Cellular signaling crosstalk between osteoporosis and diabetes: Common mechanisms and therapeutic targets (Review)

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Abstract. Osteoporosis and diabetes typically occur together. The present review aimed to summarize the molecular mechanisms and intracellular signaling pathways that connect osteoporosis and diabetes. In diabetic conditions, persistent hyperglycemia triggers excessive oxidative stress, sustains low-grade inflammation and perturbs insulin signaling pathways. In turn, bone metabolic abnormalities affect glucose regulation through the bone-pancreas axis and osteoimmune signaling pathways, highlighting a bidirectional relationship between skeletal and metabolic health. Several antidiabetic agents (metformin, glucagon-like peptide-1 receptor agonists) protect against bone loss, while certain anti-osteoporotic drugs (bisphosphonates, denosumab) exert favorable effects on glucose metabolism and diabetic complications. These dual benefits suggest overlapping molecular pathways and shared therapeutic targets. The present review aimed to summarize the inflammation-insulin signaling axis, RANKL/OPG system, Wnt/β-catenin pathway, AGE/RAGE signaling and bone-derived endocrine factors as key mediators of inter-organ communication. It also underscores the importance of systems biology and integrated cross-tissue analyses in uncovering the mechanisms underlying diabetes-associated bone disorder. Future research defining the molecular basis of intercellular and interorgan crosstalk may lead to precise, mechanism-driven strategies for the integrated treatment of diabetes and osteoporosis.

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1. Introduction

Osteoporosis (OP) is a chronic, progressive metabolic bone disorder characterized by an imbalance between osteoblastic bone formation and resorption. This imbalance leads to decreased bone mineral density, disruption of bone microarchitecture, increased skeletal fragility and a higher risk of fractures (1). Diabetes mellitus (DM) represents a cluster of metabolic diseases that cause widespread systemic complications. Among these, type 2 DM (T2DM) is the most common subtype, marked initially by peripheral insulin resistance that progressively leads to pancreatic β cell dysfunction and inadequate insulin secretion (2,3). Epidemiological studies have consistently shown comorbidity between OP and DM, suggesting an intricate pathological association between these disorders (4-6).

A growing body of evidence has identified chronic inflammation, oxidative stress, hormonal dysregulation and aberrant stem cell differentiation as the key molecular mechanisms shared by OP and DM (7-9). On one hand, hyperglycemia and impaired insulin signaling disrupt osteoblast differentiation, bone matrix synthesis and bone marrow microenvironment integrity (3,10); conversely, disturbed bone remodeling feeds back to influence systemic glucose regulation via the bone-pancreas axis (11) and bone-immune signaling pathways (12,13). This bidirectional interplay reflects a complex network of molecular and cell communication linking bone and metabolic homeostasis, providing a biological rationale for cross-targeted therapeutic strategies. Recent pharmacological and experimental data further support this interconnection (14-16). Several antidiabetic drugs (metformin, GLP-1 receptor agonists) have demonstrated the ability to preserve bone mass and mitigate osteoporotic changes (17,18),

while certain anti-osteoporotic treatments (bisphosphonates, denosumab) exhibit favorable effects on glucose metabolism and diabetic complications (19,20). These dual actions imply overlapping molecular signaling pathways and shared pharmacological targets that could be leveraged for combined disease management. The present review aimed to summarize the molecular mechanisms and signaling networks underlying the interplay between T2DM and OP. By emphasizing the interconnected biological pathways and identifying potential therapeutic nodes, the present study aimed to offer novel perspectives on their shared pathophysiology and highlight opportunities for developing integrated, mechanism-based treatment strategies.

2. Association between OP and DM

Interactive risk between OP and DM. Epidemiological studies have established an association between OP and DM, which is particularly evident in the elderly (4-6). Epidemiological studies based on population-level data have reported that the prevalence of osteoporosis varies across populations, ranging from 9 to 38% in female and 1 to 8% in male patients (21). In addition, large-scale meta-analyses estimate the global prevalence to be 18-20% (22). It has been estimated that by 2050, >30 million individuals in Europe will be affected by OP (23). In mainland China, among female patients aged >40 years, the incidence of OP is 20.6% (24). The prevalence of diabetes in China is ~11.2%, corresponding to a substantial disease burden in the adult population (25). The prevalence of osteoporosis among patients with T2DM is ~37.8% based on a meta-analysis (26). There is a potential connection between DM and OP (27). Patients with DM are at a higher risk of bone loss due to chronic hyperglycemia, insulin resistance, accumulation of advanced glycation end products (AGEs), oxidative stress and pro-inflammatory cytokines, which may eventually lead to the development of OP (28). Moreover, bone metabolic status, particularly the level of bone turnover, serves a crucial role in regulating glucose metabolism (29). The Hong Kong OP Study has demonstrated a cross-sectional association between low levels of bone turnover markers and poor glycemic control, suggesting that decreased bone metabolic activity may impair the regulatory function of the bone-pancreas axis (30). Evidence indicates that this underlying pathological interplay may involve shared mechanisms such as chronic inflammation, oxidative stress and increased production of reactive oxygen species (ROS) (31). These findings highlight the need for heightened clinical awareness of the comorbidity risk between these conditions to enable earlier intervention.

Shared cellular signaling and pathological mechanisms

Inflammation-associated signaling pathways (NF-κB, JNK, p38-MAPK and FoxO1). Recently, the mediatory role of inflammation between metabolic disorders and bone metabolism-associated diseases has received increasing attention (7,32). Chronic low-grade inflammation is typically observed in patients with T2DM and OP, with key proinflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-6 and IL-1β serving as the primary drivers. These inflammatory mediators activate signaling pathways, including NF-κB, MAPK and FoxO1, thereby leading to insulin signaling blockade, enhanced gluconeogenesis, β cell apoptosis, suppression of osteoblast differentiation and enhanced osteoclast activity in multiple target organs (Fig. 1) (9). Consequently, there is a pathological link between dysregulated glucose metabolism and abnormal bone remodeling (33).

NF-κB signaling. NF-κB is a key transcription factor regulating the expression of numerous inflammatory mediators. Upon activation by cytokines such as TNF-α, IL-1β, and IL-6, NF-κB translocates into the nucleus, where it promotes the transcription of multiple proinflammatory genes, including TNF-α, IL-1β, IL-8 and COX-2. This amplifies both local and systemic inflammatory responses (34). In skeletal muscles and hepatocytes, the activation of the NF-κB pathway leads to the nuclear translocation of the p65/p50 heterodimer, the active form of NF-κB, which regulates a cascade of inflammation-associated genes. NF-κB can indirectly facilitate abnormal serine/threonine phosphorylation (such as at Ser312) of insulin receptor substrate (IRS)-1/2 by upregulating suppressor of cytokine signaling 3 (SOCS3). This mechanism dysregulates normal tyrosine phosphorylation and disrupts downstream PI3K/Akt signaling. Inhibition of AS160 phosphorylation impairs the translocation of glucose transporter type 4 (GLUT4) to the plasma membrane, thereby decreasing cell surface GLUT4 levels and decreasing glucose uptake (35). In addition, NF-κB may transcriptionally suppresses GLUT4 expression (36). Collectively, these mechanisms attenuate insulin responsiveness in target tissue such as skeletal muscle and liver, increasing blood glucose levels and contributing to insulin resistance.

