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Review

Incretin-Based Therapies and the Associated Impact on Bone Health

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Abstract

Incretin-based therapies are being increasingly used in the treatment of type 2 diabetes mellitus and obesity, both of which are associated with impaired bone quality, altered skeletal remodeling, and increased fracture risk. Experimental studies suggest that incretin signaling may affect bone through osteoblast and osteoclast activity, Wnt/β-catenin signaling, adipose tissue inflammation, metabolic regulation, and the gut–bone axis. However, clinical evidence remains heterogeneous, with most studies indicating neutral or context-dependent effects on bone mineral density and fracture risk rather than consistent skeletal benefit. Interpretation is further complicated by treatment-induced weight loss, changes in lean mass and mechanical loading, diabetes-related skeletal fragility, and the limited number of trials specifically designed to assess bone endpoints. Evidence for newer dual and triple agonists is especially limited, despite their growing use and substantial weight-loss effects. Incretin-based therapies appear reassuring from a skeletal safety perspective; however, long-term studies with dedicated skeletal endpoints are needed to determine their effects on bone quality, falls, and fracture risk in high-risk populations. This review summarizes current mechanistic, preclinical, and clinical evidence on the effects of glucagon-like peptide-1 receptor agonists, dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors on bone turnover, bone mineral density, bone quality, and fracture outcomes.

Keywords: incretins; glucagon-like peptide-1 receptor agonists; dipeptidyl peptidase-4 inhibitors; tirzepatide; bone density; bone fractures; osteoporosis; type 2 diabetes mellitus

1. Introduction

Incretins are gut-derived hormones that play an important role in metabolic regulation. The glucose-lowering effects of incretins are mediated by several complementary mechanisms, including stimulation of insulin secretion, delayed gastric emptying, suppression of glucagon release, reduced appetite, decreased intestinal nutrient absorption, and enhanced pancreatic β-cell function [1]. Therefore, incretin-based therapies have become important in the treatment of type 2 diabetes mellitus (T2DM) and obesity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists improve glycemic control, reduce body weight, and provide cardiovascular benefits [2,3,4]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, another class of incretin-based therapies, are widely used oral antidiabetic agents with favorable safety and tolerability profiles, although individual compounds differ in the associated pharmacokinetic properties [5]. The expanding use of incretin-based therapies is particularly relevant, as T2DM and obesity are increasingly recognized as conditions that have important effects on skeletal health. Interestingly, Li et al. [6] reported a substantial increase in GLP-1 RA and dual GIP/GLP-1 RA prescription rates between 2010 and 2024, from 2.4% to 34.3% among individuals with both T2DM and obesity, and from 0.04% to 7.1% among individuals with obesity alone. Individuals with T2DM have an increased risk of fractures, especially in the presence of poor glycemic control, longer disease duration, and diabetes-related complications [7]. Notably, fractures in patients with T2DM are also associated with poorer outcomes, including higher mortality, increased complication rates, and impaired recovery compared with individuals without diabetes [7]. In a population-based cohort study, Tebé et al. [8] showed that individuals with T2DM had an increased risk of post-hip fracture mortality; after adjustment, men with T2DM had a 28% higher risk of death after hip fracture, while women had a 57% excess risk compared with matched non-diabetic controls. Both obesity and T2DM are associated with osteoporosis, osteopenia, and metabolic bone diseases such as osteomalacia, which complicate the assessment of fracture risk and clinical management [7,9]. The relationship between obesity and fracture risk is complex and site-specific. Obese adults may have an increased risk of certain non-vertebral fractures, including fractures of the upper leg, proximal humerus, and ankle, while the risk may be lower at vertebral sites and the proximal femur; these associations are further influenced by age and sex [9]. These findings challenge the traditional view that higher body mass is uniformly protective through mechanical loading. Instead, metabolic disturbances associated with obesity and diabetes may impair

bone quality, partly through altered collagen synthesis and non-enzymatic cross-linking, thereby weakening the bone matrix independently of bone mineral density (BMD) [10]. Diabetes and osteoporosis are closely connected through several mechanisms, and the effects of antidiabetic drugs on bone metabolism have attracted increasing interest. Some glucose-lowering agents used in T2DM may adversely affect bone tissue [11]. Importantly, accumulation of advanced glycation end products, together with increased oxidative stress, contributes to skeletal fragility in T2DM, particularly in trabecular bone [12]. This may explain why patients with T2DM can experience fragility fractures despite normal or elevated BMD measured by dual-energy X-ray absorptiometry (DXA), highlighting the dissociation between bone density and bone strength [13]. GLP-1 RAs, dual GLP-1/GIP receptor agonists, and DPP-4 inhibitors may influence bone metabolism through indirect mechanisms, including weight loss, improved glycemic control, reduced inflammation, and altered mechanical loading, as well as through direct effects on bone cells and remodeling [14]. Preliminary evidence suggests that these agents may affect bone turnover, bone quality, and fracture risk, although the overall skeletal effects remain incompletely defined [14]. While recent reviews have addressed the skeletal consequences of anti-obesity pharmacotherapy in general, this review offers a more targeted synthesis of incretin-based and incretin-adjacent therapies. This approach provides added value by combining mechanistic and clinical evidence with an updated discussion of dual and triple agonists, microbiota-mediated skeletal effects, limitations of cardiovascular outcome trials, translational discrepancies between preclinical and human data, and practical clinical implications for patients at increased fracture risk. Thus, this review summarizes and evaluates mechanistic, preclinical, and clinical evidence regarding the impact of incretin-based therapies on bone health, with particular emphasis on fracture risk, bone quality, and metabolic bone complications in patients with T2DM and obesity.

