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REVIEW

Headline: Fracture Risk in Type 2 Diabetes: Systematic Review of Cardiovascular Outcome Trials with Glucagon Like Peptide Receptor Agonists

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Abstract

Purpose of Review This systematic review examined the available evidence on fracture risk in people with type 2 diabetes (T2D) using cardiovascular outcome trials with glucagon-like peptide-1 receptor agonist (GLP-1RA).

Recent Findings A systematic Literature search identified 797 records, of which 643 remained after duplicate removal. Following screening, 20 studies met the criteria for inclusion.

Summary Although GLP-1 RAs have demonstrated well-established benefits in glycaemic control, weight reduction, and cardiovascular protection, their impact on bone health remains incompletely understood. Preclinical studies suggest potential bone-protective effects, including increased bone mass, improved microarchitecture, and reduced bone resorption. However, evidence from human studies has been inconsistent. While some findings indicate a possible reduction in fracture risk with long-term GLP-1 RA therapy, further research is needed to clarify their role in bone metabolism and fracture prevention among people with T2D, particularly within the context of cardiovascular outcome trials.

Keywords Diabetes mellitus type 2 · Cardiovascular disease · Fracture · BMD · GLP1-RA

Abbreviations

AGE	Advanced glycation end-product
ABMD	Areal bone mineral density
BMD	Bone mass density
CTX	C-terminal telopeptide of type I collagen
CVD	Cardiovascular disease
DPP-4i	Dipeptidyl peptidase-4 inhibitors
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon like peptide-1 receptor agonists
GRADE	Grades of recommendation, assessment, development, and evaluation
HbA1c	Hemoglobin A1c
HDAC1	Histone deacetylase 1
IL-6	Interleukin-6
MACE	Major adverse cardiovascular events
MOF	Major osteoporotic fracture
NOS	Newcastle-ottawa scale
OPG	Osteoprotegerin
P1NP	Procollagen type 1 N-terminal propeptide
RAGE	Receptor for advanced glycation end-products
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor κB ligand
RCT	Randomized controlled trial
REMS	Risk evaluation and mitigation strategy
ROS	Reactive oxygen species
SGLT-2i	Sodium–glucose cotransporter 2 inhibitors
T2D	Type 2 diabetes
Wnt	Wingless-type MMTV integration site

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Introduction

Understanding Fracture Risk in Diabetes

Type 2 diabetes (T2D) represents a growing global health concern, with prevalence projected to exceed 783 million individuals by 2045. The condition is linked to a higher risk of both microvascular and macrovascular complications, an increased burden of comorbidities, elevated mortality rates, and a marked decline in health-related quality of life [1].

Among various comorbidities associated with T2D, an elevated risk of fractures has been consistently observed compared to individuals without diabetes [2, 3]. This phenomenon is often referred to as the 'diabetic bone paradox,' wherein people with T2D typically present with normal or even elevated areal bone mineral density (aBMD) yet exhibit impaired bone quality. This impairment is not fully understood but is thought to involve a range of pathophysiological changes, including the accumulation of advanced glycation end-products (AGEs), reduced bone turnover - particularly diminished resorption - osteocyte dysfunction, increased bone marrow adiposity, and chronic low-grade inflammation [4]. Collectively, these alterations compromise the biomechanical integrity of bone, and may increase susceptibility to fragility fractures [5].

Fall Risk in T2D and Coexisting CVD

Another important comorbidity in T2D is an elevated risk of falls - a multifactorial condition influenced by factors such as deteriorated blood pressure regulation, physical inactivity, impaired postural control, neuropathy, and cardiovascular disease (CVD) [6–8]. People with T2D have approximately a 1.5-fold higher risk of falling compared to those without diabetes, a risk further associated with an increased incidence of fracture-related hospitalizations [3]. Consequently, fall risk represents a key factor in understanding fracture susceptibility in people with T2D, particularly in the context of coexisting conditions.

The association between falls and CVD reflects a complex interplay of shared risk factors and overlapping pathophysiological mechanisms, posing significant clinical challenges. CVD may therefore contribute to an elevated risk of falls. It encompasses a broad range of conditions, including major adverse cardiovascular events (MACE), hypo- and hypertension, heart failure, arrhythmias, myocardial infarction, stroke, and atherosclerosis. The coexistence of T2D and CVD is driven by shared risk factors and contributes to their rising prevalence. Current estimates indicate that over 30% of people with T2D have established CVD.

As a result, treatment strategies must extend beyond glycaemic control and adopt a multifaceted pharmacological approach aimed at improving cardiovascular outcomes. Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated class-wide efficacy in reducing diabetic complications and managing comorbid CVD. In addition, their potential impact on bone health is promising, despite their known role in promoting fat loss [9]. The multifaceted relationship among T2D, CVD, falls, and bone fragility is illustrated in Fig. 1.

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1s are incretin-based therapies [10] that exert a dual effect on the endocrine pancreas by stimulating insulin secretion from beta cells and inhibiting glucagon secretion from alpha cells—both in a glucose-dependent manner. As a result, the risk of hypoglycaemia is minimal [11]. This class of treatment not only limits hypoglycaemic events and supports weight loss but also achieves similar or superior control of HbA1c compared to older antidiabetic agents [12, 13]. In people with T2D, weight reduction and improved HbA1c levels have demonstrated significant clinical benefits for glycaemic control [13–15]. Recent studies highlight the cardiovascular benefits of GLP-1RAs, showing significant reductions in overall cardiovascular events (by 14%), cardiovascular mortality (13%), nonfatal stroke (16%), and hospitalizations for heart failure (10%) [16, 17]. Collectively, these findings underscore the role of GLP-1RAs in addressing both glycaemic and cardiovascular risk profiles in people with T2D.

However, the lack of skeletal health assessments in cardiovascular outcomes trials involving people with T2D using GLP-1RAs may hinder optimal treatment decision-making and limit opportunities for targeted fall-prevention strategies, such as exercise and rehabilitation.

This systematic review aimed to summarize the current evidence on fracture risk in people with T2D, based on data from GLP-1RA trials that were primarily designed to evaluate cardiovascular outcomes.

Method

Literature Survey

This study was registered in the PROSPERO database (Registration ID: CRD420251003233). A comprehensive Literature search was conducted on March 6, 2025, with a backward cut-off date of January 1, 2020. The search was carried out in collaboration with experienced medical librarians at the Aalborg University Hospital Library.