Under chronic inflammatory conditions, excessive and sustained release of proinflammatory cytokines (TNF-α, IL-1β, IL-6) persistently activates the NF-κB pathway, leading to a bidirectional imbalance in bone metabolism. Activated NF-κB (p65/p50 complex) translocates into the nucleus of osteoblasts, suppressing key osteogenic transcription factors Runx2 and osterix and downregulating bone matrix proteins such as type I collagen (Col1a1). This induces osteoblast apoptosis, thereby impairing bone formation (37,38). Concurrently, inflammatory cytokines (TNF-α and IL-1β) trigger NF-κB signaling in osteoblasts to upregulate receptor activator of nuclear factor-κB ligand (RANKL) expression while suppressing the decoy receptor osteoprotegerin (OPG), elevating the RANKL/OPG ratio. Excessive RANKL binds RANK on osteoclast precursors, activating downstream transcription factors such as c-Fos and NFATc1, to promote osteoclast differentiation and maturation, thereby enhancing bone resorption (39). This reciprocal imbalance, characterized by inhibited osteogenesis and excessive osteoclastogenesis, uncouples the normal balance between bone resorption and bone formation, leading to progressive bone loss (40).

JNK signaling. JNK, a stress-activated member of the MAPK family, is triggered by inflammation and oxidative stress (41). During chronic inflammation, proinflammatory cytokines such as TNF-α, IL-6 and IL-38 activate the JNK pathway through mechanisms analogous to those of NF-κB, leading to its activation via dual phosphorylation at Thr183 and Tyr185 (42). Activated JNK partly remains in the cytoplasm and partly translocates into the nucleus, where it regulates gene transcription (43). In skeletal muscle and hepatocytes, JNK directly phosphorylates IRS-1 at Ser307 in mice (Ser312

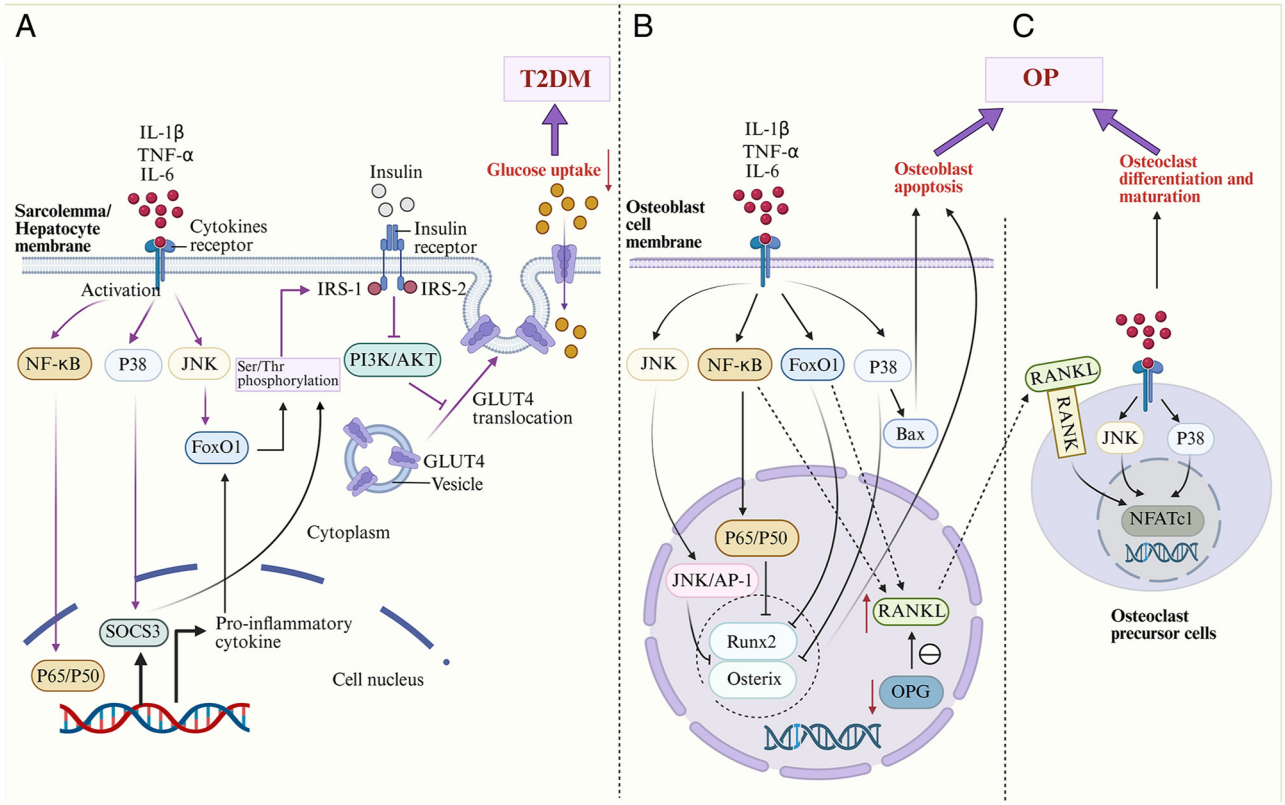

Figure 1. Inflammatory cytokine-mediated signaling pathways involved in the interaction between glucose metabolism and bone remodeling. (A) In skeletal muscle and hepatocytes, inflammatory cytokines (TNF-α, IL-1β and IL-6) bind cytokine receptors and activate the NF-κB, JNK and p38 signaling pathways. These pathways are associated with the insulin signaling cascade, including phosphorylation of IRS-1 and IRS-2 and activation of the PI3K/AKT pathway. This process is associated with GLUT4 vesicle translocation to the plasma membrane and glucose uptake. Key signaling molecules such as FoxO1, SOCS3 and P65/P50 are expressed in the cytoplasm and, upon activation, translocate to the nucleus to regulate the transcription of genes involved in insulin resistance, inflammation and osteoblast differentiation. (B) In osteoblasts, inflammatory cytokines activate multiple intracellular signaling pathways via their receptors, including NF-κB, JNK, p38 and FoxO1. These signaling events are associated with transcriptional regulation in the nucleus, involving osteogenic transcription factors such as Runx2 and osterix. Molecules such as Bax are associated with apoptotic processes. (C) In osteoclast precursor cells, RANKL binds to RANK on the cell surface, recruiting signaling molecules and activating downstream pathways, including JNK and NFATc1. NFATc1 is associated with gene transcription in the nucleus. IRS, insulin receptor substrate; GLUT, glucose transporter; NFATc1, nuclear factor of activated T cells cytoplasmic 1; SOCS, suppressor of cytokine signaling; T2DM, type 2 diabetes mellitus; OP, osteoporosis; OPG, osteoprotegerin.

in humans), inhibiting PI3K/Akt signaling (44,45). This disruption impairs insulin signal transduction and decreases insulin sensitivity, exacerbating hyperglycemia (46).

