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Effects of GLP-1 Receptor Agonists on Bone Metabolism and Fracture Risk in Type 2 Diabetes and Obesity: Mechanisms and Clinical Evidence — A Narrative Review

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ABSTRACT

Introduction and purpose: Type 2 diabetes (T2D) is associated with increased fragility fracture risk despite preserved or elevated bone mineral density (BMD) ("diabetic bone paradox"). As glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used in T2D and obesity, this narrative review synthesizes evidence on their effects on bone turnover, BMD and fracture outcomes, contrasting diabetic and non-diabetic populations.

Brief description of the state of knowledge: Preclinical data suggest GLP-1 RAs may promote osteoblastogenesis and reduce marrow adipogenesis (e.g., via Wnt/β-catenin and OPG/RANKL signalling). Clinically, effects appear context-dependent and strongly influenced by weight loss. In T2D, most trials report neutral or small favourable changes in BMD and bone turnover markers. Some meta-analyses report a possible reduction in fractures (notably with longer liraglutide exposure), but fracture events were often secondary/safety endpoints and were not adjudicated, limiting certainty.

Summary (conclusions): Overall, current evidence to date suggests no major skeletal safety signal for GLP-1 RAs in T2D, while definitive fracture-prevention effects remain unproven. In obesity, baseline risk assessment and monitoring of bone health should be considered in high-risk individuals, and future studies should prioritize adjudicated fracture endpoints and longer follow-up.

Keywords: Glucagon-like peptide-1 receptor agonists; Diabetes Mellitus, Type 2; Obesity; Osteoporosis; Fractures, Bone; Bone Density.

1. Introduction and purpose

The rising global prevalence of type 2 diabetes (T2D) and obesity has necessitated the widespread use of therapeutic agents that effectively manage hyperglycemia and induce weight loss. However, skeletal health in these populations presents a complex clinical picture. Patients with T2D frequently exhibit the "diabetic bone paradox," a condition characterized by an increased risk of fragility fractures despite maintaining normal or elevated bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry. This susceptibility is driven by compromised bone quality, including the accumulation of advanced glycation end-products (AGEs) and microarchitectural deterioration, which renders the skeleton fragile despite preserved mass. [1] [2] [3]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become a cornerstone treatment for T2D and are increasingly utilized for chronic weight management in obesity. Preclinical evidence suggests that GLP-1 RAs may possess osteoanabolic properties, potentially enhancing osteoblast differentiation and inhibiting resorption via the Wnt/β -catenin pathway. However, the clinical translation of these mechanisms is confounded by the potent weight-lowering effects of these drugs. Rapid and significant weight loss, particularly in non-diabetic obesity, reduces mechanical loading on the skeleton. According to the "mechanostat" theory, this unloading triggers physiological bone resorption and density loss, which may counteract direct drug-mediated skeletal benefits. [3] [4] [5]

Consequently, the net impact of GLP-1 RAs on bone health remains a subject of ongoing investigation, with outcomes likely divergent based on the clinical indication and the magnitude of weight reduction. This narrative review aims to synthesize current evidence regarding the impact of GLP-1 RAs on bone metabolism, bone mineral density, and fracture risk, specifically distinguishing between effects observed in patients with type 2 diabetes versus those treated for obesity without diabetes. [6] [7]

DESCRIPTION OF THE STATE OF KNOWLEDGE

1. Baseline problem: Bone fragility in T2D and obesity

1.1 T2D: paradox of normal/high BMD vs higher fracture risk

Patients with type 2 diabetes mellitus (T2D) exhibit a clinical contradiction often termed the “diabetic bone paradox,” characterized by a significantly increased risk of fragility fractures despite maintaining normal or even elevated areal bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA). This dissociation between density and strength indicates that standard DXA screening frequently underestimates fracture probability in this population, as the increased susceptibility is driven primarily by deterioration in bone quality rather than bone mass loss. [1] [2] [8]

The pathophysiology of this fragility involves structural and material alterations within the bone tissue. Chronic hyperglycemia facilitates the accumulation of advanced glycation end-products (AGEs) in the bone matrix, which induce non-enzymatic cross-linking of type 1 collagen, rendering the bone stiff and brittle. Additionally, diabetic osteopathy is associated with microarchitectural defects, such as increased cortical porosity and suppressed bone turnover, which compromise mechanical integrity without necessarily reducing areal BMD. [1] [2] [9]