The primary search was conducted in PubMed using a combination of predefined MeSH terms ("Glucagon-Like

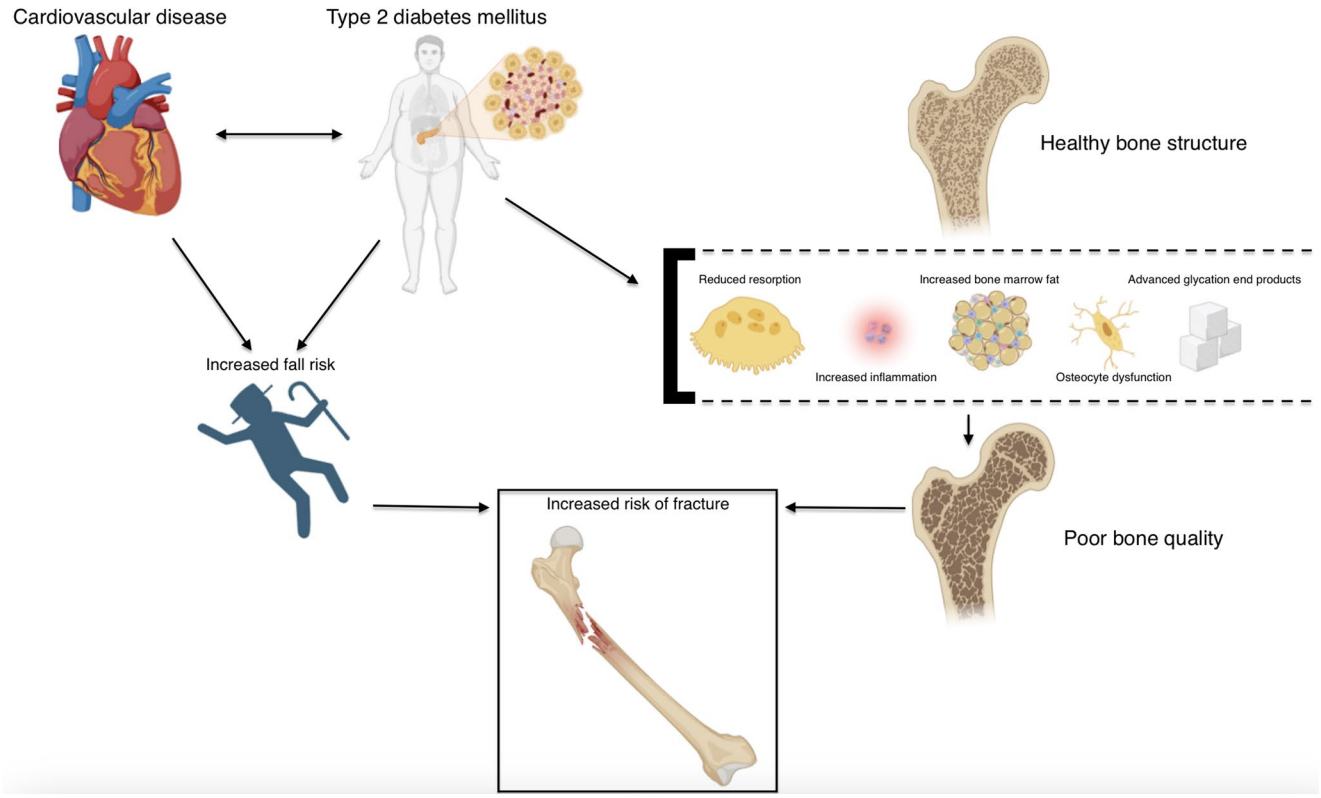

Fig. 1 The interplay between type 2 diabetes, fractures, and cardiovascular disease. Illustration of the multifactorial mechanisms by which type 2 diabetes (T2D) and cardiovascular disease (CVD) contribute to increased fracture risk. T2D is associated with impaired bone quality resulting from reduced bone resorption, increased bone marrow adiposity, chronic inflammation, osteocyte dysfunction, and accumulation of advanced glycation end-products (AGEs). In parallel, both T2D and CVD elevate fall risk, further amplifying fracture susceptibility. Together, these mechanisms establish a pathophysiological link between metabolic disease, skeletal fragility, and fracture outcomes

Peptide-1 Receptor Agonists", "Incretins", "Cardiovascular Diseases", "Fractures, Bone", and "Diabetes Mellitus, Type 2") along with relevant free-text terms. Due to limited retrieval of eligible studies focusing on cardiovascular outcomes, the search was subsequently expanded to include Embase and the Cochrane Library.

Key search concepts included GLP-1RA, fracture, bone turnover, bone mineral density (BMD), T2D, and CVD. These terms were systematically combined using the boolean operators such as AND and OR. Only studies published in English or Danish were eligible for inclusion. The screening process was independently performed by both authors (AAM and NHR).

Search Strategy

Specific search strings were constructed, yielding a total of 797 potential hits from PubMed ($n=406$), Embase ($n=234$), and the Cochrane Library ($n=157$). The full search strategies are provided in the supplementary materials.

Inclusion and Exclusion

Systematic reviews and meta-analyses were prioritized. Original studies not incorporated into meta-analyses—either due to omission or later publication—were included where relevant. Older meta-analyses were cited alongside newer ones in cases of conflicting findings; otherwise, they were excluded if their conclusions were concordant.

Reference lists of included articles were systematically screened to identify additional eligible studies. Priority was given to studies involving people with T2D; however, studies involving non-T2D populations were also considered to ensure a comprehensive evaluation.

For cardiovascular disease, the focus was on MACE, blood pressure regulation, cardiac electrophysiology, and cardiovascular autonomic neuropathy. Both human and animal studies involving GLP-1RAs were eligible for inclusion. Among all eligible studies, randomized controlled trials were prioritized over observational study designs.