In osteoblasts, activated JNK promotes the nuclear translocation of c-Jun and the formation of the activator protein-1 (AP-1) complex, which binds to the Runx2 promoter and suppresses its transcriptional activity (47). The JNK/AP-1 pathway suppresses osterix expression by inducing chromatin remodeling and recruiting inhibitory coregulators such as histone deacetylases (HDACs) (48).

In osteoclast precursor cells, JNK signaling is predominantly activated via RANKL-RANK interactions or proinflammatory stimuli (49). A cytoplasmic phosphorylation cascade, comprising TNF receptor-associated factor 6(TRAF6), mitogen-activated protein kinase kinase kinase (MAPKKK), MAPKK and JNK, culminates in the activation of c-Jun. Phosphorylated c-Jun then translocates to the nucleus and heterodimerizes with c-Fos to form the AP-1-transcriptional complex. This complex induces nuclear factor of activated T cells, cytoplasmic 1(NFATc1) expression and drives osteoclast differentiation and activity (50).

p38/MAPK signaling. In hepatocytes and skeletal muscle cells, the activation of the p38/MAPK pathway induces SOCS3 expression, which inhibits tyrosine phosphorylation of IRS-1/2, blocking PI3K/Akt signaling (51,52). In insulin-resistance models, mRNA and protein levels of SOCS3 are markedly elevated, whereas SOCS3 inhibition restores insulin sensitivity (53,54).

Under inflammatory conditions, sustained p38/MAPK activation impairs osteoblast function through multiple mechanisms; it suppresses the transcription of Runx2 and osterix while promoting their proteasomal degradation, induces osteoblast apoptosis via Bax and caspase-dependent pathways and it upregulates inflammatory mediators such as IL-6 and COX-2, further disrupting the osteogenic microenvironment (55). Similarly to JNK, p38/MAPK signaling enhances RANKL expression and promotes osteoclast differentiation; concurrently, it suppresses OPG production, resulting in excessive bone resorption (50).

FoxO1 signaling. FoxO1 is a key transcription factor involved in the regulation of glucose metabolism, oxidative stress responses and inflammatory signaling (56). Under chronic inflammatory conditions, proinflammatory cytokines such as TNF-α and IL-6 activate upstream signaling pathways, including NF-κB, JNK and p38-MAPK, which collectively promote FoxO1 nuclear translocation and transcriptional

activity (57-59). Through these mechanisms, FoxO1 serves as an important mediator linking chronic inflammation with metabolic dysfunction in T2DM and OP (60).

FoxO1 contributes to insulin resistance by inducing negative regulators of IRS-mediated signaling (61). JNK-dependent signaling promotes FoxO1 nuclear localization, while NF-κB-mediated transcription of inflammatory and oxidative stress-associated genes further enhances FoxO1 activity. Activated FoxO1 promotes serine phosphorylation while inhibiting tyrosine phosphorylation of IRS proteins, thereby disrupting downstream IR signaling and thus aggravating insulin resistance (62).

In hepatic tissue, nuclear FoxO1 upregulates key gluconeogenic enzymes, including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, thereby enhancing hepatic gluconeogenesis and increasing endogenous hepatic glucose production. This exacerbates hyperglycemia and contributes to the progression of diabetes (63). Under chronic inflammatory conditions, cytokines such as TNF-α and IL-6 activate FoxO1, amplifying gluconeogenic activity and sustaining persistently high blood glucose levels (64).

In bone metabolism, FoxO1 activation suppresses the osteogenic transcription factor Runx2, which is key for osteoblast differentiation and bone formation (65). FoxO1 can also regulate additional osteogenic factors such as osterix, further impairing osteoblast function and reducing bone formation (66).

Additionally, FoxO1 influences osteoclastogenesis by upregulating RANKL and downregulating OPG expression, thereby enhancing osteoclast differentiation and bone resorption (67).

Chronic inflammation increases ROS levels, which further activate FoxO1 and amplify the activity of proinflammatory transcription factors such as NF-κB and AP-1. This establishes a self-perpetuating cycle of inflammation, oxidative stress and metabolic dysfunction that disrupts insulin sensitivity and bone homeostasis (68).

Dysregulation of the RANKL/RANK/OPG signaling pathway: A key mechanism linking bone loss and metabolic dysfunction. During OP pathogenesis, excessive activation of the RANKL/RANK/OPG signaling pathway disrupts skeletal homeostasis (69). This pathological imbalance is marked by aberrant upregulation of RANKL and/or compensatory downregulation of OPG, driving sustained osteoclastic activity and accelerating progressive bone resorption (Fig. 2) (70). Upregulated RANKL binds to its cognate receptor RANK on osteoclast precursor, recruiting the adaptor protein TRAF6 and inducing the activation of NF-κB, MAPK, c-Fos and NFATc1 (71-73). This signaling cascade promotes the full differentiation of osteoclast precursors into mature, functional osteoclasts (74). TRAF6 reinforces this process by promoting autoamplification and transcriptional activation of NFATc1, thereby promoting osteoclastogenesis (75). Simultaneously, decreased OPG expression enhances RANKL-RANK interactions, further potentiating osteoclast formation and activity (69). Under elevated RANKL conditions, the expression of osteogenic differentiation markers such as COL1 and Runx2 is markedly decreased (76). This effect is exacerbated by the suppression of the p38 MAPK/CREB signaling cascade, further hindering osteoblast maturation (77). RANKL downregulates key transcription factors, including Runx2 and osterix, thereby abrogating the commitment of mesenchymal stem cells (MSCs) to the osteoblastic lineage and impairing bone formation (78).