Fracture risk in T2D is further amplified by extra-skeletal factors that increase the likelihood of falls. Microvascular complications, including peripheral neuropathy and retinopathy, impair

balance and vision, while episodes of hypoglycemia associated with antidiabetic therapy can lead to acute loss of stability. Furthermore, general frailty and polypharmacy in older patients with T2D contribute to a high-risk environment where even minor trauma can result in fracture. [1] [2] [10]

1.2 Obesity and weight loss: mechanical loading, muscle, and nutrition

In populations with obesity or overweight, excess body weight traditionally imposes increased static mechanical loading on the skeleton, which stimulates bone formation and often results in higher bone mineral density (BMD) compared to lean individuals. However, this increased bone mass does not confer absolute protection against fractures. The relationship is complex; while mechanical load supports density, factors such as poor bone quality, increased fall impact forces due to higher body mass, and metabolic dysregulation can compromise skeletal integrity. Consequently, the assumption that obesity is purely protective against fragility fractures is increasingly challenged, particularly when metabolic comorbidities are present. Furthermore, systematic reviews confirm that agents like liraglutide and semaglutide drive clinically relevant weight reduction in individuals with obesity but without diabetes, making the skeletal consequences of this significant mass loss a pertinent clinical concern. [1] [11] [12]

Therapeutic weight loss, while beneficial for metabolic health, introduces a distinct challenge to skeletal homeostasis. Significant reduction in body weight leads to mechanical unloading, which triggers a physiological response characterized by increased bone turnover and elevated resorption markers, such as C-terminal telopeptide (CTX). This process frequently results in a decline in BMD, particularly at weight-bearing sites like the hip and lumbar spine. A critical component of this phenomenon is the potential loss of lean mass. The reduction of muscle mass during weight loss, potentially leading to sarcopenia, diminishes the dynamic strain on bone surfaces, further exacerbating bone density decline and potentially elevating fracture risk in vulnerable cohorts. [13] [14] [15]

The extent of skeletal deterioration during weight reduction is modulated by nutritional and behavioral factors. Adequate intake of protein, calcium, and vitamin D is recognized as essential to support bone remodeling processes during periods of caloric restriction. Furthermore, physical activity, specifically resistance training, plays a pivotal role in preserving both lean mass and bone density. Evidence suggests that maintaining mechanical stimulation through exercise can attenuate the resorptive signals generated by weight loss, highlighting the importance of a multimodal approach to managing skeletal health in patients undergoing obesity treatment. [11] [16]

Determinant / mechanism	Clinical correlate	Suggested assessment / note
“Diabetic bone paradox” (bone quality > BMD)	Higher fracture risk despite normal/high DXA	Consider that DXA may underestimate risk in T2D; interpret results cautiously
AGE accumulation and collagen cross-linking	Increased fragility, reduced toughness	Emphasize glycemic control as indirect modifier of bone quality
Altered microarchitecture (e.g., cortical porosity)	Fragility not captured by areal BMD	Note value of advanced imaging (when available) and surrogate measures
Falls risk (neuropathy, retinopathy, hypoglycemia, frailty)	Higher incidence of low-trauma fractures	Always discuss falls as parallel pathway independent of BMD
Weight loss–related mechanical unloading	Decline in hip/spine BMD; increased resorption markers	Highlight magnitude/speed of weight loss as key confounder in GLP-1RA studies
Loss of lean mass / sarcopenia	Reduced protective loading + higher fall risk	Mention resistance training as mitigation strategy
Nutritional factors during caloric restriction	Calcium/Vit D/protein deficits may worsen bone turnover	Note need to maintain adequate calcium, vitamin D, and protein intake
Comorbid CKD / CKD-MBD risk	Abnormal mineral metabolism affects bone	Mention kidney disease as an important modifier (esp. in long-standing diabetes)
Concomitant medications affecting bone	TZDs, glucocorticoids, PPIs, etc.	Flag as confounders in observational studies and clinical interpretation

Table 1. Caption: This table summarizes key determinants of fracture risk in type 2 diabetes and obesity that are not fully captured by areal BMD measured by DXA. It highlights bone-quality mechanisms (e.g., advanced glycation end-products and microarchitectural deterioration) and non-skeletal contributors such as falls and frailty, which are essential for

interpreting skeletal outcomes during pharmacologically induced weight loss (including GLP-1 receptor agonist therapy). Abbreviations: T2D = type 2 diabetes; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; AGE = advanced glycation end-product; CKD-MBD = chronic kidney disease–mineral and bone disorder; TZD = thiazolidinedione; PPI = proton pump inhibitor.