2. Data Sources and Methodology

A narrative literature review was conducted to identify mechanistic, preclinical, and clinical studies evaluating the effects of incretin-based therapies on bone health. PubMed, Scopus, and Web of Science were searched for articles published up to April 2026, using combinations of the following terms: “GLP-1 receptor agonist”, “DPP-4 inhibitor”, “GIP”, “dual GLP-1/GIP receptor agonist”, “tirzepatide”, “semaglutide”, “incretin-based therapy”, “bone metabolism”, “bone mineral density”, “bone turnover”, and “fracture risk”. Relevant original studies, clinical trials, meta-analyses, and review articles were considered eligible and included.

3. Physiological Basis: Incretins and the Gut–Bone Axis

3.1 Incretins as Osteotropic Hormones

In addition to the established metabolic actions of these agents, incretins are becoming increasingly recognized as potential regulators of skeletal homeostasis. This concept is supported by the postprandial suppression of bone resorption, during which gut-derived hormones such as GIP and GLP-1 appear to help regulate bone turnover [15,16]. These observations have led to the concept of a gut–bone axis, in which nutrient-induced hormonal signals influence bone remodeling through both direct effects on bone cells and indirect effects mediated by inflammation, adipose tissue metabolism, insulin secretion, and body weight [16]. Among incretin hormones, GIP appears to exert particularly important osteotropic effects. Experimental studies suggest that GIP receptor activation may promote osteoblast activity and bone formation while reducing bone resorption, thereby contributing to the maintenance of bone mass [17,18]. In a preclinical study, Hansen et al. [18] reported that GIP acted directly on primary human osteoclasts and osteoblasts, reducing osteoclast activity and differentiation while improving osteoblast survival through GIP receptor-mediated signaling pathways. GLP-1 may also influence bone metabolism, although the associated skeletal actions are likely mediated through both direct and indirect mechanisms. These include effects on osteoblast and osteoclast activity, improved glycemic control, changes in insulin secretion, reduced inflammation, and alterations in body weight and mechanical loading [14,15]. The relevance of incretin signaling to bone is amplified in metabolic diseases such as obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), and T2DM, which are characterized by chronic low-grade inflammation and altered adipose tissue function [15]. Excess white adipose tissue promotes the release of inflammatory cytokines and adipokines, which may disturb bone remodeling [15]. In addition, obesity-related metabolic dysfunction may shift the differentiation of bone marrow mesenchymal stem cells toward adipogenesis rather than osteoblastogenesis, while also promoting osteoclast activity [19]. These changes may contribute to reduced bone quality and increased skeletal fragility despite normal or elevated BMD in some patients [20]. Preclinical studies generally support a potential beneficial role of incretin signaling in bone metabolism. GIP and GLP-1 have been reported to promote osteoblast function, inhibit osteoclast activity, and improve bone mass or microarchitecture in experimental models [21]. Ma et al. [22] reported that exendin-4, a GLP-1 RA, prevented osteopenia in aged ovariectomized rats by promoting bone formation and suppressing bone resorption. Similarly, Yu et al. [23] showed that liraglutide improved tibial BMD and partially restored trabecular microarchitecture in diabetic mice, in part by suppressing osteoclastogenesis-related pathways. However, findings

from human studies remain limited, and further research is needed to clarify receptor-specific effects, dose–response relationships, and long-term skeletal outcomes [24]. These mechanisms provide a rationale for studying incretin-based therapies as potential modulators of bone health. GLP-1 RAs have shown promising but not fully consistent effects on bone turnover, bone mass, and fracture-related outcomes [25]. Meanwhile, newer incretin-based agents, including dual glucagon-like peptide-1 receptor/glucose-dependent insulinotropic polypeptide receptor (GLP-1R/GIPR) agonists, dual GLP-1R/glucagon receptor agonists, and triple GLP-1R/GIPR/glucagon receptor agonists, may also influence skeletal metabolism; however, clinical evidence remains limited [26]. GIP may also affect bone indirectly through its role in adipose tissue metabolism. Indeed, by modulating lipid handling and adipokine secretion, GIP could influence the inflammatory and endocrine environment that regulates bone remodeling [27]. Notably, the skeletal effects of glucagon receptor activation remain less clearly defined. Although glucagon receptors are expressed predominantly in metabolically active tissues such as the liver and kidney, the impact of glucagon receptor agonism on human bone metabolism has not yet been established [25]. Overall, this physiological background supports the hypothesis that incretin-based therapies may influence bone health through multiple interconnected pathways; however, the clinical significance of these effects remains to be fully established.