Overactivation of the RANKL/RANK/OPG pathway is also implicated in T2DM development and progression (79). Through its receptor RANK, RANKL activates the NF-κB-signaling cascade, inducing the release of proinflammatory cytokines such as TNF-α and IL-6 (80). These mediators contribute to insulin resistance and pancreatic β cell dysfunction, exacerbating T2DM pathogenesis (81). Mechanistically, the RANKL-RANK interaction promotes the deubiquitination of TNF receptor-associated factor 3, activating NF-κB-inducing kinase. This phosphorylates IKKα, mediating the proteolytic conversion of NF-κB2 (p100) to p52. The resulting p52-v-rel reticuloendotheliosis viral oncogene homolog B complex translocates into the nucleus, where it induces the transcription of proapoptotic genes such as Bax, Bim and FasL. This cascade increases β cell apoptosis, impairs insulin secretion and promotes pancreatic structural degeneration (Fig. 3). RANKL and hyperglycemia form a positive feedback loop that promotes β cell apoptosis and sustains hyperglycemic states (79). By contrast, OPG exerts a protective influence on pancreatic islets; thus, its downregulation may compromise this defense mechanism, further aggravating glucose dysregulation (82).

Collectively, dysregulation of the RANKL/RANK/OPG pathway contributes to the chronic low-grade inflammatory milieu characteristic of diabetes and highlights a key molecular target for therapeutic intervention in both OP and T2DM.

Inactivation of the Wnt/β-catenin pathway: Disrupted crosstalk between bone marrow mesenchymal stem cell (BMSC) differentiation and metabolic homeostasis. The Wnt/β-catenin signaling pathway is a highly conserved regulatory cascade that orchestrates cell proliferation, differentiation and tissue homeostasis. Its downregulation is documented in both T2DM and OP, implicating this pathway as a common molecular mechanism driving the pathogenesis of these associated metabolic disorders (83,84).

The Wnt pathway is a key regulator of both skeletal remodeling and systemic glucose metabolism (85,86). Canonical Wnt/β-catenin signaling promotes osteoblast differentiation and bone formation, while non-canonical Wnt pathways influence osteocyte activity, lipid homeostasis and inflammatory responses (85). In the differentiation of BMSCs into osteoblasts, Wnt/β-catenin signaling is key (87). Physiologically, Wnt ligands such as Wnt1 and Wnt3a bind the Frizzled receptor and its co-receptor low-density lipoprotein receptor-related protein 5/6 (LRP5/6), suppressing glycogen synthase kinase-3β (GSK-3β)-mediated β-catenin phosphorylation and proteasomal degradation (88,89). Stabilized β-catenin accumulates in the cytoplasm and translocates to the nucleus, where it activates osteogenic transcription factors including Runx2 and osterix (90). This tightly regulated pathway not only promotes osteogenic commitment of BMSCs but also inhibits their differentiation into adipocytes, maintaining the balance between bone formation and marrow adiposity (91,92).

Inactivation or suppression of Wnt/β-catenin signaling disrupts the regulated network governing bone homeostasis,

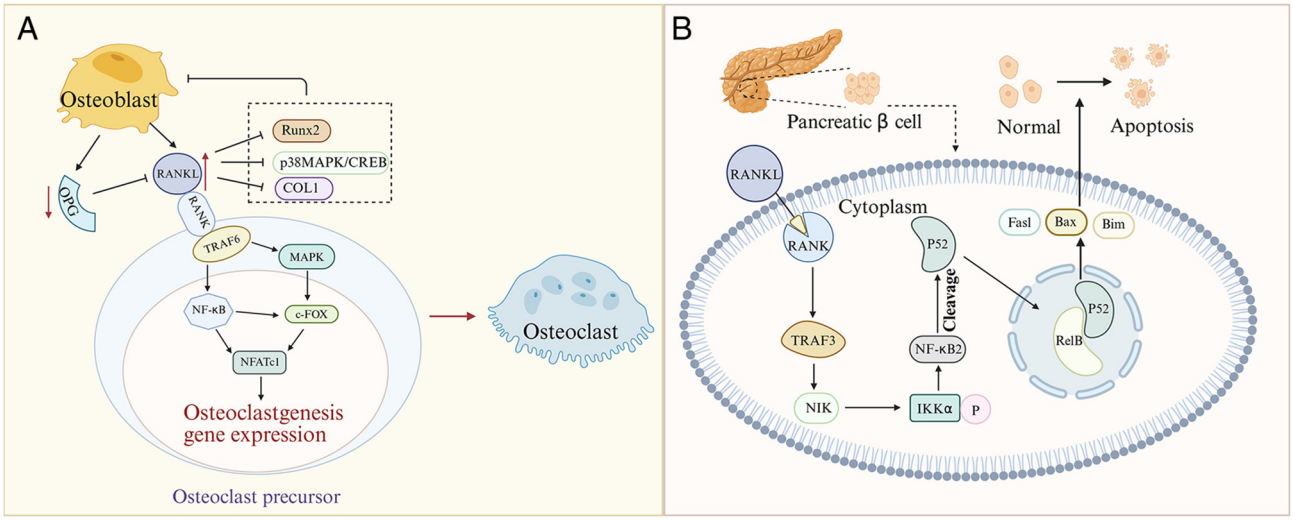

Figure 2. RANKL/RANK/OPG signaling in bone remodeling and pancreatic β cell-associated signaling. (A) In bone tissue, osteoblasts produce RANKL and OPG. RANKL binds RANK on osteoclast precursor cells, leading to recruitment of TRAF6 and activation of downstream signaling pathways, including NF-κB and MAPK. These signaling events are associated with activation of transcription factors such as c-Fos and NFATc1 and the expression of osteoclast-associated genes. (B) In pancreatic β cells, RANKL interacts with RANK on the cell membrane and activates downstream signaling involving TRAF3, NIK and IKKα. This signaling cascade is associated with processing of NF-κB2 (p100) to p52 and formation of the p52-RelB complex. The complex is involved in transcriptional regulation in the nucleus. OPG, osteoprotegerin; TRAF, TNF receptor-associated factor; NFATc1, nuclear factor of activated T cells cytoplasmic 1; NIK, NF-κB-inducing kinase; RelB, v-rel reticuloendotheliosis viral oncogene homolog B (a member of the NF-κB family); COL, collagen (e.g., type I collagen, COL1); Bim, Bcl-2 interacting mediator of cell death.