2. GLP-1 receptor biology relevant to bone (mechanisms)

2.1 Biological Mechanisms: The Incretin–Bone Axis

2.1.1 GLP-1R expression and direct cellular targets

Glucagon-like peptide-1 receptors (GLP-1R) have been identified in various extra-pancreatic tissues, including the skeleton, suggesting a direct role for incretins in bone metabolism. Preclinical studies utilizing RT-PCR and immunohistochemistry have confirmed the presence of GLP-1R mRNA and protein in bone marrow cells, primary osteoclasts, and osteoblasts. Furthermore, these receptors are expressed on bone marrow stromal cells (BMSCs), which serve as common progenitors for both osteoblasts and adipocytes. Activation of GLP-1Rs appears to influence the lineage fate determination of BMSCs, promoting differentiation toward the osteoblastic lineage while simultaneously suppressing adipogenesis. This modulation of the "fat-bone axis" suggests that GLP-1 receptor agonists (GLP-1 RAs) may enhance bone formation by increasing the pool of osteoblasts available for matrix synthesis and reducing marrow adiposity, a factor often inversely correlated with bone mass. [5] [17] [18]

2.1.2 Key signaling pathways (Wnt/β-catenin; OPG/RANKL; sclerostin)

The anabolic effects of GLP-1 are mediated through several intracellular signaling cascades. A primary mechanism involves the activation of the Wnt/β-catenin signaling pathway, which is critical for osteoblast differentiation and survival. GLP-1 RAs stabilize β-catenin, allowing its nuclear translocation and subsequent upregulation of osteogenic genes such as *Runx2*, alkaline phosphatase (*ALP*), and osteocalcin (*OC*). Concurrently, GLP-1 signaling has been shown to downregulate the expression of sclerostin (encoded by *SOST*), a potent inhibitor of bone formation secreted by osteocytes. Additionally, GLP-1 RAs modulate the OPG/RANKL/RANK system, which governs osteoclastogenesis. Treatment with agents like exendin-4 or liraglutide increases the expression of osteoprotegerin (OPG) relative to the receptor activator of nuclear factor-κB ligand (RANKL), thereby inhibiting osteoclast differentiation and reducing bone resorption activity. Other involved pathways include the MAPK and PI3K/AKT signaling routes, which further support cell proliferation and prevent apoptosis in osteoblastic cells. [5] [18] [19]

2.1.3 Evidence from animal models (OVX mice/rats)

In ovariectomized (OVX) rodent models of osteoporosis, which simulate postmenopausal bone loss, GLP-1 RAs have demonstrated consistent protective effects. Chronic administration of liraglutide or exenatide to OVX mice significantly improved trabecular bone mass, connectivity, and structural parameters compared to vehicle-treated controls, although beneficial effects on cortical bone were less pronounced. Similarly, in non-diabetic OVX rats, daily liraglutide injections prevented bone loss and preserved bone mineral density (BMD) by stimulating osteoblastogenesis and inhibiting marrow adiposity, evidenced by reduced expression of the adipogenic transcription factor *PPARγ*. Histomorphometric analyses in these models reveal that GLP-1 RAs can increase trabecular thickness and number while reducing trabecular separation. Importantly, these anabolic benefits appear independent of the glucose-lowering effects of the drugs, as they occur in non-diabetic animals, suggesting a direct skeletal mechanism or modulation via other systemic factors such as calcitonin. [17] [19] [20]

2.1.4 Gut–bone axis context (GLP-2/GIP) and translational caveats

GLP-1 functions within a broader "gut–bone axis" alongside other incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-2 (GLP-2). Clinical studies indicate that subcutaneous injections of GIP and GLP-2 acutely reduce the bone resorption marker CTX in patients with type 2 diabetes, with GIP also increasing the formation marker P1NP. While GLP-2 has shown potential to increase spinal BMD in conditions like short-bowel syndrome, the direct translational relevance of GLP-1 specific preclinical data to humans remains complex. A major translational limitation is the interspecies difference in GLP-1 receptor expression in the thyroid; while GLP-1 strongly stimulates calcitonin secretion (an anti-resorptive hormone) in rodents, human thyroid C-cells express very low levels of GLP-1 receptors, and GLP-1 RAs do not acutely stimulate calcitonin release in humans. Consequently, the potent anti-resorptive effects mediated by calcitonin in murine models may not be replicable in human physiology. [5] [17] [21] [22]