3.2 Molecular Pathways Linking Incretin Signaling and Bone Remodeling

The skeletal effects of incretin-based therapies appear to involve several interconnected molecular pathways that govern osteoclast activity, osteoblast differentiation, inflammation, adipose tissue signaling, and gut–bone communication. Among these, the Wnt/β-catenin pathway is particularly important because this pathway regulates osteoblastogenesis and bone formation [28]. Meanwhile, disruption of Wnt/β-catenin signaling has been implicated in metabolic disorders such as obesity and MASLD, both of which are associated with impaired bone remodeling [28]. Experimental evidence further supports the involvement of β-catenin-related osteogenic signaling. Meng et al. [29] showed that exendin-4 increased bone mass and bone quality in a rat unloading-induced bone loss model, in part by enhancing osteogenic differentiation of bone marrow stromal cells via protein kinase A (PKA)/β-catenin signaling. Sclerostin, an osteocyte-derived glycoprotein, is a major inhibitor of canonical Wnt/β-catenin signaling and acts as a negative regulator of bone formation [30]. Therefore, by suppressing Wnt signaling, sclerostin limits osteoblast activity and bone matrix formation; however, the relationship between Wnt signaling and BMD appears complex and may vary with metabolic status, vitamin D levels, and disease context [30]. Importantly, Kim et al. [31] showed that exendin-4 reduced *SOST*/sclerostin mRNA and protein expression in osteocyte-like MLO-Y4 cells and, in type 2 diabetic *OLETF* rats, decreased circulating sclerostin, increased osteocalcin, and increased femoral BMD. These findings suggest that GLP-1 receptor activation may relieve sclerostin-mediated inhibition of Wnt/β-catenin signaling and support bone formation in diabetic bone disease [31]. In addition, Wu et al. [32] reported that liraglutide promoted osteoblast proliferation and differentiation in MC3T3-E1 cells by activating cyclic adenosine monophosphate (cAMP)-, protein kinase B (AKT)-, extracellular signal-regulated kinase (ERK)-, and β-catenin-related signaling pathways. DPP-4, a serine protease responsible for the degradation of incretin hormones, may also influence bone metabolism through several mechanisms [33]. The skeletal effects of DPP-4 have been described through an entero–endocrine–osseous axis, involving intestinal substrates such as GIP, GLP-1, and GLP-2, as well as through adipose- and immune-related pathways involving leptin, adiponectin, inflammatory cytokines, and other adipokines [33]. Furthermore, a pancreatic–endocrine–osseous axis may link DPP-4 activity with bone and energy metabolism [34]. Meanwhile, receptor activator of nuclear factor κB ligand (RANKL) has been shown to stimulate DPP-4 expression in osteoclasts, which may reduce GLP-1 availability and contribute to impaired glucose control and altered bone remodeling [33]. These mechanisms support the hypothesis that DPP-4 inhibition could have favorable skeletal effects by preserving incretin activity and modulating osteoclast-osteoblast balance; however, the clinical relevance of these pathways remains incompletely established. Emerging evidence also highlights the gut microbiota as a potential mediator of incretin-related skeletal effects. In db/db obese diabetic mice, Chen et al. [15] reported that tirzepatide reduced bone mass accrual and altered gut microbiota composition, including a marked reduction in Lachnospiraceae. Since tirzepatide did not directly drive osteoblast or osteoclast differentiation *in vitro*, the authors proposed an indirect microbiota-mediated mechanism; transplantation of Lachnospiraceae ameliorated bone loss, while the Lachnospiraceae-related metabolite evodiamine suppressed osteoclastogenesis [15]. The molecular effects of incretin-based therapies on bone appear to involve several overlapping pathways, including Wnt/β-catenin signaling, sclerostin regulation, RANKL-mediated osteoclast activity, DPP-4-dependent incretin degradation, adipokine signaling, inflammation, and gut microbiota-derived metabolites. The major proposed signaling pathways linking incretin-based therapies with bone remodeling are summarized in Fig. 1.

4. Clinical Evidence on Bone Health Outcomes

GLP-1 RAs and DPP-4 inhibitors have been used to treat T2DM since the late 2000s, and the number of incretin-