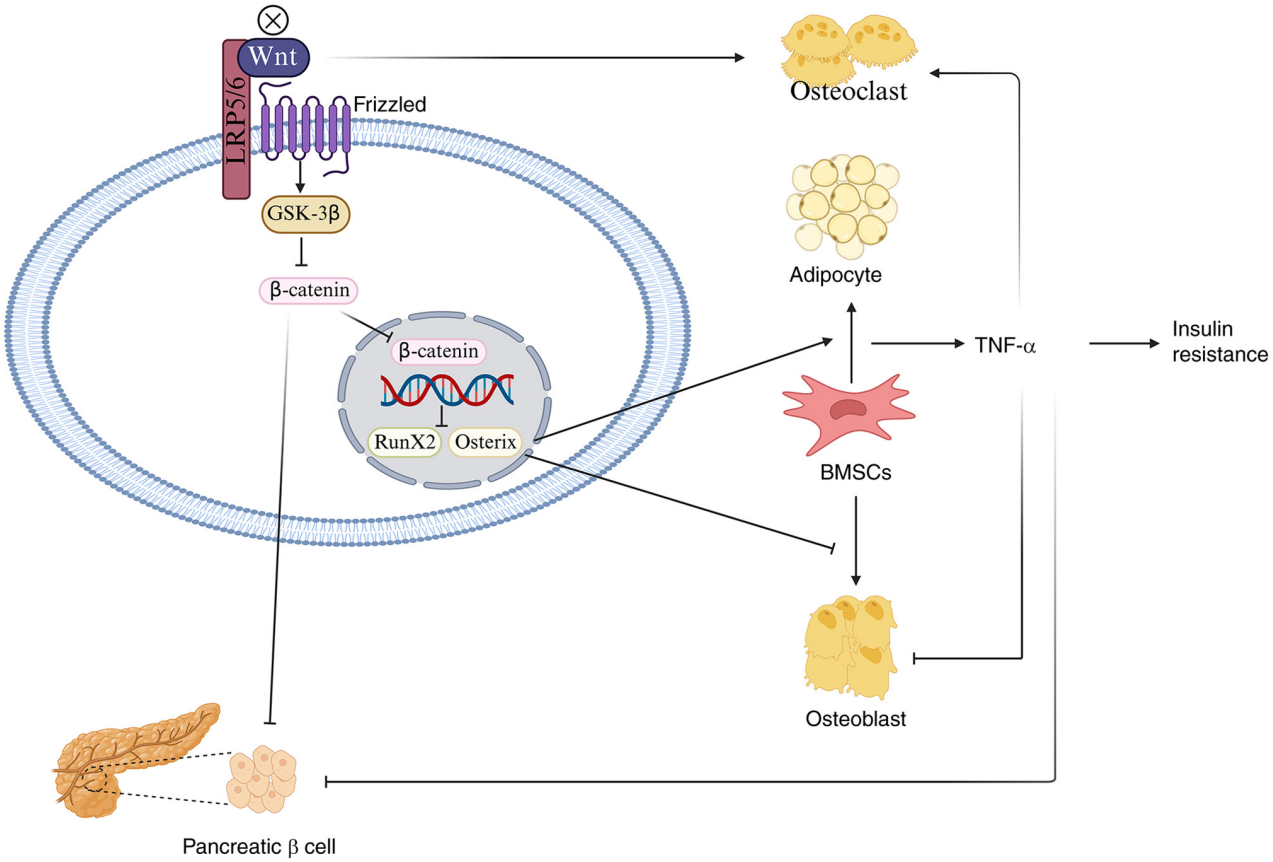

Figure 3. Wnt/β-catenin signaling in the regulation of BMSC differentiation and metabolic homeostasis. Wnt binds the Frizzled receptor and co-receptor LRP5/6 on the cell membrane, associated with regulation of GSK-3β activity and stabilization of β-catenin. β-catenin translocates into the nucleus, where it is associated with transcriptional regulation involving osteogenic factors such as Runx2 and osterix. BMSCs differentiate into adipocytes and osteoblasts. During adipogenic differentiation, BMSC-derived adipocytes secrete TNF-α. This cytokine suppresses osteoblast activity and bone formation, promotes osteoclastogenesis and bone resorption, and impairs insulin signaling, thereby contributing to insulin resistance. Pancreatic β cells secrete insulin to control blood glucose levels and their function is impaired under insulin-resistant conditions. Osteoclasts resorb bone, whereas osteoblasts form bone, and the balance between these two cell types determines net bone mass. BMSC, bone marrow mesenchymal stem/stromal cell; LRP, low-density lipoprotein receptor-related protein; GSK, glycogen synthase kinase.

leading to skeletal and metabolic abnormalities. Decreased expression of β-catenin impairs the initiation of the osteogenic transcriptional program, limiting BMSC differentiation and compromising the functionality of mature osteoblasts. This is reflected by decreased alkaline phosphatase (ALP) activity, decreased production of COL1 and osteocalcin (OCN) and impaired mineral deposition, which are hallmarks of osteoblast dysfunction (93). In addition, Wnt signaling also skews BMSCs toward adipogenic differentiation, resulting in increased marrow adipocyte accumulation and a 'bone-fat conversion' phenotype (94). This shift not only diminishes osteogenic potential but also enhances the local secretion of proinflammatory cytokines, including TNF-α, which inhibit osteoblast activity, stimulate osteoclastogenesis and exacerbate insulin resistance, as aforementioned. Moreover, inhibition of Wnt pathway signaling disrupts the RANKL/OPG balance, favoring osteoclast differentiation and activity and promoting bone resorption (95). Persistent suppression of Wnt signaling results in bone loss, trabecular deterioration and decreased mechanical strength, recapitulating key features of OP (83).

Wnt/β-catenin downregulation is associated with pancreatic β cell dysfunction and the progression of T2DM (96). β-catenin expression in β cells is essential for their survival and secretory competence (97). Activation of β-catenin via Wnt3a enhances insulin gene transcription, promotes insulin release and protects β cells from glucotoxicity and oxidative stress (98). Conversely, inhibition of Wnt signaling decreases β-catenin levels, leading to impaired β cell proliferation, increased apoptosis and reduced insulin synthesis and secretion, thus promoting diabetes progression (99). Together, these findings suggest that restoring or enhancing Wnt/β-catenin activity represents a potential therapeutic strategy to address skeletal and metabolic dysfunction (Fig. 3).

Decreased insulin-like growth factor-1 (IGF-1) Levels: A Key mediator between bone and glucose metabolism. IGF-1 is a pleiotropic peptide hormone structurally associated with insulin (100), with key roles in enhancing insulin sensitivity, promoting glucose uptake and supporting bone formation and skeletal integrity (101).

Declining circulating IGF-1 levels are associated with impaired insulin sensitivity, β cell dysfunction and disrupted glucose homeostasis (102). Functionally, IGF-1 mimics insulin by activating IR, enhancing glucose uptake in skeletal muscle, and suppressing hepatic gluconeogenesis, glycogenolysis and ketogenesis (103). Reduced IGF-1 weakens these regulatory effects, leading to decreased peripheral glucose use and insulin resistance (104). IGF-1 is key for pancreatic β cell survival and function (102). Low IGF-1 expression impairs glucose-stimulated insulin secretion, resulting in insufficient insulin release (105). Mechanistically, IGF-1 binding to insulin-like growth factor 1 receptor triggers the PI3K/Akt signaling cascade, modulating expression and trafficking of glucose transporters such as GLUT4 (106). Attenuated IGF-1 signaling decreases cellular proliferation, migration and glucose uptake under hyperglycemic or lipotoxic conditions by limiting GLUT4 translocation to the plasma membrane (107).

