski and Alicja Cyrzan.; project administration, Bartosz Fronczak and Martyna Iwanowska.

All authors have read and agreed to the published version of the manuscript."

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The data presented in this study are available on request from the corresponding author.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

## Originality

The submission has not been previously published, nor is it under consideration by another journal.

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