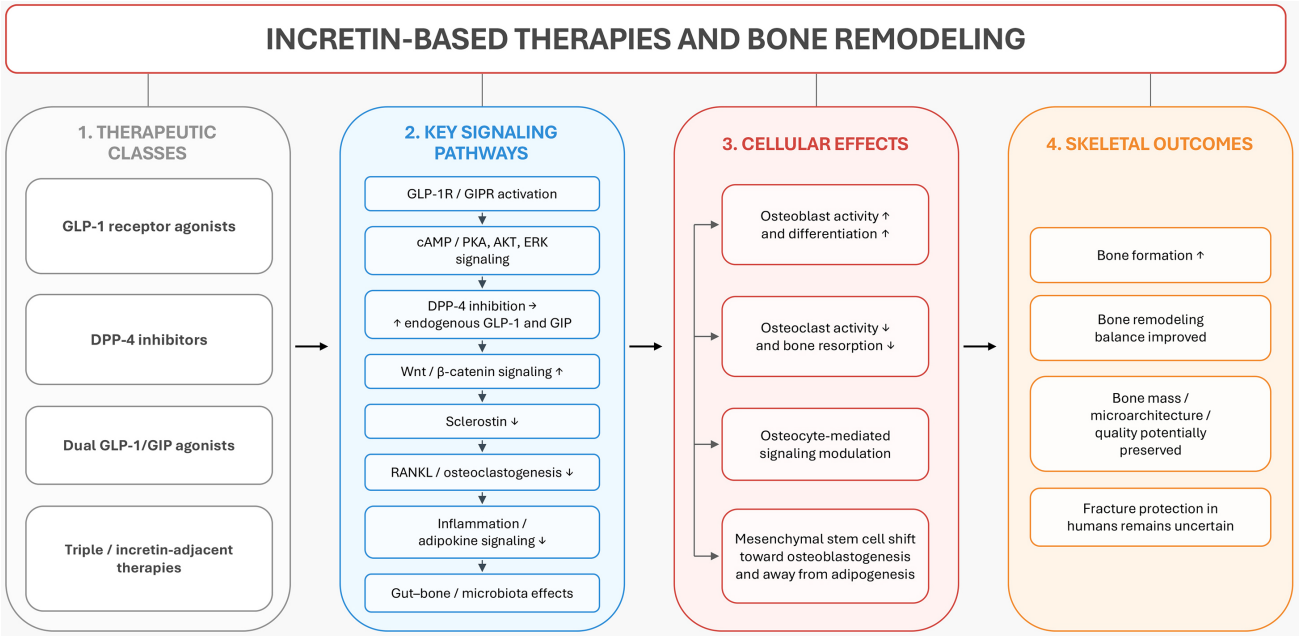

Fig. 1. Proposed molecular pathways linking incretin-based therapies with bone remodeling. Abbreviations: AKT, protein kinase B; cAMP, cyclic adenosine monophosphate; DPP-4, dipeptidyl peptidase-4; ERK, extracellular signal-regulated kinase; GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; PKA, protein kinase A; RANKL, receptor activator of nuclear factor κB ligand. ↑ - increase; ↓ - decrease.

based therapies continues to expand. However, despite the widespread metabolic use of these inhibitors, clinical evidence regarding the associated effects on bone health remains limited and heterogeneous [35]. In clinical studies, skeletal assessment most commonly includes bone turnover markers (BTMs), DXA-derived BMD, fracture incidence, and, less frequently, the trabecular bone score (TBS). The TBS may be particularly useful in individuals with diabetes because this metric provides indirect information on trabecular microarchitecture and may improve the assessment of fracture risk when BMD alone is insufficient [36]. Available human data suggest that GLP-1 RAs have either neutral or modest, context-dependent effects on bone metabolism. Most clinical studies have not demonstrated consistent adverse effects on BMD, BTMs, or fracture risk. However, findings vary according to population, treatment duration, baseline metabolic status, and degree of weight loss [37,38]. Although preclinical findings suggest favorable skeletal effects of GLP-1 receptor activation, these effects have not yet translated into consistent improvements in BMD or fracture outcomes in humans [39]. A major clinical consideration is that GLP-1 RAs induce substantial weight loss, which may, in turn, affect the skeleton. In the STEP-1 trial, 2.4 mg of semaglutide administered once-weekly produced a mean body weight reduction of 14.9% at 68 weeks in adults with overweight or obesity without diabetes, compared with 2.4% with placebo; 86% of participants receiving semaglutide achieved at least 5% weight loss [40]. Interestingly, the STEP-1 DXA substudy suggested a greater reduction in fat mass than lean mass; however, DXA was performed only in a subgroup, and bone-specific outcomes were not the primary focus of the trial [40]. Since weight loss can be accompanied by reductions in lean mass, mechanical loading, and potentially BMD, the skeletal impact of semaglutide and other GLP-1 RAs should be interpreted in the context of changes in body composition rather than drug exposure alone. More recent analyses have specifically examined bone outcomes during GLP-1 RA therapy. For example, Dinkla et al. [38] evaluated semaglutide in a 20-week pilot trial of 20 older adults with overweight or obesity and prediabetes or T2DM. Although semaglutide caused greater weight loss than lifestyle counseling alone (–5.32% vs. –0.89%; $p = 0.006$), no significant between-group differences were observed in whole-body BMD or BTMs, with only a numerical increase in CTX in the semaglutide group (+9.96% vs. +2.02%; $p = 0.08$). Current reviews generally conclude that GLP-1 RAs do not show a major skeletal safety signal; however, these agents may slightly increase bone remodeling or cause small reductions in BMD in some settings, especially when weight loss is substantial [25]. Importantly, most trials were not designed with fracture incidence as a primary endpoint, limiting conclusions about long-term fracture risk. Clinical data for DPP-4 inhibitors are also generally reassuring. Most observational studies and meta-analyses do not demonstrate a significant increase in fracture risk among