2.2 Diabetic osteopathy and baseline risk factors

Patients with type 2 diabetes mellitus (T2D) exhibit a condition often described as the “diabetic bone paradox,” characterized by an increased risk of fragility fractures despite maintaining normal or even elevated areal bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA). This discrepancy indicates that fracture risk in T2D is driven principally by compromised bone quality rather than reduced bone mass. The pathophysiology of this diabetic osteopathy is multifactorial, involving chronic hyperglycemia which fosters the

accumulation of advanced glycation end-products (AGEs) within the bone matrix. These AGEs induce non-enzymatic cross-linking of type 1 collagen, resulting in stiff, brittle bone with impaired material properties and reduced ability to absorb energy before fracturing. Furthermore, diabetic bone is often characterized by microarchitectural deterioration, such as increased cortical porosity, and a state of low bone turnover with uncoupled remodeling, features that standard densitometry often fails to capture. Consequently, BMD T-scores frequently underestimate the true fracture probability in this population. [1] [2] [5] [19]

In contrast to type 1 diabetes, where absolute insulin deficiency typically leads to reduced peak bone mass and lower BMD early in the disease trajectory, T2D affects the skeleton through pathways involving insulin resistance and hyperinsulinemia that may initially preserve bone density while degrading its quality. Beyond these skeletal deficits, fracture risk in T2D is significantly amplified by extra-skeletal factors that increase the propensity for falls. Long-standing diabetes is associated with microvascular complications, including peripheral neuropathy, which impairs balance and proprioception, and retinopathy, which compromises vision. Additionally, episodes of hypoglycemia, whether induced by tight glycemic control or specific antidiabetic medications, further elevate fall risk. Frailty and sarcopenia also contribute to this complex risk profile, creating a clinical scenario where maintaining bone strength is paramount yet difficult to monitor via conventional imaging. [1] [9]

Understanding the distinct nature of diabetic osteopathy is critical when evaluating the safety and efficacy of glucose-lowering therapies such as GLP-1 receptor agonists. Because the diabetic skeleton is already compromised by altered material properties and suppressed bone turnover, therapeutic agents must be scrutinized for their potential to either exacerbate or mitigate these underlying quality deficits. This baseline fragility provides the essential context for interpreting changes in bone turnover markers and fracture outcomes, as therapies that normalize remodeling processes without inducing further cortical deterioration may offer specific advantages in this high-risk population. [1] [2]

2.3 Weight loss, body composition, and skeletal unloading

The relationship between body weight and skeletal health is governed largely by the “mechanostat” theory, which posits that bone tissue adapts its strength and mass to the mechanical strains placed upon it. Mechanical loading stimulates osteocytes to suppress sclerostin and upregulate osteogenic pathways, thereby maintaining bone density. Conversely, significant weight reduction results in skeletal unloading, reducing the mechanical strain on weight-bearing bones such as the lumbar spine and hip. This reduction in strain provides a physiological signal to downregulate bone formation and upregulate resorption, leading to a

decline in bone mineral density (BMD) as the skeleton adapts to a lighter body mass. Consequently, diet-induced weight loss is frequently associated with acute increases in bone resorption markers, such as C-terminal telopeptide of type 1 collagen (CTX), and subsequent loss of bone mass. [11] [13] [14]

Beyond total body weight, changes in body composition—specifically the ratio of lean mass to fat mass—play a critical role in mediating skeletal adaptation. Lean mass exerts a stronger positive influence on bone mass than fat mass, likely due to the dynamic loads applied by muscle contraction on bone surfaces. While GLP-1 receptor agonists (GLP-1 RAs) are effective at reducing visceral adipose tissue and total body weight, this weight reduction often includes a loss of lean mass unless counteracted by specific interventions. The preservation of lean tissue during weight loss is therefore a crucial factor in mitigating the skeletal deficits associated with rapid weight reduction. Interventions that combine GLP-1 RAs with exercise, particularly resistance training, have been shown to preserve lean mass and attenuate the decline in hip and spine BMD observed with pharmacological weight loss alone. [11] [16]

