VOLUME - 15, ISSUE - 09, SEPTEMBER - 2026 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Orthopaedics

GLP 1 RECEPTOR AGONISTS AND BONE HEALTH

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ABSTRACT A higher incidence of bone fragility and fractures is linked to diabetes mellitus. Bone metabolism may be impacted by glucagon-like peptide-1 receptor agonists (GLP-1RAs), which are frequently used to treat type 2 diabetes. Animal research, randomized controlled trials, and meta-analyses were among the experimental and clinical data examined.According to research on animals, GLP-1RAs may increase bone formation and decrease bone resorption via mechanisms involving sclerostin, OPG/RANKL, and Wnt/β-catenin. Human studies, however, typically show no consistent correlation with fracture risk and neutral effects on BMD and bone turnover.Without raising the risk of fracture, GLP-1RAs seem to have a neutral and possibly advantageous effect on bone health. To determine their skeletal effects, additional long-term randomized controlled trials are required.

KEYWORDS : GLP-1RAs; Diabetes Mellitus; Bone Metabolism; BMD; Osteoporosis; Fracture Risk.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND BONE METABOLISM

Although the exact processes connecting diabetes to poor bone health are yet unknown, patients with diabetes mellitus have a higher risk of fragility fractures [1]. The process of bone remodeling involves both osteoblast-mediated bone production and osteoclast-mediated bone resorption. The RANKL/RANK/osteoprotegerin (OPG) system is one of the mechanisms that controls this balance. While OPG, which is mostly generated by osteoblasts, suppresses osteoclastogenesis by sequestering RANKL, RANKL stimulates osteoclast differentiation and activation by binding to RANK [2].There is growing evidence that GLP-1 may affect bone metabolism in both direct and indirect ways. Increased expression of osteogenic markers, such as RUNX2, alkaline phosphatase (ALP), collagen type I (COL1), osteocalcin (OC), and procollagen type I N-terminal propeptide (P1NP), has been linked to GLP-1 receptor (GLP-1R) activation [3]. Since chronic hyperglycemia has been linked to poor bone quality and decreased bone mineral density (BMD), GLP-1 may also indirectly enhance bone health through better glycemic control [4].Several intracellular pathways that support osteoblast formation and function are activated at the cellular level by GLP-1R signaling, including PI3K/AKT, MAPK, ERK1/2, p38, and JNK [5]. Additionally, GLP-1 interacts with the canonical Wnt/ -catenin pathway, which is a key regulator of bone formation and osteoblastogenesis [6]. Additionally, it has been documented that GLP-1 inhibits the production of sclerostin (SOST), which may increase Wnt signaling and osteoblast activity [7].

By influencing osteoclast activity, GLP-1 may also lessen bone resorption. GLP-1 receptor agonists may have antiresorptive effects via a calcitonin-dependent mechanism and have been linked to decreases in bone-resorption indicators such as urine deoxypyridinoline and C-terminal telopeptide of type I collagen (CTX-1) [8]. Furthermore, through the MAPK, PKC, and PKA/PI3K/AKT/GSK-3β pathways, GLP-1R signaling may affect mesenchymal stem-cell differentiation by increasing osteoblastogenesis and decreasing adipogenic differentiation [9].

GLP-1 may control bone remodeling by stimulating osteoblast-mediated bone production and inhibiting osteoclast-mediated bone resorption, according to experimental data. However, more research is needed to determine the clinical importance of these effects, especially how they affect human bone mineral density and fracture risk.