DPP-4 inhibitor users, and some reports suggest a potential neutral or modestly protective effect on BMD or fracture outcomes [33,35]. These potential effects may be related to preservation of endogenous incretin activity and modulation of osteoblast–osteoclast balance, but clinical confirmation remains incomplete. Large cardiovascular outcome trials have provided important long-term safety data for incretin-based therapies, but these trials were not primarily designed to assess bone health. Trials such as LEADER, which evaluated liraglutide, and SUSTAIN-6, which evaluated semaglutide, established cardiovascular safety and efficacy in patients with T2DM at high cardiovascular risk; however, fractures were not primary endpoints and were generally captured as adverse events rather than systematically adjudicated skeletal outcomes [41,42]. Therefore, these studies are useful for safety surveillance but cannot definitively determine whether GLP-1 RAs prevent or increase fracture risk.

This limitation is particularly relevant because fracture outcomes in cardiovascular outcome trials are usually captured passively as adverse events rather than systematically assessed skeletal endpoints. Consequently, non-hip, low-trauma, outpatient-managed, or asymptomatic vertebral fractures may be underreported, and events are rarely adjudicated using standardized radiological or clinical criteria. Therefore, fracture findings from cardiovascular outcome trials should be interpreted as supportive safety signals rather than definitive evidence of skeletal benefit or harm. Dual and multiple receptor agonists represent an important newer area of clinical uncertainty. Tirzepatide has demonstrated substantial efficacy in obesity and T2DM. In SURMOUNT-1, tirzepatide produced mean body weight reductions of 15.0%, 19.5%, and 20.9% at 72 weeks with the 5 mg, 10 mg, and 15 mg doses, respectively, compared with 3.1% with placebo [43]. In addition, a DXA substudy reported that fat mass decreased more than lean mass, with approximately a 3-fold greater percentage reduction in fat mass than lean mass [43]. Preclinical evidence suggests that tirzepatide may indirectly influence bone through gut microbiota-related mechanisms, but human data on BMD, BTMs, bone quality, and fracture outcomes remain limited [15]. Ongoing and future trials comparing tirzepatide with other incretin-based agents may help clarify whether dual GIP/GLP-1 receptor activation has skeletal effects beyond those attributable to weight loss and metabolic improvement. Retatrutide, a triple GIP/GLP-1/glucagon receptor agonist, is another emerging therapy with potentially important implications for bone. In a phase 2 trial in adults with obesity, retatrutide produced dose-dependent weight reduction, with a mean weight loss of up to 24.2% at 48 weeks at the highest dose [44]. However, current retatrutide-specific data on BMD, bone microarchitecture, BTMs, and fracture risk are insufficient to define the associated impacts on bone health. Overall, skeletal effects should not be interpreted as uniform across incretin-based therapies, as these outcomes may vary with receptor targets, weight-loss magnitude, and gut–bone interactions. Current clinical evidence suggests that GLP-1 RAsand DPP-4 inhibitors do not substantially increase fracture risk, although their potential protective effects on bone remain uncertain. For newer dual and triple agonists, including tirzepatide and retatrutide, the main concern is not only receptor-specific skeletal signaling but also the consequences of marked weight loss, changes in body composition, reduced mechanical loading, and possible alterations in gut microbiota.

5. Emerging Therapies and Evidence Gaps

The rapid development of incretin-based and incretin-adjacent therapies has expanded treatment options beyond established GLP-1 RAs and DPP-4 inhibitors. However, the skeletal effects of many newer agents remain insufficiently characterized [45]. For several compounds, available evidence is indirect, deriving mainly from experimental studies, metabolic trials, or ongoing studies without dedicated skeletal endpoints. This is particularly important because newer agents often produce greater weight loss than earlier therapies, raising questions about the balance between metabolic benefits and potential skeletal consequences [45]. Orforglipron, an oral non-peptide GLP-1 RA, is one example of an emerging therapy for which bone-specific data remain limited. Orforglipron has been evaluated for T2DM and obesity; meanwhile, an ongoing trial is assessing orforglipron in adults with obesity or overweight and knee osteoarthritis [46]. However, available trial descriptions focus primarily on efficacy, safety, weight-related outcomes, and knee pain rather than dedicated skeletal endpoints [47]. Therefore, although orforglipron may become clinically relevant for patients with obesity-related musculoskeletal disease, its direct effect on bone health remains to be established. Although amylin-based therapies are incretin-adjacent rather than true incretin-based therapies, they should also be considered in this context. Cagrilintide, an amylin analog, is being investigated in postmenopausal women with obesity during weight loss to determine whether it can reduce weight-loss-associated decline in bone mass compared with placebo, semaglutide, and cagrilintide plus semaglutide (CagriSema) [47]. Cell-based and preclinical evidence for DPP-4 inhibitors suggests potential osteoblast-related effects, but these findings require cautious interpretation. Omarigliptin and trelagliptin were associated with increased osteogenic differentiation, mineralization, alkaline phosphatase activity, and activation of osteoblast-related pathways in MC3T3-E1 cells [48,49]. However, such *in vitro* findings do not necessarily translate into lower fracture risk in humans. Clinical evidence remains inconsistent, as illustrated by reports of variable skeletal effects among antidiabetic agents in patients with T2DM, including uncertainty regarding the long-term skeletal profile of individual DPP-4 inhibitors [50,51]. A similar evidence gap applies to investigational

Table 1. Evidence gaps for selected emerging incretin-based and incretin-adjacent therapies regarding bone health.