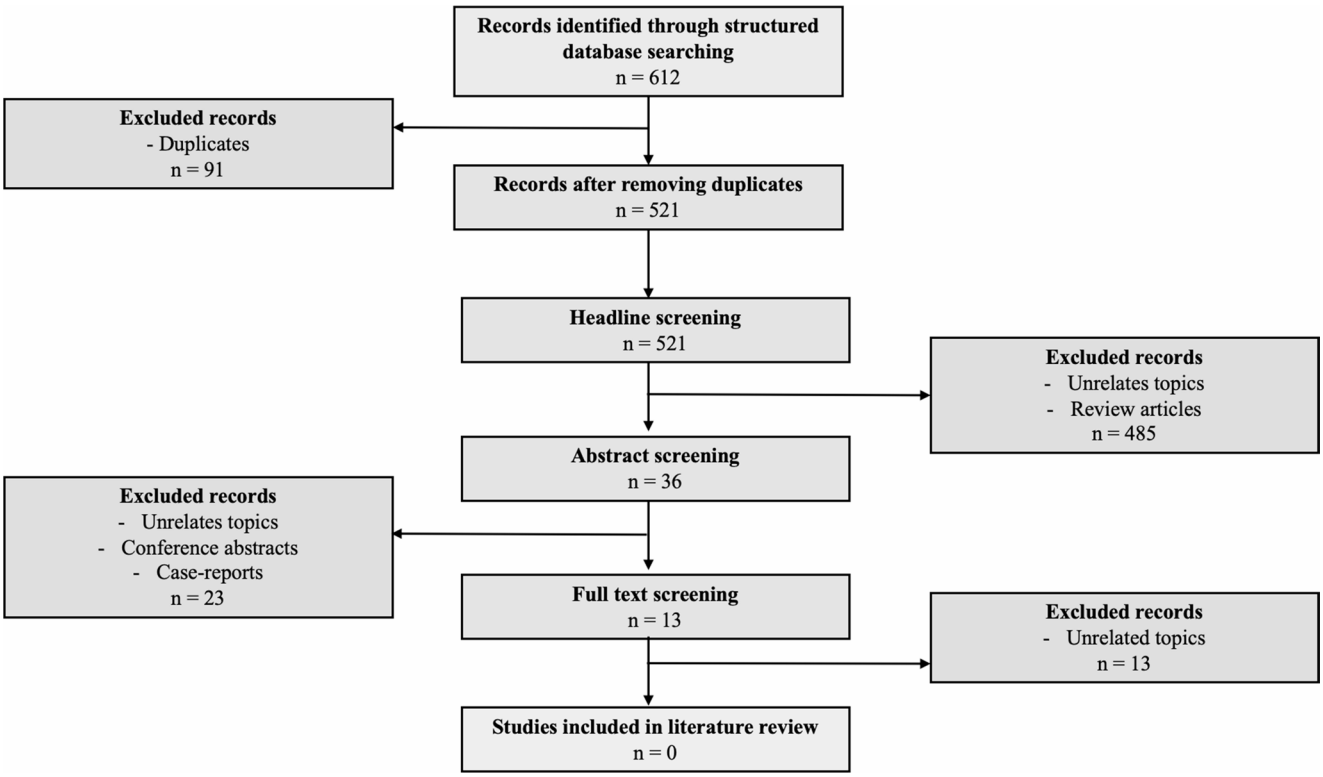

Fig. 2 PRISMA flow diagram. PRISMA flow diagram of the Literature search process related to diabetes, falls, balance, and cardiovascular disease. A total of 797 records were identified across PubMed, Embase, and the Cochrane Library. After removing duplicates, 643 unique records remained. Following title, abstract, and full-text screening, 20 studies met the eligibility criteria for inclusion in the systematic review

In total, 20 studies met the eligibility criteria; however, none addressed cardiovascular outcomes as a primary endpoint in relation to fracture risk among people with T2D (see Fig. 2).

Quality Assessment

Study quality was assessed using validated tools: the Jadad score [18] (Oxford quality scoring system) for randomized controlled trials (RCTs), the Newcastle-Ottawa scale (NOS) [19] for observational studies, and the grades of recommendation, assessment, development, and evaluation (GRADE) [20] for overall evidence assessment. All evaluations were performed using standardized data extraction forms.

Each study was assessed for methodological rigor, including risk of bias, sample size, study design, and population characteristics. For RCTs, specific criteria included randomization methods, blinding, and allocation concealment. For observational studies, cohort selection and comparability were examined, along with the reliability of outcome measures.

Additional factors such as confounding variables, dropout rates, and follow-up duration were analysed to evaluate the robustness of the findings. Studies identified as having a high risk of bias or insufficient control for confounding were interpreted with caution. Discrepancies in quality assessments between reviewers were resolved through discussion and consensus (see Table 1 for quality assessment).

Results

Animal Studies

Liraglutide

Chen et al. reported significantly lower bone mineral density (BMD) in controls compared to all intervention groups ($p<0.05$), with the liraglutide plus insulin group exhibiting higher BMD than liraglutide alone. Inflammatory markers—tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta—were elevated in controls and negatively correlated with BMD in the combination group [21].

Moreover, Wang et al. found that liraglutide improved callus formation, osseous union, and bone strength in ovariectomized rats, while reducing osteoclast numbers and enhancing trabecular architecture and femoral BMD [22]. Additionally, Cheng et al. observed that Liraglutide preserved trabecular microarchitecture and increased levels

Table 1 Quality assessment

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Experimental									
Chen	2021	Diabetes induced osteoporosis via bilateral ovariectomy and streptozotocin injection	40 Sprague-Dawley rats China	6 months	To compare the therapeutic efficacy of liraglutide alone versus liraglutide combined with insulin on osteoporosis in diabetic rats, focusing on their effects on BMD	Liraglutide combined with insulin significantly improved BMD, reduced inflammatory markers ($p<0.05$) compared to liraglutide alone	-	-	-
Abo-Elenin	2024	Ovariectomy to induce postmenopausal osteoporosis	30 adult female Sprague–Dawley rats Egypt	6 weeks	To investigate the osteoprotective effects of semaglutide, focusing on its impact on BMD, bone microarchitecture, and the Wnt/β-catenin signaling pathway	Improved BMD in the spine, femur, and tibia. Enhanced bone microarchitecture and trabecular bone structure. Increased expression of β-catenin and BMP-2, promoting osteoblast differentiation. Decreased levels of RANKL, IL-6, and bone resorption markers	-	-	-
Lv	2024	T2D induced by high-fat diet and streptozotocin injections	38 female C57BL/6J mice USA	8 weeks	To evaluate the effects of semaglutide and tirzepatide on bone metabolism in a T2D mouse model, focusing on bone mass, microarchitecture, turnover biomarkers, and gene expression related to bone health	Semaglutide had a neutral effect on bone mass and microarchitecture in T2D mice after 4 weeks ($p>0.05$). However, semaglutide increased the OPG/RANKL ratio and Runx2 expression, suggesting a potential inhibitory effect on bone resorption ($p<0.05$).	-	-	-
Wang	2023	Osteoporosis induced via bilateral ovariectomy, followed by a fracture model via femoral osteotomy	36 Female Sprague Dawley rats China	5 months	To evaluate the effects of GLP-1RA liraglutide on fracture healing and bone regeneration	Liraglutide enhanced callus formation, increased BMD, improved bone strength, and reduced osteoclast numbers, suggesting it promotes bone regeneration and inhibits bone resorption in osteoporotic fracture rats	-	-	-
Cheng	2022	28 obese rats and 7 lean control rats, divided in (1) control group, saline injected, (2) Insulin treated, (3) Saxagliptin treated, (4) Liraglutide treated	35 Male Zucker Diabetic Fatty rats China	8 weeks	To evaluate whether liraglutide can mitigate diabetes-associated osteoporosis in rats, potentially through the AGEs–RAGE–ROS pathway	Liraglutide improved bone microarchitecture and strength, enhanced osteoblast proliferation and differentiation, and reduced bone resorption markers. It also downregulated RAGE expression and oxidative stress ($p<0.05$), indicating its bone-protective role is mediated via the AGEs–RAGE–ROS pathway	-	-	-