The magnitude and velocity of weight loss are major confounders when interpreting the direct effects of GLP-1 RAs on bone metabolism. In clinical trials where GLP-1 RAs induce substantial weight loss (e.g., >5–10%), an increase in resorption markers and a decrease in BMD are frequently observed. This effect is likely driven by the physiological response to unloading rather than a direct toxic effect of the drug on bone cells. This dynamic is particularly evident in the post-bariatric surgery setting, where GLP-1 RAs are increasingly utilized to manage weight regain, inducing significant additional weight loss that further reduces mechanical loading on the skeleton. For instance, correlations have been observed between the degree of weight loss and the extent of BMD reduction in the pelvis and other weight-bearing sites. Conversely, in trials involving patients with type 2 diabetes where weight loss is more modest, bone turnover markers and BMD often remain stable or show slight improvements, potentially unmasking the direct, non-weight-dependent effects of GLP-1 signaling on the skeleton. [15] [23] [24] [25]

Therefore, separating the direct skeletal effects of GLP-1 RAs from the indirect consequences of weight loss requires careful consideration of the study population and the magnitude of weight reduction achieved. While nutritional factors such as adequate calcium and vitamin D intake are standard countermeasures, the dominant force driving bone turnover changes in obesity trials appears to be the mechanical unloading associated with the potent weight-lowering efficacy of these agents. [3] [14]

Given that substantial weight loss inherently drives skeletal resorption through mechanical unloading, clinical data regarding GLP-1 RAs must be interpreted within the context of weight change magnitude. Distinguishing whether observed bone turnover alterations result from physiological adaptation to a lower body mass or specific pharmacological actions is essential for evaluating the net safety profile of these agents in clinical practice. [14] [23]

3. Clinical evidence – outcomes by domain (BMD, BTM, fractures)

3.1 BMD and bone turnover markers (clinical evidence)

In non-diabetic populations with obesity or high fracture risk, GLP-1 receptor agonist (GLP-1 RA) treatment appears strongly linked to weight-loss-associated bone turnover changes. Trials utilizing semaglutide 1.0 mg or liraglutide 3.0 mg report significant weight reductions ranging from approximately 7 kg to 14 kg, accompanied by increases in the resorption marker CTX and reductions in hip or spine bone mineral density (BMD) compared to placebo or exercise alone [11] [14] [15]. However, one study in weight-reduced women maintained on lower-dose liraglutide (1.2 mg) showed increased formation marker P1NP (+16%) and preserved bone mineral content, suggesting the magnitude of ongoing weight loss and dosage may modulate the mechanical unloading effect on bone [13].

In patients with T2D, the data regarding BMD and turnover markers are discordant across meta-analyses. While one meta-analysis reports significant increases in lumbar spine BMD and a decrease in the resorption marker CTX, another reports a significant increase in CTX without significant changes in site-specific BMD [8] [23]. Individual T2D trials have shown potential benefits, such as exenatide preventing age-related BMD decline or increasing hip BMD compared to baseline, and real-world evidence suggests a reduced incidence of osteoporosis diagnosis among GLP-1 RA users [26] [27]. A critical limitation in interpreting these findings is the high heterogeneity across studies and the confounding effect of weight loss on direct bone metabolism measurements [8] [14]. Key clinical trials and meta-analyses reporting BMD and BTMs are summarized in Table 2.

Table 2. Clinical trials and meta-analyses reporting bone mineral density (BMD) and bone turnover markers (BTMs) with GLP-1 receptor agonists.

Study (Author, Year)	Population	Agent /Dose	Duration	Comparator	Weight Change	BMD Outcome (Site)	BTM Outcome
Li et al., 2024 (Meta-analysis)	T2D	GLP-1 RAs (pooled)	4–104 weeks	Anti-diabetic drugs or Placebo	NR	Increased Lumbar Spine and Femoral Neck BMD	Decreased CTX; Increased BALP, Osteocalcin
Kim et al., 2024 (Meta-analysis)	Mixed (T2D and Obesity)	GLP-1 RAs (pooled)	>4 weeks	Placebo or Untreated	NR	No significant change (Femoral Neck, Total Hip, Spine)	Increased CTX; No significant change in P1NP
Hansen et al., 2024	Increased fracture risk (No diabetes)	Semaglutide 1.0 mg/w	52 weeks	Placebo	-6.8 kg (ETD vs placebo)	Decreased Lumbar Spine (-1.8%) and Total Hip (-2.0%)	Increased CTX; No change in P1NP
Jensen et al., 2024	Obesity without diabetes	Liraglutide 3.0 mg/d	52 weeks	Placebo, Exercise, Combination	-13.74 kg (Lira) vs -7.03 kg (Placebo)	Liraglutide alone reduced Hip/Spine BMD; Combination preserved BMD	CTX increased with weight loss
Dinkla et al., 2025	Older adults (Overweight, Pre-DM/T2D)	Semaglutide 1.0 mg/w	20 weeks	Lifestyle counseling	-5.3% (Sema) vs -0.89% (Control)	No significant difference (Whole body)	No significant difference (CTX, P1NP)