Therapy	Current evidence	Potential bone-related mechanism	Bone-related interpretation
Orforglipron	Clinical trials in T2DM, obesity, and obesity-related knee osteoarthritis	May influence bone indirectly through weight loss, improved glycemic control, reduced inflammation, and changes in mechanical loading; direct skeletal effects remain unclear	Bone-specific outcomes not yet established
Cagrilintide/CagriSema	Ongoing study in postmenopausal women with obesity including bone-health assessment	Amylin-related signaling may reduce bone resorption, while semaglutide-related weight loss may reduce mechanical loading; net skeletal effect remains uncertain	Relevant to weight loss-associated bone loss; incretin-adjacent rather than true incretin-based therapy
Omarigliptin/trelagliptin	Mainly cell-based osteoblast studies and limited clinical data	DPP-4 inhibition may preserve endogenous incretin activity and promote osteoblast differentiation, mineralization, and osteogenic signaling *in vitro*	Possible osteoblast effects *in vitro*; fracture relevance uncertain
CT-868	Phase 2 metabolic data in overweight/obese adults with diabetes	Dual GLP-1/GIP receptor activation may combine metabolic improvement and GIP-related osteotropic signaling, but weight loss-related reductions in mechanical loading may counterbalance potential benefits	Bone outcomes not established

Abbreviations: T2DM, type 2 diabetes mellitus; CagriSema, cagrilintide plus semaglutide; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

dual agonists such as CT-868 [52], which is a dual GLP-1/GIP receptor agonist currently being studied for glycemic control in overweight or obese adults with type 2 diabetes. Although phase 2 data suggest clinically meaningful reductions in HbA1c after 26 weeks, bone outcomes have not yet been established [52]. Therefore, its relevance to skeletal health remains indirect at present and will require dedicated assessment in future studies [52]. The main evidence gaps for selected emerging incretin-based and incretin-adjacent therapies are summarized in Table 1.

6. Comparative Effects of Antidiabetic and Weight-Loss Therapies on Bone Health

The skeletal effects of incretin-based therapies should be interpreted in the broader context of other antidiabetic and weight loss interventions. Pharmacological management of T2DM and obesity has evolved substantially, and it is increasingly recognized that glucose-lowering and weight-reducing therapies may influence bone health [53]. Among antidiabetic agents, thiazolidinediones have one of the clearest adverse skeletal profiles [54]. Pioglitazone and related drugs have been associated with increased fracture risk, probably through a shift in mesenchymal stem cell differentiation toward adipogenesis at the expense of osteoblastogenesis [55]. Evidence from the IRIS trial showed that fractures occurred in 8.8% of placebo-treated patients within 5 years after ischemic stroke or transient ischemic attack, while pioglitazone increased absolute fracture risk by 1.6–4.9% and relative fracture risk by 47–60%, depending on fracture classification [56]. In contrast, metformin has generally shown a neutral or potentially favorable skeletal profile, although evidence for fracture protection remains inconsistent. For example, Wang et al. [57] reported no significant overall reduction in fracture risk among patients with T2DM receiving metformin (relative risk (RR) 0.91; 95% confidence interval (CI) 0.81–1.02), despite earlier meta-analyses suggesting a possible modest benefit. Insulin and sulfonylureas are relevant mainly because of indirect skeletal risk mediated by hypoglycemia-related falls, particularly in older or frail patients. Severe hypoglycemia has been associated with more than a 2-fold higher risk of falls and with a 70% higher prevalence of falls in older adults with diabetes [58,59]. Sodium–glucose cotransporter 2 (SGLT2) inhibitors provide another useful comparator because their skeletal signal appears mixed and may differ between agents. In a meta-analysis of 78 randomized controlled trials, canagliflozin appeared to be associated with increased fracture risk, whereas other SGLT2 inhibitors did not show higher fracture incidence [60]. Weight loss therapies are relevant because weight reduction may affect bone through reduced mechanical loading, loss of lean mass, and hormonal adaptations. In a meta-analysis of 32 randomized controlled trials, calorie restriction-induced weight loss was associated with reductions in hip and lumbar spine BMD,