Table 1 (continued)

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Deng	2021	T2D induced by a high-fat/high-sucrose diet followed by streptozotocin injections	50 male ICR mice China	12 weeks	To investigate how exendin-4, affects bone formation in diabetic mice, and to explore the underlying mechanisms via the HDAC1-Wnt/β-catenin signaling pathway	Exendin-4 significantly improved BMD, bone strength, and microarchitecture ($p<0.05$) in T2D mice. It enhanced osteogenic differentiation, downregulated HDAC1 ($p<0.05$), and activated the Wnt/β-catenin pathway, suggesting it improves diabetic bone loss by targeting this axis	-	-	-
Mieczkowska	2020	Diabetes induced via high-fat diet+streptozotocin	32 Male Swiss mice UK	8–10 weeks	To compare the effects of dapagliflozin and liraglutide on bone strength, material properties, and matrix biomechanics in a T2D mouse model	Both drugs improved bone material properties and matrix biomechanics at the bone formation site but did not significantly restore bone strength or microarchitecture in the short term ($p>0.05$). Liraglutide particularly enhanced collagen maturity and reduced collagen glycation, suggesting additional effects beyond glucose control	-	-	-
Li	2020	Divided in two groups (1) chow diet, (2) high-fat diet and treated with streptozotocin to induce diabetes	32 Male C57BL/6J mice China	8 weeks	To evaluate whether liraglutide improves osteogenic differentiation in diabetic mice and human ADSCs, and to explore the role of the Wnt/GSK-3β/β-catenin signaling pathway	Liraglutide improved glucose metabolism and promoted osteogenic differentiation while reducing adipogenic markers in diabetic mice and hADSCs ($p<0.05$). These effects were mediated via the Wnt/GSK-3β/β-catenin signaling pathway, highlighting GLP-1's role in bone formation under diabetic conditions	-	-	-
Effects of GLP-1 on skeletal health in T2D – Human studies									
Randomized controlled trial (RCT)									
Jensen	2024	RCT	195 participants (124 women, 71 men), (BMI 32–43) Denmark	42.84 ± 11.87	To assess the effects of exercise, liraglutide, and their combination on BMD after weight loss in adults with obesity.	The combination of exercise and liraglutide preserved BMD at hip, spine, forearm while achieving the greatest weight loss. Liraglutide alone reduced BMD; exercise alone preserved it ($p=0.03$).	4	-	High

Table 1 (continued)

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Cai	2021	RCT	65 patients with T2D China	Exenatide: 62.95 ± 1.70 Dulaglutide: 57.42 ± 1.81 Insuline glargine: 64.36 ± 2.93 Placebo: 62.00 ± 1.21	To evaluate the effects of exenatide, dulaglutide and insulin on BMD in patients with T2D over 52 weeks.	Exenatide increased BMD at the hip; dulaglutide showed slight femoral neck BMD loss but less than placebo ($p = 0.131$); overall, GLP-1RAs were beneficial or neutral for BMD compared to placebo.	3	-	Moderate
Hansen	2024	RCT	64 adults (86% post-menopausal women) with increased fracture risk but without diabetes Denmark	Semaglutide: 62.7 ± 5.6 Placebo: 63.6 ± 5.4	To assess whether once weekly semaglutide increases bone formation and improves bone health in adults at increased fracture risk.	Semaglutide did not increase bone formation ($p = 0.42$); instead, it increased bone resorption ($p = 0.021$) and caused reductions in BMD ($p < 0.01$) at the lumbar spine and total hip. These effects were likely due to weight loss.	5	-	Moderate
Akyay	2023	RCT	30 postmenopausal women with T2D Turkey	Exenatide: 52.73 ± 4.68 Glargine: 53.00 ± 4.07	To compare the effects of exenatide and insulin glargine on bone turnover markers and BMD in postmenopausal women with T2D over 24 weeks.	Exenatide led to significant weight loss and improved bone metabolism markers (↑ OPG, ↓ RANK and RANKL), with no loss of BMD ($p < 0.05$). Glargine showed no significant effect on bone markers or BMD ($p > 0.05$).	2	-	Low-Moderate
Hygum	2019	RCT	60 adults with T2D Denmark	Liraglutide: 62.00 [59.00–65.00] Placebo: 64.00 [61.00–67.00]	To evaluate the effect of liraglutide on bone turnover markers and BMD in patients with T2D over 26 weeks.	Liraglutide did not change bone resorption ($p = 0.16$) but preserved hip BMD ($p = 0.01$) despite weight loss, suggesting a possible antiresorptive effect.	5	-	Moderate-High

Table 1 (continued)