Beyond its metabolic role, IGF-1 is key for maintaining bone homeostasis throughout adulthood (108). It coordinates osteoblastic bone formation and osteoclastic resorption to preserve skeletal integrity. Declining IGF-1 levels impair osteoblast differentiation and activity while tipping the balance toward increased osteoclast-mediated bone resorption, resulting in a net loss of bone mass (101). Mechanistically, IGF-1 exerts its effects primarily through binding the IGF-1 receptor, which activates the PI3K/Akt pathway (109). Disruption of this pathway decreases Akt phosphorylation, diminishes mTOR signaling and compromises protein synthesis and extracellular matrix production in osteoblasts. These molecular perturbations collectively hinder bone formation and weaken skeletal architecture, highlighting IGF-1 as a key mediator of bone homeostasis.

Effects of DM on bone metabolism: Intercellular signaling perturbations in a hyperglycemic environment

Dysregulation of calcium and phosphate metabolism. Chronic hyperglycemia in diabetes disrupts systemic calcium and phosphate homeostasis. Hyperglycemia-induced osmotic diuresis increases urinary calcium excretion, decreasing serum calcium levels and promoting compensatory mobilization of calcium from bone (110). Insulin deficiency or resistance typically coincides with secondary disturbances in parathyroid hormone and active vitamin D [$1,25(OH)_2D_3$] signaling, impairing both intestinal and renal reabsorption of calcium and phosphate (111). Diabetes-associated nephropathy and chronic low-grade inflammation exacerbate these imbalances (112). Collectively, these disruptions suppress bone formation, compromise mineralization and promote bone loss, thereby increasing susceptibility to OP and fragility fractures.

Hyperglycemia and AGE/RAGE signaling: Cell injury and crosstalk among bone-associated cells. In the hyperglycemic milieu, AGEs and chronic high glucose target key bone-resident cells, osteocytes, osteoblasts, BMSCs and osteoclasts, disrupting bone remodeling (7).

Osteocytes, as primary mechanosensory cells, are susceptible to hyperglycemia-induced endoplasmic reticulum stress and mitochondrial dysfunction, which increase apoptosis (113). AGEs bind RAGE on osteocyte membranes, activating NF-κB signaling and inducing the secretion of proinflammatory cytokines, including IL-6 and TNF-α (114,115). This inflammatory cascade disrupts the sclerostin feedback loop, further impairing the regulation of bone remodeling and contributing to skeletal imbalance (116).

Osteoblasts exposed to hyperglycemia show markedly impaired differentiation and mineralization, with downregulation of osteogenic transcription factors (RUNX2 and osterix) and inhibition of Wnt/β-catenin signaling (117). AGEs also interfere with collagen cross-linking, diminishing bone matrix quality, and induce autophagic dysregulation and cell senescence (118).

In vitro studies have shown that BMSCs under high-glucose or AGE exposure exhibit decreased osteogenic potential and a shift toward adipogenic differentiation, contributing to bone marrow adiposity (119-121). Notably, this phenotypical shift may persist following normalization of glucose levels, indicating long-lasting reprogramming of SC fate (122,123). Mechanistically, activation of the AGE-RAGE axis stimulates the p38 MAPK signaling pathway, which promotes BMSC senescence and apoptosis. Supporting this mechanism,

additional *in vitro* studies using SC models, including human periodontal ligament SCs and BMSCs derived from diabetic rats have demonstrated that silencing RAGE or pharmacologically inhibiting p38 MAPK (with SB203580) restores osteogenic differentiation and decreases marrow adiposity, highlighting a potential therapeutic strategy for diabetes-associated skeletal deterioration (124,125).

Osteoclast activity is also indirectly amplified in hyperglycemic conditions. AGE/RAGE signaling enhances osteoclastogenesis by increasing RANKL expression and activating NF-κB-dependent inflammatory pathways (114). The combination of impaired osteoblast function and increased osteoclast activity disrupts the balance of bone formation and resorption, constituting a hallmark of diabetic bone disease.

Feedback effects of OP on glucose metabolism: Skeletal endocrine function. Cross-sectional studies reveal that bone loss is associated with decreased OCN secretion (126-128). OCN enhances insulin secretion and improves insulin sensitivity; thus, its decrease impairs glucose homeostasis and contributes to hyperglycemia (129). Concurrently, OP-induced chronic inflammation activates signaling pathways that inhibit insulin action and impair glucose uptake, increasing the risk of fasting hyperglycemia (130).

OCN signaling and the bone-pancreas interplay. Bone serves not only as a structural organ but also as an active endocrine organ. OCN, secreted by osteoblasts, plays a key role in regulating insulin sensitivity and glucose metabolism (131). In osteoporotic conditions, impaired bone formation diminishes OCN secretion, potentially exacerbating insulin resistance and metabolic dysfunction (132). *In vivo* studies in demonstrate that administration of undercarboxylated OCN improves glucose tolerance and insulin sensitivity under normal dietary conditions and prevents high-fat diet-induced T2DM (133,134).

IRs are expressed in both pancreatic β cells and osteoblasts, as well as other tissues. Insulin signaling within osteoblasts enhances OCN bioactivity, promoting systemic glucose homeostasis via the bone-pancreas axis (135). Both animal and human studies demonstrate that enhancing insulin signaling in osteoblasts improves systemic glucose metabolism, whereas disruption of this signaling impairs glucose homeostasis, primarily through a bone resorption-dependent mechanism (135-137). These findings reveal a feed-forward regulatory circuit in which insulin signaling within osteoblasts stimulates OCN production. OCN enhances glucose metabolism, and the resulting improvement in glycemic control reinforces insulin action, thereby establishing a reciprocal bone-pancreas communication loop.

Peroxisome proliferator-activated receptor γ (PPARγ) and Wnt/β-catenin signaling mediate adipogenic shift of BMSCS and impact glucose homeostasis. BMSCs retain the capacity to differentiate into osteoblasts or adipocytes; the balance between these lineages is key for skeletal integrity and systemic metabolic homeostasis. In OP, BMSCs typically exhibit a bias toward adipogenic differentiation, resulting in impaired osteogenesis and excessive bone marrow adipose tissue accumulation (138,139). Mechanistically, this lineage shift is driven by upregulation of PPARγ alongside suppression of canonical Wnt/β-catenin signaling (140,141). PPARγ activation promotes adipocyte differentiation and regulates lipid storage, insulin sensitivity and inflammatory signaling, thus exerting systemic effects on glucose metabolism (142). By contrast, restoration of Wnt signaling, such as through the LINC00473/microRNA (miRNA or miR)-23a-3p/LRP5 pathway, enhances osteogenic commitment while restraining adipogenesis (143).