particularly when interventions lasted longer than one year [61]. Notably, exercise-induced weight loss appeared less detrimental to hip BMD [61]. Bariatric and metabolic surgery provide an important comparator because these treatments produce substantial and durable weight loss but are also associated with clinically relevant bone loss [62]. Several mechanisms drive postoperative skeletal deterioration and may reflect reduced mechanical loading, hormonal changes, secondary hyperparathyroidism, impaired calcium and vitamin D absorption, and loss of lean mass [62]. In a large population-based cohort in the United States, Roux-en-Y gastric bypass was associated with a 73% higher risk of nonvertebral fractures compared with adjustable gastric banding, including increased risks of hip, wrist, and pelvic fractures [63]. Similarly, a meta-analysis showed that bariatric surgery was associated with lower total body BMD and, in some analyses, lower lumbar spine BMD, with more pronounced decreases becoming evident beyond 12 months after surgery [64]. Compared with thiazolidinediones and bariatric surgery, incretin-based therapies appear less concerning from a skeletal safety perspective. However, the long-term effects of these therapies on bone remain difficult to determine because they are closely influenced by weight loss, changes in body composition, and the underlying metabolic risk of treated patients. The comparative skeletal profiles of selected antidiabetic and weight-loss therapies are summarized in Table 2 (Ref. [35,45,56,57,59,60,61,63,64,65,66]).

7. Limitations and Confounding Factors in Current Evidence

Several methodological and biological factors limit the interpretation of current evidence on incretin-based therapies and bone health. Much of the available clinical data have been generated from cardiovascular outcome trials or metabolic studies that were not primarily designed to assess skeletal endpoints [65,66]. A major challenge is distinguishing direct pharmacological effects from weight loss-related skeletal changes. Incretin-based therapies can induce substantial weight reduction, which may independently affect bone metabolism, BMD, and fracture risk [11]. Therefore, observed changes may reflect the consequences of weight loss rather than receptor-specific effects of GLP-1, GIP, or DPP-4 modulation. Patient-related confounding also complicates interpretation. Individuals with T2DM are often older, multimorbid, and exposed to medications that may independently influence bone metabolism [67]. Hypogonadism, inflammation, chronic kidney disease, liver disease, altered calcium–phosphate metabolism, sarcopenia, frailty, and fall risk may all contribute to skeletal fragility [68]. These factors are not always adequately controlled for in available studies. There is also a disconnect between preclinical and clinical evidence. Although animal and *in vitro* studies suggest that incretin pathways may improve bone health, these findings have not consistently translated into improved BMD or reduced fracture risk in humans [68]. This translational gap may reflect several biological and methodological factors. Experimental studies are usually conducted in controlled animal or cell-based models that do not fully reproduce the complexity of patients with T2DM and obesity. In addition, preclinical studies often assess cellular activity, bone turnover, or microarchitecture. In contrast, clinical trials commonly rely on DXA-derived BMD or fracture reporting, which may not capture changes in bone quality. Potential direct skeletal benefits may also be offset by treatment-induced weight loss, reduced mechanical loading, and loss of lean mass. Thus, the lack of consistent clinical benefit likely reflects both biological and methodological barriers rather than a simple absence of skeletal activity. Consequently, current evidence does not permit a definitive conclusion regarding whether incretin-based therapies exert beneficial, neutral, or adverse long-term effects on bone.

8. Future Directions and Clinical Implications

Future research should prioritize longer-term randomized controlled trials specifically designed to assess skeletal outcomes in patients receiving incretin-based therapies. This need is particularly important given the rapidly expanding use of these agents in the management of both diabetes and obesity. Ukhanova et al. [69] reported that, among GLP-1 RA users in a commercially insured US population, the proportion receiving semaglutide increased from 5% in 2018 to 60% in 2023. Consistent with this trend, data from the Centers for Disease Control and Prevention/National Center for Health Statistics (CDC/NCHS) showed that in 2024, 26.5% of US adults with diagnosed diabetes, corresponding to approximately 6.9 million individuals, reported GLP-1 injectable use, with the proportion increasing to 32.4% among those with both diabetes and obesity [70]. An important research priority is distinguishing direct receptor-mediated skeletal effects from the consequences of weight loss. Newer agents produce substantial reductions in body weight, but their effects on lean mass, mechanical loading, and bone quality remain incompletely understood. Although tirzepatide may be associated with a proportionally lower loss of lean mass than some GLP-1 RA-based therapies, this does not yet establish a protective effect on bone [71]. Therefore, future studies should assess not only total weight loss but also fat mass, lean mass, sarcopenia risk, BMD, and fracture outcomes. Emerging combination strategies may also be relevant for musculoskeletal preservation during pharmacological weight loss. Agents targeting activin and myostatin signaling, such as bimagrumab or trevogrumab, are being investigated for their potential to reduce fat mass while preserving or increasing lean mass [72]. Such approaches could be clinically important if they help counteract muscle loss and reduced skeletal loading during incretin-based obesity treatment. How-

Table 2. Summary of bone-health effects of selected antidiabetic and weight-loss therapies.