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Observational (Case-control, longitudinal, cohort and cross-sectional)									
Xiao	2024	Case-control	490,107 adverse event reports for patients with diabetes Groups: (1) Insulin users: 202,755 reports, (2) GLP-1RA users: 98,625 reports, (3) Non-GLP-1RA (excluding insulin): 211,734 reports North america	GLP-1RA: 61 [58.00–66.00] Insulin: 64.00 [58.00–69.00] Non-GLP-1RA: 63 [58.00-70.88]	To assess the risk of fracture events associated with GLP-1RAs using the FDA Adverse Event Reporting System, comparing it to other glucose-lowering drugs.	GLP-1RAs were associated with a significantly lower risk of fracture-related adverse events in diabetic patients compared to other glucose-lowering drugs. This protective effect remained consistent for overall, osteoporotic, and hip fractures, even after adjusting for confounders and excluding insulin users. Any fractures related to adverse events, aROR = 0.45 (0.40–0.50) Osteoporotic fracture, aROR = 0.44 (0.37–0.52) Hip fracture, aROR = 0.43 (0.33–0.54) Albiglutide and fracture, aROR = 0.11 (0.05–0.21)	-	7	Moderate
Huang	2023	Cohort	265 diabetic patients with osteoporosis or osteopenia Taiwan	Study: 61.9 ± 6.7 Control: 63.4 ± 5.9	To evaluate the effect on BMD when switching from DPP-4i to GLP-1RA in diabetic patients.	Switching from DPP-4i to GLP-1RA in diabetic patients led to decrease in lumbar spine bone mineral density ($p = 0.04$). There was no significant difference in femoral neck BMD ($p > 0.05$). This suggests that while GLP-1RAs are effective for blood sugar management, they may negatively impact spinal bone health compared to continued use of DPP-4i.	-	8	Low-moderate
Al-Mashhadi	2022	Cohort	32,266 Danish patients with T2D Denmark	GLP-1RA: 56.6 ± 12.0 DPP-4i: 63.6 ± 12.4	To compare the risk of major osteoporotic fractures (MOF) between GLP-1RA and DPP-4i as add-on therapies to metformin in patients with T2D	The risk of MOF was slightly lower in the GLP-1RA group but not statistically significant. However, GLP-1RAs significantly reduced the risk of hip fractures. Other fracture types showed neutral effects. Subgroup and sensitivity analyses consistently supported these findings. MOF with GLP-1RA compared to DPP-4i, HR = 0.89 [0.76–1.05], aHR = 0.86 [0.73–1.03] Hip fracture, HR = 0.68 [0.49–0.96]	-	8	Moderate

Table 1 (continued)

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Refaie	2024	Longitudinal	65 patients with type 2 diabetes mellitus Italy	66.4 ± 8.45	To evaluate the effects of 12 months of GLP-1RA therapy on bone turnover, BMD, and bone quality in T2D patients.	GLP-1RA therapy increased bone turnover markers and adiponectin ($p < 0.05$), while reducing myostatin ($p = 0.05$). Femoral BMD showed a modest but significant reduction by both DXA and REMS ($p < 0.05$). Lumbar spine BMD decreased significantly by DXA but not by REMS. Trabecular Bone Score slightly increased, indicating preserved bone microarchitecture. These findings suggest that despite some BMD loss likely related to weight reduction, GLP-1RAs may preserve or improve aspects of bone quality.	-	5	Low
Deng	2025	Cross-sectional	GWAS data from up to 462,933 individuals of European ancestry Europe	NA	To assess the causal effects of five antidiabetic drugs (Metformin, GLP-1RAs, SGLT-2i, Insulin, and Gliclazide) on osteoporosis and its subtypes, including pathological fractures, using Mendelian Randomization.	Found that metformin has a strong protective effect against osteoporosis, while gliclazide significantly increases the risk of pathological fractures. GLP-1RA were associated with a modest but significant increase in osteoporosis with pathological fractures. SGLT-2i showed a weak, non-robust protective effect, and insulin showed no significant impact on bone health. GLP-1RA and osteoporotic fractures, OR [95% CI]: 1.1247 [1.0043–1.2594], $p = 0.0420$	-	-	Low-moderate
Effects of GLP-1 on BMD and body composition *Observational (Case-control, longitudinal, cohort and cross-sectional)*									
Nelson	2024	Cohort	241 adult patients (151 women, 90 men) USA	60.4 ± 12.4	To assess changes in body composition (fat, muscle, liver, bone) using AI-based CT analysis before and after semaglutide initiation.	Patients with weight loss after starting semaglutide showed significant reductions in visceral fat, subcutaneous fat, muscle area, and liver volume, along with improved liver attenuation—indicating decreased fat content ($p < 0.05$). In contrast, those with weight gain exhibited increases in fat depots and a significant decline in muscle quality ($p < 0.05$) (lower attenuation), indicating possible myosteatosis. Across the full sample, there was a statistically significant decrease in BMD ($p < 0.05$).	-	5	Low

Table 1 (continued)

Articles	Year	Study design/animal model	Population and country	Age (Years)	Aim	Outcome	JADAD	NOS	GRADE
Effects of GLP-1 on skeletal health in T2D – Animal studies									
Chen	2024	Cross-sectional	70 overweight Chinese patients with T2D China	44.19 ± 10.57	To assess changes in body composition and their relationship with glucose control after 3 months of dulaglutide treatment in overweight T2D patients.	Dulaglutide treatment significantly improved glucose control, reduced body weight, visceral fat area, and total body fat ($p < 0.05$). While lean body mass and skeletal muscle mass slightly decreased in absolute terms, their percentages increased, suggesting preserved muscle quality ($p < 0.05$). Importantly, bone mineral quality did not change, indicating no bone loss ($p = 0.30$). The percentage change in body fat was independently associated with the improvement in HbA1c.	-	5	Low
Effects of GLP-1 on CVD outcome trials on fracture risk									
None									

Quality grading of included studies based on study design and characteristics of the study populations

Abbreviations: *ADSC* Adipose-Derived Stem Cell, *AGE* Advanced Glycation End-products, *BMD* Bone Mass Density, *BMP-2* Bone Morphogenetic Protein 2, *CVD* Cardiovascular Diseases, *DPP-4i* Dipeptidyl Peptidase-4 Inhibitors, *FDA* Food and Drug Administration, *GLP-1* Glucagon Like Peptide 1,*GLP-1RA* Glucagon Like Peptide 1 Receptor Agonist, *GSK3β* Glycogen Synthase Kinase-3 Beta, *hADSC* Human Adipose-Derived Stem Cell, *HDAC1* Histone Deacetylase 1, *IL-6* Interleukin-6, *MOF* Major Osteoporotic Fracture, *OPG* Osteoprotegerin, *RAGE* Receptor for Advanced Glycation End-products, *RANKL* Receptor Activator of Nuclear Factor κB Ligand, *REMS* Risk Evaluation and Mitigation Strategy, *ROS* Reactive Oxygen Species, *SGLT-2i* Sodium-Glucose Cotransporter-2 Inhibitors, *T2D* Type 2 Diabetes Mellitus, *WNT* Wingless-Related Integration Site

of bone formation markers including alkaline phosphatase, osteocalcin, and procollagen type 1 N-terminal propeptide (P1NP), while reducing C-terminal telopeptide of type I collagen (CTX). In vitro, GLP-1 attenuated AGE-induced osteogenic damage by reducing reactive oxygen species (ROS) and receptor for advanced glycation end-products (RAGE) expression [23].