Diabetes and Bone Metabolism

Impaired bone quality and a higher incidence of fragility fractures are linked to diabetes mellitus. Thiazolidinediones (TZDs), especially pioglitazone, have been linked to decreased bone mineral density (BMD) and an increased risk of fracture among antidiabetic treatments, particularly when used over an extended period of time in women [10]. Skeletal fragility may result from TZD-induced PPAR activation, which encourages mesenchymal stem cells to differentiate into adipogenic rather than osteogenic cells [11]. Insulin therapy and fracture risk have a more complicated relationship that may be influenced by patient-related variables, hypoglycemia, and the severity of the disease [12]. By increasing glucose-dependent insulin secretion, inhibiting glucagon, and encouraging weight loss, on the other hand, GLP-1 receptor agonists (GLP-1RAs) improve glycemic control [13]. GLP-1RAs may promote bone formation and decrease bone resorption, according to emerging research, but their effects on human BMD and fracture risk are yet unknown, especially as treatment-related weight loss may negatively impact bone density [14]. Therefore, further long-term research is required to determine their overall impact on the skeleton.

Table 1. Human Studies Evaluating the Effects of GLP-1 Receptor Agonists on Bone Metabolism and Fracture Risk

Study	Population / Sample	Intervention & Duration	Bone Outcomes	Main Findings
Bunck et al., 2011 [15]	Patients with T2D receiving metformin	Exenatide twice daily; 44 weeks	BMD, ALP, Ca^{2+}, phosphate	No significant effect on BMD or bone metabolism markers. Significant weight loss was observed.
Li et al., 2015 [16]	62 newly diagnosed patients with T2D	Exenatide 5 μg twice daily vs insulin/pioglitazone; 24 weeks	BMD, osteocalcin, CTX-1, TRAcP5b	No significant improvement in BMD or bone turnover markers, despite improved glycemic control.
Gilbert et al., 2016 [17]	Patients with T2D	Liraglutide 1.2 or 1.8 mg/day vs glimepiride; 52–104 weeks	Total BMD	No significant difference in BMD between treatment groups.
Iepsen et al., 2015 [18]	37 healthy obese women	Liraglutide 1.2 mg/day	P1NP, CTX-1	P1NP increased by 16%, suggesting increased bone formation; CTX-1 was unchanged.

Mabilleau et al., 2014 [19]	Meta-analysis of 28 RCTs in T2D	Various GLP-1RAs	Fracture risk	No significant effect on fracture risk compared with other antidiabetic therapies.
Su et al., 2015 [20]	Meta-analysis of 16 RCTs	Liraglutide or exenatide vs placebo/active treatment	Fracture risk	Liraglutide was associated with reduced fracture risk, whereas exenatide was associated with increased fracture risk.
Zhang et al., 2018 [21]	Network meta-analysis; 49,602 participants	Exenatide, liraglutide, semaglutide, dulaglutide, albiglutide, lixisenatide	Fracture risk	Exenatide showed the lowest fracture risk, followed by dulaglutide, liraglutide, albiglutide, lixisenatide and semaglutide.
Driessen et al., 2015 [22]	Meta-analyses of clinical trials	Various GLP-1RAs	Fracture risk	No significant association between GLP-1RA use and fracture risk.

Table 2. Animal Studies Evaluating the Effects of GLP-1 and GLP-1 Receptor Agonists on Bone Metabolism