The shift of BMSCs toward adipogenic differentiation exerts a notable impact on systemic glucose homeostasis through multiple connected mechanisms. Adipocytes arising from BMSCs secrete key hormones, including leptin and adiponectin, which modulate insulin sensitivity in the liver and skeletal muscle (144). In parallel, this osteogenic-to-adipogenic transition is accompanied by metabolic reprogramming, such as altered glycolytic flux and fatty acid oxidation, and epigenetic remodeling, including dysregulated miRNAs such as miR-601 that target SIRT1, collectively diminishing insulin responsiveness and contributing to metabolic dysfunction (145,146).

Emerging studies from both *in vivo* and *in vitro* models have identified novel regulatory nodes (8,115,147). For example, *in vivo* studies have shown that IL-27 suppresses adipogenesis and improves glucose metabolism via the HDAC6/TGF-β/Smad3 pathway (148) and 14-3-3 proteins have been implicated in regulating glucose uptake and adipogenic signaling (149). *In vitro* evidence suggests that copper homeostasis, mediated by ATP7A, suppresses PPARγ-dependent adipogenesis (150).

Collectively, elevated PPARγ activity coupled with attenuated Wnt/β-catenin signaling promotes the adipogenic differentiation of BMSCs, undermining bone remodeling and systemic glucose regulation. Therapeutic strategies targeting these pathways or their metabolic regulators, such as IL-27, 14-3-3 proteins or copper homeostasis, may provide dual benefits for the treatment of both OP and diabetes.

3. Dual-targeted therapeutic opportunities

Chronic inflammation, oxidative stress, RANKL/OPG imbalance, disrupted Wnt/β-catenin signaling, AGE/RAGE activation and impaired bone-derived endocrine function constitute the key molecular mechanisms linking OP and T2DM (151). Although classical inflammatory pathways, such as NF-κB, JNK, p38-MAPK and FoxO1, play key roles in both diseases, direct pharmacological inhibition is constrained by limitations (152). Their broad involvement in immunity, host defense and metabolic regulation raises the risk of adverse effects, including immunosuppression, infection susceptibility and cardiovascular complications. Furthermore, pathway redundancy and compensatory mechanisms decrease the efficacy of single-target interventions (147). Consequently, research has increasingly focused on molecular targets at critical signaling intersections, which offer greater pathological specificity, higher translational potential and improved safety profiles (Table I).

Inflammation/oxidative stress signaling. Inflammation and oxidative stress are key connected drivers of both OP and T2DM. Downstream regulatory molecules, such as thioredoxin-interacting protein (TXNIP), vanin-1 (VNN1)

Table I. Shared signaling pathways and potential intervention targets in OP and T2DM.

A, Inflammation/oxidative stress

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
TXNIP	Animal studies	HFD/STZ mice (C57BL/6); BMSCs	Inhibits osteogenesis; promotes osteoclastogenesis	Promotes insulin resistance and β cell apoptosis	Inhibitor SRI-37330
VNN1	Clinical and animal studies	DSS-induced mice (C57BL/6); human datasets (GEO)	Promote bone resorption	Exacerbates pancreatic islet injury	Elevated in patient serum/animal models
SIRT3	Animal studies	HFD/STZ mice (C57BL/6)	Protects osteoblasts; inhibits bone resorption	Improves insulin sensitivity	Honokiol; irisin
Nrf2	Cell and animal studies	HFD/STZ mice (C57BL/6); BMSCs; OVX C57BL/6 mice	Antioxidant protection of osteoblasts	Improves insulin sensitivity	Salidroside
NLRP3	Animal studies	OVX mice; macrophages; HFD/STZ mice (C57BL/6)	Promotes osteoclast differentiation and enhances bone resorption	Exacerbates insulin resistance	Inhibitor MCC950

B, RANKL/RANK/OPG

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
RANKL	Clinical drug	Not applicable	Inhibits osteoclasts and increases bone mass	Improves islet function	Denosumab
OPG	Mechanistic studies (proposed)	Not applicable	Protects osteoblasts and inhibits bone resorption	Protects pancreatic β cells	OPG-Fc fusion protein
TRAF6	Cell and animal studies	HFD/STZ mice (C57BL/6); palmitate-treated insulin-resistant HepG2 cells; normal HepG2 cells; adipose tissue cells	Promotes osteoclast differentiation	Exacerbates insulin resistance	Rictor deficiency

C, AGE/RAGE

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
RAGE	Animal studies	HFD-induced obese mice (C57BL/6)	Inhibits osteoblasts and promotes bone resorption	Activation of inflammatory pathways contributes to the development of insulin resistance	Metformin

Table I. Continued.

C, AGE/RAGE

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
AGE	Preclinical	Not applicable	Decreases bone quality and enhances osteoclast activity	Exacerbates insulin resistance	Inhibitor aminoguanidine
Glo-1	Animal studies	HFD/STZ mice (C57BL/6)	Restores HG-impaired BMSC osteogenesis	Decreases AGE accumulation	Morroniside

D, Wnt/β-catenin

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
β-catenin	Mechanistic studies (proposed)	Not applicable	Initiates osteogenic differentiation	Enhances insulin secretion	Nuclear translocation enhancer assay
GSK-3β	Clinical studies	Not applicable	Stabilizes β-catenin to promote osteogenesis	Improves glucose metabolism	Tideglusib
TM9SF4	Cell and animal studies	Primary BMSCs from TM9SF4$^{+/+}$ and TM9SF4$^{-/-}$ mice; OVX-induced TM9SF4 knockout mice	Decreases osteoblast activity, impairs bone turnover; shifts BMSC differentiation toward adipogenesis	Improves islet function	TM9SF4 deficiency (knockout model)

E, Bone-pancreas endocrine axis

Representative targets	Research stage	Model	Effect on bone metabolism	Effect on glucose metabolism	Therapeutic strategies and supporting evidence
OCN	Clinical and animal studies	Human subjects; mouse models; pancreatic β cells	Promotes bone formation	Enhances insulin secretion and sensitivity	uOCN supplementation experiment
SPPARγ-Ms	Cell and animal studies	HFD/STZ mice (C57BL/6); BMSCs	Prevents bone loss	Modulates downstream signaling to improve insulin sensitivity	Alpinetin
IGF-1	Clinical studies	Not applicable	Promotes osteoblast survival	Improves β cell function and insulin sensitivity	IGF-1 supplementation experiment

TXNIP, thioredoxin-interacting protein; HFD, high-fat diet; STZ, streptozotocin; BMSC, bone marrow mesenchymal stem/stromal cell; VNN, vanin ; DSS, dextran sulfate sodium; GEO, Gene Expression Omnibus; OVX, ovariectomized; OPG, osteoprotegerin; TRAF, TNF receptor-associated factor; Glo, glyoxalase; GSK, glycogen synthase kinase; TM9SF4, transmembrane 9 superfamily member 4; uOCN, undercarboxylated osteocalcin; SPPARγ-Ms, selective peroxisome proliferator-activated receptor γ modulators; IGF, insulin-like growth factor.

and sirtuin 3 (SIRT3), Nrf2 and NLRP3, serve as key nodal hubs within the inflammation-oxidative stress axis (153-155). Unlike classical inflammatory mediators, these molecules exert more specific regulatory effects by integrating metabolic stress signals with skeletal remodeling processes (153). Their nodal positioning within disease networks confers greater translational potential, making them promising candidates for dual-action therapeutic strategies aimed at simultaneously improving metabolic control and preserving bone integrity (9).