Iepsen et al., 2015	Weight-reduced obese women (No T2D)	Liraglutide 1.2 mg/d	52 weeks	Control (No treatment)	-0.2 kg (Lira) vs +1.7 kg (Control)	Prevented BMC loss vs Control	P1NP increased +16% vs Control
Cai et al., 2021	T2D	Exenatide; Dulaglutide	52 weeks	Insulin Glargine; Placebo	-1.58 kg (Exenatide); +0.08 kg (Dulaglutide)	Exenatide increased Total Hip; Dulaglutide attenuated FN loss	NR
Eriksson et al., 2019	Obese, antipsychotic-treated (No T2D)	Exenatide	3 months	Placebo	Significant reduction (NR kg)	Increased Lumbar Spine BMD (+0.01 g/cm²)	Trend decrease in P1NP (p=0.06)
Chen et al., 2025	T2D	GLP-1 RAs	Observational (Real-world)	Non-GLP-1 RA users	NR	Reduced incidence of Osteoporosis diagnosis	NR

Table 2 Caption: This table summarizes key randomized controlled trials and meta-analyses investigating the effects of GLP-1 receptor agonists on bone mineral density (BMD) and bone turnover markers (BTMs). In T2D, analyses suggest neutral to modestly anabolic signals in some datasets, trials in non-diabetic obesity involving significant weight loss often report increased resorption markers (CTX) and reduced BMD unless counteracted by exercise. Abbreviations: BMC = Bone Mineral Content; CTX = C-terminal telopeptide; P1NP = Procollagen type 1 N-terminal propeptide; FN = Femoral Neck; LS = Lumbar Spine; ETD = Estimated Treatment Difference; NR = Not Reported.

Notes:

Li 2024—very high heterogeneity (I^2 >90%); mostly liraglutide-driven data.

Kim 2024—only 7 RCTs; heterogeneity in agents/doses and short follow-up in several trials.

Hansen 2024—between-group weight-loss difference likely confounds direct skeletal effects; small sample size; HR-pQCT subset.

Jensen 2024—secondary analysis; outcomes not primary endpoints; combination with exercise mitigated BMD loss.

Dinkla 2025—pilot RCT, n≈20; 20-week duration; post-hoc analysis.

Iepsen 2015—maintenance phase after weight loss; no placebo injections.
Cai 2021—small sample (n=65); BTMs not reported.
Eriksson 2018—short duration (3 months); specific antipsychotic-treated population.
Chen 2025—observational; osteoporosis defined by diagnosis codes rather than DXA; residual confounding.

3.2 Fracture outcomes in T2D and obesity (clinical evidence)

Meta-analyses of randomized controlled trials (RCTs) present a duration-dependent signal regarding GLP-1 RAs and fracture risk. While network meta-analyses including shorter trials with a median of 26 weeks report neutral associations with fracture risk compared to placebo or other active comparators, analyses focusing on long-term exposure demonstrate potential protective effects [28]. Specifically, pooled data indicate that significant fracture risk reduction (RR 0.77; OR 0.71) is primarily observed in trials with treatment durations exceeding 52 to 78 weeks, suggesting that skeletal benefits may require sustained exposure to manifest [2] [7] [29] Agent-specific analyses frequently identify liraglutide as a primary driver of fracture risk reduction, with subgroup analyses showing significant benefits (RR 0.42 to OR 0.62) not consistently seen with other agents like exenatide or semaglutide in pooled T2D datasets [7] [10]. In network rankings, GLP-1 RAs appear effective but may rank lower than SGLT-2 inhibitors for fracture prevention in real-world settings [30]. A major limitation of this evidence is that fractures were frequently reported as safety adverse events rather than primary adjudicated endpoints, and many included trials had follow-up periods insufficient to fully capture osteoporotic changes [7] [29].

Table 3. Meta-analyses and network meta-analyses on fracture outcomes with GLP-1 receptor agonists.