Study	Animal Model	Intervention	Bone Outcomes	Main Findings
Nuche-Berenguer et al., 2009 [23]	T2D and insulin-resistant rats	GLP-1 treatment	OPG/RANKL ratio, bone formation	GLP-1 increased the OPG/RANKL ratio, suggesting reduced osteoclast activity and enhanced bone formation.
Nuche-Berenguer et al., 2010 [24]	T2D and insulin-resistant rats	Exendin-4	Wnt signaling, bone formation	Exendin-4 promoted bone formation, partly through activation of the Wnt signaling pathway.
Mabilleau et al. [25]	Old ovariectomized (OVX) rats	Exendin-4, 3 or 10 μg/kg/day; 16 weeks	ALP, CTX-1, OPG/RANKL	Exendin-4 increased ALP, decreased CTX-1, and increased the OPG/RANKL ratio, indicating enhanced bone formation and reduced bone resorption.
Nuche-Berenguer et al., 2011 [26]	Hyperlipidemic rat model	Exendin-4	OPG/RANKL ratio, osteocalcin	Exendin-4 significantly increased the OPG/RANKL ratio and osteocalcin, supporting an anabolic effect on bone.
Yamamoto et al. [27]	GLP-1R knockout (GLP-1R$^{-/-}$) mice	Calcitonin treatment	Urinary DPD, bone resorption	GLP-1R deficiency increased urinary DPD, while calcitonin reduced this increase, suggesting that GLP-1 inhibits bone resorption through a calcitonin-dependent mechanism.
Kim et al. [28]	T2D OLETF rats and MLO-Y4 osteocyte-like cells	Exendin-4	SOST/sclerostin, osteocalcin, femoral BMD	Exendin-4 reduced SOST/sclerostin expression, increased osteocalcin and improved femoral BMD, suggesting enhanced bone formation.
Meng et al. [29]	Ovariectomized animal models	GLP-1 receptor agonists	Bone mass, osteoblast differentiation	GLP-1RAs demonstrated anabolic effects, increasing trabecular and cortical bone mass and promoting osteoblast differentiation through MAPK/Wnt signaling and RunX2 activation.

DISCUSSION

The effects of GLP-1 receptor agonists (GLP-1RAs) on bone turnover, fracture risk, and bone mineral density (BMD) were assessed in this systematic review. Fragility fractures are more common in people with diabetes mellitus, and some antidiabetic medications, especially thiazolidinediones, may make skeletal risk even higher [30]. In addition to providing good glucose control and a low risk of hypoglycemia, GLP-1RAs are frequently used in type 2 diabetes and may have potential skeletal advantages [31].

Overall, GLP-1RA medication has not consistently improved BMD or bone turnover markers in human investigations. While some studies showed increases in bone-formation indicators such P1NP, several clinical trials found no appreciable changes in BMD after therapy with exenatide or liraglutide [32]. In a similar vein, meta-analyses on fracture risk have yielded contradictory findings; some have reported no significant connection, while others have suggested a neutral or perhaps protective effect [33]. Variations in GLP-1RA type, dosage, length of treatment, patient characteristics, and study design may be the cause of these discrepancies.

On the other hand, preclinical research consistently shows that GLP-1RAs have positive effects on bone. Increased BMD and osteogenic activity have been demonstrated in animal models, along with Wnt pathway regulation, elevated OPG/RANKL ratios, increased osteoblast activity, and decreased sclerostin expression [34]. By a calcitonin-dependent mechanism, GLP-1 may also lessen bone resorption [35].

Differences in medication dosages, treatment length, GLP-1 receptor expression, and underlying metabolic disorders could account for the disparity between animal and human results. Additionally, a lot of clinical studies had short follow-up periods, involved very small and younger populations, and weren't expressly developed to evaluate fractures. Several studies also lacked adequate characterization of baseline bone state and sex-specific effects. Significantly, significant weight loss linked to GLP-1RA treatment may have an independent impact on bone turnover and BMD.All things considered, the available data points to a possible advantageous function of GLP-1RAs in bone metabolism, especially from animal investigations; nevertheless, conclusive proof of their capacity to maintain BMD or lower the risk of fracture in humans is still missing. To determine their clinical skeletal effects, larger, longer-term, well powered randomized trials including fracture outcomes and thorough bone evaluations are required.

CONCLUSIONS

Antidiabetic medications may have an impact on skeletal health, and patients with diabetes mellitus are more susceptible to fragility fractures. Despite encouraging skeletal improvements noted in preclinical investigations, current evidence indicates that GLP-1 receptor agonists (GLP-1RAs) have a mainly neutral effect on bone mineral density (BMD) and fracture risk. As a result, GLP-1RAs seem to be safe for the skeleton, although it is still unknown if they will have any protective effects on bone. To fully understand their impact on BMD, bone turnover, and fracture risk, large-scale, long-term,

double-blind randomized controlled trials are required.

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