In contrast, Mieczkowska et al. reported reduced mechanical strength in diabetic controls without microarchitectural alterations. Liraglutide did not restore strength but altered matrix composition, including collagen structure and tissue hydration ($p<0.05$) [24].

Another study by Li et al. demonstrated that liraglutide upregulated osteoblast-related markers—osteocalcin, Runx2, and collagen type I—and promoted mineralization [25].

Semaglutide

Abo-Elenin et al. reported that semaglutide mitigated ovariectomy-induced bone deterioration by improving bone microarchitecture and preserving bone mineral content. Additionally, semaglutide enhanced β-catenin expression, thereby promoting bone formation and inhibiting receptor activator of nuclear factor κB ligand (RANKL) activation [26].

In contrast, Lv et al. found that semaglutide did not significantly alter cortical or trabecular bone parameters in diabetic mice over a four-week period, except for a reduction in cortical thickness observed in the semaglutide group ($p=0.032$). Although levels of C-terminal telopeptide of type I collagen (CTX) and procollagen type 1 N-terminal propeptide (P1NP) declined, intergroup differences were not statistically significant ($p>0.05$). Semaglutide modulated messenger RNA expression of RANKL and osteoprotegerin (OPG), resulting in an increased OPG/RANKL ratio [27].

Exendin-4

Deng et al. demonstrated that exendin-4 promoted osteogenic differentiation of bone marrow-derived mesenchymal stem cells in T2D models. This effect was associated with downregulation of histone deacetylase 1 (HDAC1) and phosphorylated β-catenin, along with upregulation of wingless-type MMTV integration site (Wnt) family member 3, β-catenin, and Runx2 expression. In vivo, exendin-4 significantly reduced blood glucose levels, increased body weight, and improved bone density and microarchitectural quality in the right tibia of T2D mice [28].

Human Studies

BMD and Bone Turnover Markers

Jensen et al. reported no significant changes in hip or lumbar spine BMD in the liraglutide plus exercise group compared to placebo. However, liraglutide alone was associated with a modest but statistically significant decrease in BMD at both the hip ($p=0.03$) and lumbar spine ($p=0.04$) compared to exercise alone [29].

In addition, Cai et al. observed site-specific effects of GLP-1RAs: exenatide increased total hip BMD, while dulaglutide caused a mild reduction at the femoral neck. Placebo was associated with generalized BMD loss, whereas insulin glargine increased BMD at several lumbar spine levels. Both exenatide and insulin glargine improved BMD at the femoral neck and total hip compared to placebo [30].

In contrast, Hansen et al. reported no significant effect of semaglutide on P1NP levels but observed a significant increase in the bone resorption marker P-CTX ($p=0.021$). After 52 weeks, lumbar spine and total hip aBMD were significantly lower in the semaglutide group compared to placebo, while femoral neck aBMD remained unchanged [31].

Moreover, Akyay et al. found that exenatide significantly modulated bone remodelling markers by decreasing RANK/RANKL and increasing OPG levels ($p<0.05$). However, no significant changes in BMD or conventional bone turnover markers were observed in either the exenatide or insulin glargine groups [32].

Another study by Hygum et al. reported that P-CTX levels increased in both liraglutide and placebo groups, though the between-group difference was not significant. Liraglutide induced an initial decline in P1NP followed by a sustained increase, while placebo showed no change. Hip BMD remained stable with liraglutide but declined in the placebo group ($p=0.01$ between groups) [33].

Furthermore, Huang et al. found that GLP-1RA therapy resulted in a greater reduction in lumbar spine BMD compared to controls ($p=0.041$), with no significant effect on femoral neck BMD [34].

In addition, Refaie et al. demonstrated that 12 months of GLP-1RA therapy increased bone turnover markers and adiponectin, along with a modest reduction in myostatin. Lumbar spine BMD declined significantly as measured by DXA but not by risk evaluation and mitigation strategy (REMS). Femoral BMD decreased slightly but significantly using both imaging modalities, while trabecular bone score showed marginal improvement [35].

Fracture Risk

Xiao et al. reported that GLP-1RA use was associated with the lowest risk of fracture-related adverse events among antidiabetic medications. This included reduced risk for overall fractures (adjusted reporting odds ratio [aROR] = 0.44), osteoporotic fractures (aROR = 0.39), and hip fractures (aROR = 0.34). Albiglutide demonstrated the most favourable profile (aROR = 0.11). Exclusion of insulin users did not alter the findings, suggesting a consistent protective association [36].

In addition, Al-Mashadi et al. found a non-significant reduction in major osteoporotic fracture (MOF) risk with GLP-1RA use compared to Dipeptidyl Peptidase-4 Inhibitors (DPP-4i) (adjusted hazard ratio [aHR] = 0.86; 95% CI: 0.73–1.03). However, hip fracture risk was significantly lower among GLP-1RA users (HR = 0.68; 95% CI: 0.49–0.96), particularly at higher daily doses and in extended follow-up analyses. Subgroup and sensitivity analyses supported these findings [37].

In contrast Deng et al. identified a modest but statistically significant increase in the risk of osteoporosis with pathological fractures among GLP-1RA users (odds ratio [OR] = 1.12, $p = 0.042$), raising concern about a potential detrimental effect. However, this association was limited and contrasts with the overall protective trends observed in other studies [38].

A study by Patil et al. reported no significant association between GLP-1RA use and the incidence of either all clinical fractures or osteoporotic fractures (adjusted hazard ratio [aHR] = 0.94; 95% CI: 0.86–1.03). However, a subgroup analysis of hip fractures among women showed a higher aHR (2.19; 95% CI: 0.59–8.17), although the wide confidence interval indicates statistical non-significance [39].

Adverse drug reactions related to GLP-1RA use have also been examined. In a study by Terauchi et al., no cardiovascular events were reported, and only a single case of femoral neck fracture was observed during the study period [40].