Analysis	Design Data	/Population	Exposure Follow-up	/Comparator	Main fracture finding	Key limitations
Chai et al. 2022	Systematic Review and Network Meta-analysis of 177 RCTs	T2DM	Median follow-up: 26 weeks	Insulin, Metformin, Sulfonylureas, TZD, AGI, Placebo	• vs Placebo: OR 1.27 (95% CI 0.88–1.83) • vs Insulin: OR 1.05 (0.54–2.04) • vs TZD: OR 1.00 (0.32–3.10)	None of the RCTs included were tested for BMD/bone metabolism indexes; results of TZD comparisons mainly indirect; considers all

						drugs in class as same intervention.
Cheng et al. 2019	Meta-analysis of 38 RCTs	T2DM	Duration ≥24 weeks; Subgroups: ≤26, 26–52, >52 weeks	Placebo and other anti-diabetic drugs	• Overall: OR 0.71 (95% CI 0.56–0.91) • Duration >52 weeks: OR 0.59 (0.44–0.80) • Liraglutide: OR 0.56 (0.38–0.81)	Fracture not a major endpoint (analyzed as serious adverse event); bone status/calcium metabolism not included.
Kong et al. 2021	Meta-analysis of 110 RCTs (40 GLP-1 RA trials)	T2DM	Duration ≥12 weeks (ranged 12–234 weeks)	Placebo or active drugs	• GLP-1 RAs overall: OR 0.94 (95% CI 0.72–1.23) • Liraglutide 1.8 mg: OR 0.621 (0.413–0.933)	Follow-up time relatively short; fracture events ignored/not reported as adverse events in many studies; lack of lifestyle records.
Zhang et al. 2025	Meta-analysis of 44 RCTs	T2DM	Subgroups included >78 weeks	Placebo or other anti-diabetic drugs	• Pooled RR: 0.77 (95% CI 0.61–0.96) • Treated >78 weeks: RR 0.77 (0.61–0.96) • Liraglutide: RR 0.42 (0.21–0.85)	Limited nature of contemporary research; limited number of studies imposed restrictions on subgroup analysis.
Alalwani et al. 2025	Network Meta-analysis of 33 RCTs	T2DM	Excluded <12 weeks	Bisphosphonates, Metformin, SGLT-2i	• Overall risk reduction: RR 0.80 (95% CI 0.65–0.94) • vs Bisphosphonates: Less effective (p=0.03) • vs SGLT-2i: Superior (p=0.01)	Limited bone-specific data for newer GLP-1 RAs; short follow-up periods; fracture outcomes generally secondary/safety endpoints.
Mostafa et al. 2024	Network Meta-analysis of 13 population-based cohort studies	T2DM	Median follow-up varies (e.g., 233 days to 3.38 years across studies)	Other GLMs, DPP-4i, SGLT-2i	• vs Other GLMs: OR 0.402 (95% CI 0.207–0.782) • vs SGLT-2i: OR 1.23 (0.73–2.05) • SUCRA Rank: ~48% (3rd after SGLT-2i combinations and SGLT-2i alone)	Potential lag or immortal time bias; did not provide data on crucial covariates (BMD, Vitamin D); did not analyze specific drug types.

Abbreviations: AGI: Alpha-glucosidase inhibitor; BMD: Bone mineral density; CI: Confidence interval; DPP-4i: Dipeptidyl peptidase-4 inhibitors; GLM: Glucose-lowering medication; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; NR: Not reported; OR: Odds ratio; RCT: Randomized controlled trial; RR: Relative risk; SGLT-2i: Sodium-glucose cotransporter-2 inhibitors; SUCRA: Surface under the cumulative ranking curve; T2DM: Type 2 diabetes mellitus; TZD: Thiazolidinedione.

Meta-analyses and network meta-analyses evaluating fracture outcomes with GLP-1 receptor agonists are summarized in Table 3. Overall, pooled estimates suggest a neutral to potentially protective association with fractures, with the most consistent signal emerging in analyses restricted to longer treatment durations and with substantial between-study heterogeneity. Importantly, across most included trials fractures were captured as adverse events rather than adjudicated primary endpoints, which limits causal inference and underscores the need for dedicated long-term skeletal outcome studies. [2] [7] [10] [28] [29] [30]