Therapy/class	Bone-health effect	Representative evidence	Overall interpretation	Ref.
Thiazolidinediones	Increased fracture risk	Pioglitazone increased absolute fracture risk by 1.6–4.9% and relative fracture risk by 47–60%, depending on fracture classification.	Unfavorable skeletal profile	[56]
Metformin	Neutral or possibly beneficial skeletal profile	Metformin was not significantly associated with overall fracture-risk reduction in T2DM, although earlier analyses suggested possible modest benefit.	Generally reassuring, but not clearly fracture-protective	[57]
Insulin/sulfonylureas	Indirect fracture risk through hypoglycemia-related falls	Severe hypoglycemia has been associated with increased fall risk, including more than a 2-fold higher risk of falls in the ARIC study	Caution in older or frail adults	[45,59]
SGLT2 inhibitors	Mixed and possibly agent-specific skeletal signal	Canagliflozin appeared to be associated with increased fracture risk, whereas other SGLT2 inhibitors were not associated with higher fracture incidence.	Uncertain/agent-specific	[60]
Weight-loss interventions	Possible BMD reduction, depending on weight-loss method	Calorie restriction-induced weight loss was associated with reductions in hip and lumbar spine BMD, particularly when interventions lasted longer than one year.	Dependent on method and duration	[61]
Bariatric surgery	Bone loss and increased fracture risk	Roux-en-Y gastric bypass was associated with a 73% higher risk of non-vertebral fractures compared with adjustable gastric banding; postoperative reductions in total-body and lumbar spine BMD have also been reported.	Higher skeletal concern	[63,64]
Incretin-based therapies	Mostly neutral or uncertain effect on BMD and fracture risk	Clinical studies and reviews generally suggest no clear increase in fracture risk with GLP-1 RAs or DPP-4 inhibitors, although consistent fracture protection has not been established.	Comparatively reassuring, but long-term bone-specific data remain limited	[35,65,66]

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMD, bone mineral density; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

ever, their long-term effects on bone density and fracture risk remain to be established [72,73]. Improved skeletal assessment methods should also be incorporated into future studies. BMD alone may underestimate fracture risk in T2DM and obesity, where bone quality may be impaired despite normal or elevated BMD. For example, Gani et al. [74] reported that older women with T2DM had significantly lower lumbar spine TBS than non-diabetic controls, despite having similar or higher BMD. Similarly, a recent meta-analysis reported that obesity was associated with site- and sex-specific fracture risk despite generally higher BMD, suggesting that increased BMD does not fully capture skeletal fragility in obesity [75]. Therefore, the TBS may provide additional information on trabecular microarchitecture, while high-resolution peripheral quantitative computed tomography may allow more detailed assessment of cortical and trabecular bone compartments [76]. Incorporating these tools into future trials could help identify patients at higher risk of fracture and clarify whether incretin-based therapies affect bone quantity, bone quality, or both. Meanwhile, future comparative studies should clarify whether pharmacological weight loss with incretin-based therapies differs from bariatric surgery in skeletal risk, as Noreña et al. [77] reported a 26% lower fracture risk with incretin-mimetic drugs compared with sleeve gastrectomy. Musculoskeletal preservation should also be considered during incretin-based therapy, especially in postmenopausal women, older adults, patients with T2DM, and

individuals with pre-existing osteoporosis, osteopenia, sarcopenia, or high fall risk. Lifestyle interventions are also important. Jensen et al. [78] reported that combining GLP-1 RA treatment with exercise helped preserve bone health during weight loss, supporting the use of resistance and aerobic exercise in the management of obesity and diabetes. Adequate intake of calcium, protein, vitamin D, and other micronutrients should also be considered, particularly in patients undergoing substantial or rapid weight reduction [79,80]. Future research should move beyond metabolic endpoints alone and systematically evaluate bone, muscle, falls, and fracture outcomes. Nonetheless, until more definitive evidence is available, incretin-based therapies appear relatively reassuring from a skeletal safety perspective; however, patients at high fracture risk may benefit from individualized monitoring of BMD, body composition, nutritional status, physical function, and fall risk.

9. Conclusions

Multiple incretin mediated pathways may support bone formation, reduce bone resorption, and improve bone microarchitecture through effects on osteoblasts, osteoclasts, adipose tissue signaling, inflammation, and the gut–bone axis. However, these experimental findings have not yet translated into consistent clinical evidence of improved BMD, bone quality, or fracture reduction in humans. Interpretation remains complicated by weight loss, changes in body composition, and the underlying skeletal risk associated with T2DM and obesity. These factors are especially relevant for newer dual and triple agonists, which produce greater weight reduction but still lack dedicated long-term bone outcome data. Incretin-based therapies should not currently be regarded as osteoporosis treatments, but neither do they appear to represent a major skeletal safety concern. Future studies should include bone-specific endpoints, longer follow-up periods, and comprehensive assessments of BMD, bone quality, bone turnover, body composition, falls, and fracture outcomes to improve the definition of their long-term role in musculoskeletal health.

Author Contributions

KŁ and JJ contributed to the conception and design of the review. KŁ, MB, ND, PJ, AN, AR, PR, and JJ contributed to the literature search, data acquisition, and manuscript drafting. KŁ, MB, ND created Table 1. PJ, AN, AR, PR created Table 2. JJ revised the manuscript critically for important intellectual content. All authors reviewed and approved the final version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors declare that DeepL Translator was used during manuscript preparation to improve language clarity, flow, and readability. The authors reviewed and edited the final text and take full responsibility for the content of the manuscript.

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