The discrepancies in fracture outcomes across these studies likely reflect significant differences in cohort characteristics, follow-up duration, data sources, and methodological rigor. Xiao et al.'s analysis was based on adverse event reporting, lacking control for confounders, while Al-Mashadi et al. utilized a well-adjusted registry cohort with longer follow-up. Deng et al. relied on administrative coding to define fractures, possibly inflating case numbers. Patil et al.'s US-based cohort was 97% male, limiting generalizability, especially for hip fractures in women where a wide confidence interval (aHR = 2.19; 95% CI: 0.59–8.17) rendered results inconclusive. Lastly, Terauchi et al. reported only a single fracture case in a prospective Japanese cohort but lacked a comparator arm and had low event rates, limiting its interpretability.

Body Composition

Nelson et al. investigated the effects of semaglutide on body composition using computed tomography (CT) imaging analysis. In the weight-loss group ($n = 67$), post-treatment scans demonstrated significant reductions in visceral adipose tissue area (309.4 vs. 341.1 cm², $p < 0.001$), subcutaneous adipose tissue area (371.4 vs. 410.7 cm², $p < 0.001$), muscle area (179.2 vs. 193.0 cm², $p < 0.001$), and liver volume (2379.0 vs. 2578.0 cm³, $p = 0.009$). An increase in liver attenuation (74.5 vs. 67.6 Hounsfield units, $p = 0.03$) was also observed, indicating improved hepatic fat content. In contrast, in the weight-gain group ($n = 48$), increases were noted in visceral adipose tissue (334.0 vs. 312.8 cm², $p = 0.002$), subcutaneous adipose tissue (485.8 vs. 448.8 cm², $p = 0.01$), and intramuscular adipose tissue (48.4 vs. 37.6 cm², $p = 0.009$), while muscle attenuation significantly decreased (5.9 vs. 13.1 Hounsfield units, $p < 0.001$). Other measured parameters showed no significant changes [41].

Chen et al. evaluated the effects of a 3-month dulaglutide intervention on body composition. Statistically significant reductions were observed in body weight, visceral fat area, total body fat, lean body mass, skeletal muscle mass, and body water content (all $p < 0.05$). Despite these absolute decreases, the relative proportions of lean body mass and skeletal muscle mass increased, indicating a favourable shift in body composition. Bone mineral quality remained unchanged. Multiple linear regression analysis revealed a significant independent association between percentage change in body fat and HbA1c ($\beta = 0.449$, $t = 3.148$, $p = 0.002$), suggesting a potential link between fat reduction and glycaemic improvement [42].

Fracture Risk Estimation in the Cardiovascular Outcome Trials

The systematic literature search identified no eligible studies assessing fracture risk in people with T2D within cardiovascular outcome trials of GLP-1RAs, and therefore no studies were available for formal quality assessment. However, several studies were identified that closely aligned with the inclusion criteria and are included in this section for contextual discussion.

Discussion

Animal and Human Studies

The cumulative evidence from preclinical studies suggests that GLP-1RAs may influence skeletal health through several biological mechanisms, including modulation of bone metabolism, suppression of inflammatory pathways, and

regulation of key osteogenic signalling cascades. Experimental models consistently show that liraglutide and semaglutide can preserve or improve BMD and trabecular architecture [21–23, 26]. These effects were primarily attributed to anti-inflammatory activity [21], enhanced callus formation and osteoblast function [22, 25], and activation of the Wnt/β-catenin signalling pathway, which plays a central role in osteogenesis [23, 26, 38]. While these findings support a potential skeletal benefit of GLP-1RAs, they are based on animal and in vitro models and thus require cautious interpretation before being extrapolated to clinical populations.

Additionally, modulation of the RANKL/OPG axis by GLP-1RAs has been implicated in the inhibition of osteoclastogenesis and bone resorption [26, 27]. Reductions in oxidative stress and advanced glycation end-product (AGE)-mediated damage—reported by Cheng and Deng—have also been proposed to promote osteoblastic differentiation in diabetic bone environments [23, 38]. However, the translational relevance of these findings is limited by interspecies differences and the lack of fracture-specific endpoints in most animal models.

Importantly, not all preclinical findings are consistent. Lv et al. reported minimal structural improvements following short-term administration of semaglutide in diabetic mice, despite observable biochemical changes [27]. Similarly, Mieczkowska et al. found no restoration of mechanical bone strength with liraglutide treatment, although changes in matrix composition were noted [24]. These findings suggest that biochemical and microarchitectural adaptations may occur earlier than measurable improvements in biomechanical properties.

In human studies, findings are more heterogeneous. Some studies report site-specific reductions in BMD associated with GLP-1RA use—such as lumbar spine decline with liraglutide monotherapy [29] and dulaglutide [30, 34]), —while others describe preservation or even improvement in BMD, particularly with exenatide and insulin glargine at the hip and spine [30]. This variability may reflect differences in study design, population characteristics, duration of treatment, and the confounding effects of weight loss—an important variable that few studies have adequately adjusted for. Notably, mechanical loading through exercise appeared to attenuate BMD loss in individuals treated with liraglutide [29].

Evidence from studies examining bone turnover markers is also inconsistent. Semaglutide has been associated with increased bone resorption without corresponding changes in bone formation markers [31], while liraglutide has shown a biphasic P1NP response alongside BMD stabilization [33]. Refaie et al. reported elevated turnover markers and a modest reduction in myostatin following GLP-1RA therapy, accompanied by marginal declines in BMD and preservation of trabecular bone score [35]. Collectively, these findings suggest that the skeletal effects of GLP-1RAs may be both agent-specific and influenced by the duration of exposure.

Mechanistic studies in humans also offer preliminary evidence that GLP-1RAs may influence osteoclastogenesis. Akyay et al. demonstrated favorable modulation of the RANK/RANKL/OPG axis with exenatide; however, no concurrent changes in BMD or bone turnover markers were observed during the study period [32]. This suggests that downstream structural effects may require longer treatment durations to become detectable.

Despite inconsistencies in BMD and bone turnover outcomes, fracture data appear more consistent. GLP-1RA use has been associated with a reduced risk of fracture-related adverse events, including hip and osteoporotic fractures, with the strongest protective effect observed for albiglutide [36]. These findings were supported by Al-Mashadi et al., who reported a significant reduction in hip fracture risk at higher GLP-1RA doses and with extended follow-up [37]. In contrast, Deng et al. observed a modest increase in osteoporosis-related fracture risk among GLP-1RA users [38]. However, the small effect size and observational design limit the interpretability of this finding, which remains inconsistent with the broader evidence base.