4. Agent- and context-specific synthesis

4.1 By molecule and potency

Evidence regarding specific GLP-1 receptor agonists suggests heterogeneity driven by molecular potency, dosing, and clinical indication. Liraglutide has been frequently identified in meta-analyses as the agent most strongly associated with fracture risk reduction in patients with type 2 diabetes (T2D), particularly in trials with extended follow-up. Pooled analyses have reported significant risk reductions for liraglutide that are not consistently observed with other agents such as exenatide or lixisenatide, although head-to-head fracture data remain limited. In contrast, trials utilizing semaglutide, particularly at doses used for obesity (1.0 mg or higher), present a different safety signal characterized by increased bone resorption markers (CTX) and reduced bone mineral density (BMD) at weight-bearing sites like the hip and spine. This discrepancy likely reflects the greater magnitude of weight loss achieved with potent newer-generation agents compared to earlier GLP-1 analogs, rather than distinct molecular toxicity. While exenatide has shown isolated benefits on BMD in some T2D cohorts, the overall class effect in T2D appears neutral to protective, whereas high-dose exposure in non-diabetic obesity aligns more closely with weight-loss-associated skeletal remodeling. [2] [7] [14] [29]

4.2 Effect modifiers and confounders

The clinical impact of GLP-1 receptor agonists on the skeleton is heavily modified by the magnitude of weight reduction, treatment duration, and concurrent mechanical loading. In trials involving substantial weight loss (e.g., >5–10%), typical of obesity management, mechanical

unloading serves as a potent stimulus for bone resorption, often masking potential direct osteoanabolic effects of GLP-1 receptor stimulation. This “unloading effect” explains why significant increases in resorption markers and declines in BMD are frequently observed in obesity trials but not in T2D trials where weight loss is more modest. Treatment duration is another critical modifier; meta-analyses indicate that fracture risk reduction in T2D is primarily observable after long-term exposure (>52 to 78 weeks), suggesting that time is required for the stabilization of bone turnover or for metabolic benefits to translate into structural competence. Furthermore, physical exercise has been identified as a vital countermeasure; combinatory interventions of GLP-1 RAs and exercise have been shown to preserve bone mass at the hip and spine despite significant weight loss, effectively mitigating the resorption signal associated with drug monotherapy. Additionally, as pooled analyses from major cardiovascular outcome trials demonstrate beneficial effects of GLP-1 RAs on albuminuria and glomerular filtration rate, the potential modulation of chronic kidney disease-mineral and bone disorder (CKD-MBD) pathways remains an important covariate when interpreting fracture risk in patients with advanced diabetic kidney disease. [11] [13] [14] [29] [31]

4.3 Clinical interpretation framework

Interpreting skeletal safety requires a framework that distinguishes between metabolic restoration in T2D and rapid unloading in obesity. In T2D, where bone quality is compromised by suppressed turnover and advanced glycation end-products despite normal BMD, GLP-1 RAs may offer a “protective” profile by normalizing turnover rates without inducing detrimental resorption. Mechanistic data suggest these agents may address the uncoupled remodeling specific to the diabetic state. Conversely, in non-diabetic obesity, the primary clinical signal is weight-loss-associated bone loss. While fracture data remain largely neutral in T2D populations, the reduction in hip and spine BMD observed in high-risk non-diabetic cohorts treated with potent agonists warrants caution. Clinicians must weigh the metabolic and cardiovascular benefits against potential skeletal risks, particularly in older adults with existing osteopenia or those achieving rapid, profound weight loss. In these scenarios, current evidence supports viewing bone health preservation as an active clinical target requiring monitoring and potentially adjunct strategies (e.g., resistance training), rather than assuming an inherent protective effect of the drug class. [2] [8] [14] [15]

Summary

Current evidence indicates that in type 2 diabetes (T2D), GLP-1 receptor agonists (GLP-1 RAs) generally exert a neutral effect on bone mineral density (BMD), with some meta-analyses suggesting a potential reduction in fracture risk following long-term exposure (>52 weeks).

This may reflect the preservation of bone quality through improved glycemic control and direct receptor stimulation, counteracting diabetic osteopathy. In contrast, among individuals with obesity but without diabetes, treatment with potent agents like semaglutide or liraglutide drives significant weight loss that is frequently accompanied by increased bone resorption markers and reduced BMD at weight-bearing sites, likely consequent to mechanical unloading. [7] [11] [14]

Significant gaps remain regarding the long-term skeletal safety of rapid weight reduction, particularly concerning changes in cortical microarchitecture and whether observed BMD declines translate into increased fragility in non-diabetic populations. While concomitant resistance exercise has been shown to mitigate weight-loss-associated bone loss, clinicians should carefully monitor skeletal health in high-risk individuals, such as postmenopausal women or those with existing osteopenia. Future investigations utilizing fracture as a primary adjudicated endpoint are essential to definitively establish the net skeletal safety profile of newer, high-potency incretin-based therapies across diverse clinical phenotypes. [2] [11] [14]

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