Body Composition and Skeletal Interaction

Changes in body composition induced by GLP-1RAs may mediate or confound their effects on skeletal health. Nelson et al. demonstrated significant reductions in visceral and subcutaneous adipose tissue, liver volume, and hepatic steatosis following semaglutide-induced weight loss; however, these changes were accompanied by concurrent reductions in muscle mass and cross-sectional area [41]. Conversely, weight gain was associated with increased fat accumulation and decreased muscle attenuation, suggesting potentially adverse effects on overall musculoskeletal quality.

Chen et al. similarly observed reductions in total fat, visceral fat, and lean mass following dulaglutide treatment, alongside an increase in the relative proportion of lean tissue [42].

Bone mineral quality remained stable, and fat loss was independently associated with improvements in HbA1c. These findings highlight a potential link between improved metabolic control and bone health. However, the implications of concurrent muscle loss remain uncertain and warrant further investigation, particularly in older adults or populations at risk for sarcopenia.

Limitations

This review is subject to several limitations. No cardiovascular outcome trials with predefined fracture endpoints were identified, limiting the clinical generalizability of the findings. The inclusion of primarily preclinical and observational studies introduces a risk of publication bias, as studies reporting positive skeletal effects of GLP-1RAs are more likely to be published than those with null or negative outcomes.

Most human studies included had relatively short follow-up durations and limited drug exposure periods, restricting the ability to assess long-term skeletal outcomes. Additionally, there was considerable heterogeneity in outcome measures, study populations, and GLP-1RA formulations, which complicated direct comparisons across studies. Results were also reported in varying formats, preventing meaningful data synthesis and precluding the possibility of meta-analysis.

Few studies adjusted for weight loss as a confounding factor, which may have biased interpretations of BMD outcomes. Moreover, postmenopausal women—who are at the highest risk for osteoporotic fractures—were underrepresented in many cohorts, further limiting the generalizability of the findings to this key population.

Finally, although changes in body composition may mediate the skeletal effects of GLP-1RAs, this review included only two studies on the topic, despite the availability of additional relevant literature. This may represent an important limitation of the search strategy and warrants broader inclusion in future reviews.

Conclusion

This systematic review highlights a critical gap in the literature: no cardiovascular outcome trials of GLP-1RAs in people with T2D have directly assessed fracture risk. While available evidence suggests that GLP-1RAs do not increase the risk of falls or fractures compared to SGLT-2 inhibitors, the current data remain insufficient to support definitive conclusions.

Experimental and mechanistic studies provide preliminary support for a potential beneficial effect of GLP-1RAs on bone metabolism; however, findings from human studies are limited and inconsistent. Given the elevated burden of both cardiovascular and skeletal complications in people with T2D, future clinical trials should incorporate bone health endpoints to enable a more comprehensive evaluation of the benefit-risk profile of GLP-1RAs.

6 Future Perspectives

Integrating Mechanistic and Clinical Evidence

The identification of GLP-1 receptor expression on osteoblasts and osteoclasts raises the possibility of a direct skeletal effect. Animal studies have shown promising outcomes, including increased trabecular bone volume, reduced osteoclast activity, and improved bone microarchitecture. These findings suggest that GLP-1RAs may modulate bone turnover and enhance skeletal strength.

However, translational evidence in humans remains limited. While some meta-analyses indicate a potential reduction in fracture risk with long-term GLP-1RA use, results remain inconclusive. Well-designed, prospective clinical trials with standardized bone-specific endpoints are needed to clarify the role of GLP-1RAs in bone health and to determine whether their effects translate into meaningful fracture risk reduction in people with T2D.

Clinical Implications and Gaps in the Literature

Despite the increasing use of GLP-1RAs in people with T2D and CVD, skeletal outcomes remain underreported in major cardiovascular outcome trials. This represents a critical gap in the evidence base, particularly given the elevated risk of falls and fractures in this population.

The absence of integrated bone health assessments—such as DXA and bone turnover markers—in large-scale trials limits the ability to comprehensively evaluate the net clinical benefit of GLP-1RA therapy. Incorporating these measures into future cardiovascular outcome trials would be both feasible and clinically meaningful, enabling a more complete understanding of their impact on multimorbidity in people with T2D.

Future Directions

Future randomized controlled trials should integrate skeletal endpoints into cardiovascular outcome trial designs, particularly in high-risk populations. Validated measures of circulatory and cardiac electrical function may serve as useful proxies for broader systemic effects but should be complemented by direct bone health assessments. Studies investigating the long-term skeletal safety and potential bone-protective effects of GLP-1RAs could clarify their role in fracture prevention strategies for people with T2D.

Further research is also needed to explore the impact of T2D subtypes, GLP-1RA subclasses, and specific CVD phenotypes on fracture risk. Variables such as body weight,

HbA1c, GLP-1RA dose, blood pressure regulation, and overall metabolic control may differentially influence skeletal vulnerability. Given the dual burden of cardiovascular disease and skeletal fragility in this population, studies should move beyond fracture incidence to investigate the underlying mechanisms linking metabolic health to bone integrity.

Key References

- Chen K, Wu R, Mo B, et al Comparison between liraglutide alone and liraglutide in combination with insulin on osteoporotic rats and their effect on bone mineral density.

  A promising animal study investigating the effects of GLP-1RA on BMD and their potential bone-protective properties, using an osteoporotic rat model. The findings highlight promising directions for future research with potential clinical implications.

- Akyay OZ, Canturk Z, Selek A, et al (2023) The effects of exenatide and insulin glargine treatments on bone turnover markers and bone mineral density in postmenopausal patients with type 2 diabetes mellitus. Medicine (United States) 102:E35394. https://doi.org/10.1097/MD.0000000000035394.

  An interesting human study investigates the molecular effects of GLP-1RA previously observed in animal models, finding notable similarities in outcomes, as well as some differences. These findings underscore the need for further research focused specifically on human models.

- Nelson LW, Lee MH, Garrett JW, et al (2024) Intrapatient Changes in CT-Based Body Composition After Initiation of Semaglutide (Glucagon-Like Peptide-1 Agonist) Therapy. American Journal of Roentgenology. https://doi.org/10.2214/ajr.24.31805.

  This study offers valuable and comprehensive insights into changes in body composition, with a broad focus on various tissues in living humans using GLP-1RA, compared to non-users.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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