TXNIP inhibition. TXNIP is a key regulator linking oxidative stress, glucose metabolism and inflammation, and plays an important role in both T2DM and OP (156). It modulates bone remodeling via regulation of the RANKL/RANK/OPG pathway. Mechanistically, TXNIP controls RANKL transcription via the ecdysoneless-P300 axis. Its deficiency in BMSCs promotes osteogenesis and inhibits osteoclast formation, leading to increased bone mass. Pharmacological inhibition of TXNIP (using SRI-37330) supports its role as a therapeutic target for preserving skeletal homeostasis (157).

TXNIP inhibition also improves metabolic parameters. In *in vivo* mouse models of both T1DM and T2DM, SRI-37330 reduces pancreatic TXNIP expression, glucagon secretion, hepatic glucagon activity, glucose production and lipid accumulation, thereby exerting hypoglycemic effects (156,158). Collectively, these findings indicate that TXNIP targeting offers a dual therapeutic opportunity for enhancing glycemic control while simultaneously preserving bone mass, making it a candidate for the integrated management of diabetes and OP (158).

Inhibition of VNN1. VNN1 is a membrane-bound pantetheinase expressed in epithelial and myeloid cells. By hydrolyzing pantetheine, VNN1 generates biologically active metabolites, including vitamin B5 and cysteamine (159,160). Elevated VNN1 expression enhances local oxidative stress and stimulates the release of proinflammatory cytokines such as TNF-α, exerting simultaneous effects on pancreatic function and the bone microenvironment (161).

Functionally, VNN1 exerts coordinated effects on both metabolic and skeletal tissues. In the pancreas, VNN1-driven oxidative contributes to β cell dysfunction and insulin resistance (162,163). In bone, similar mechanisms impair BMSC osteogenic differentiation while promoting osteoclast activation, thereby accelerating bone loss (151).

Clinical and *in vivo* studies consistently report elevated VNN1 expression in the serum, bone tissue and pancreas of human and animal models with OP and T2DM, with the highest levels observed in cases of comorbid OP and T2DM (164,165). Furthermore, *in vivo* studies in ovariectomized mice have shown upregulation of VNN1 in the pancreas, which suggests a potential role in postmenopausal insulin resistance and OP (162,163,166).

Collectively, VNN1 serves as a mechanistic bridge linking glucose dysregulation and skeletal metabolic impairment via the inflammation-oxidative stress axis, representing a dual therapeutic target for DM and OP.

Activation of SIRT3. SIRT3, a mitochondrial deacetylase, is a key regulator of cellular energy metabolism and redox homeostasis, with implications for both T2DM and OP (167). One of its key roles is maintaining mitochondrial function, which indirectly supports IGF-1-mediated metabolic and osteogenic processes (168).

In addition, SIRT3 exerts potent antioxidant and anti-inflammatory effects by enhancing Mn-superoxide dismutase activity and reducing intracellular ROS levels, thereby protecting osteoblasts from oxidative damage and preserving bone-forming capacity (169). Activation of SIRT3 through pharmacological agents such as honokiol or irisin or via genetic upregulation promotes osteogenic differentiation, improves bone microarchitecture and restores skeletal function in diabetic models (170,171). Conversely, SIRT3 deficiency attenuates estrogen deficiency-induced bone loss by impairing osteoclast mitochondrial function and decreasing bone resorption (169). These findings suggest that the role of SIRT3 in bone remodeling may be context-dependent, reflecting its dual regulatory effects on osteoblast and osteoclast activity.

Overall, SIRT3 serves as a key metabolic-skeletal integrator by coordinating mitochondrial function, oxidative stress responses and osteogenic activity. These properties underscore its therapeutic potential as a dual-action strategy for DM and OP.

Nrf2. Nrf2 is a master regulator of cell antioxidant defenses (172) and plays a central protective role in both OP and T2DM (173). By coordinating the transcription of antioxidant genes, Nrf2 mitigates oxidative stress and maintains cell homeostasis across multiple types of tissue (174).

In bone metabolism, Nrf2 supports skeletal integrity by preserving osteoblast function and limiting osteoclast overactivation, thereby maintaining the balance of bone remodeling (175). In parallel, Nrf2 contributes to metabolic regulation, partly via modulation of glucose transport and use, which may alleviate diabetes-associated complications (176).

Pharmacological Nrf2 activators, such as anemoside B4, scutellarin and salidroside, have demonstrated efficacy in both *in vitro* and *in vivo* experimental models of OP and T2DM, underscoring their therapeutic relevance (177-179).

Taken together, Nrf2 serves as a key regulator within the inflammation-oxidative stress signaling axis, offering a promising target for integrated therapeutic interventions in OP and diabetes.

Inhibition of NLRP3. The NLRP3 inflammasome is a central mediator of chronic inflammation-driven metabolic disorder, including OP and T2DM (180,181). Evidence from *in vitro* experiments and *in vivo* diabetic fracture models indicates that its activation triggers persistent low-grade inflammation, thereby impairing fracture healing and bone regeneration (182-184).

In the skeletal context, NLRP3 serves as a critical downstream effector linking inflammatory stress to bone remodeling imbalance. Its activation promotes osteoclast differentiation and pyroptotic cell death, thereby shifting bone homeostasis toward excessive resorption (185).

Conversely, targeting NLRP3 confers coordinated metabolic and skeletal benefits. Both clinical observations and preclinical studies have shown that NLRP3 inhibition improves glycemic control and insulin sensitivity, while simultaneously

restoring bone microarchitecture and enhancing osteoblast activity (186,187).

Notably, pharmacological blockade of NLRP3 (using MCC950) has demonstrated efficacy across multiple disease models, including diabetic complications, delayed fracture healing and postmenopausal OP, underscoring its role as a convergent regulatory node within the inflammation-oxidative stress axis (182,188).

Collectively, these findings identify NLRP3 as a key integrative target that links metabolic dysfunction with skeletal deterioration, highlighting its potential for dual-disease therapeutic intervention.

RANKL/RANK/OPG pathway and therapeutic targets. The RANKL/OPG pathway is a key regulator of osteoclast differentiation and bone resorption. Both RANKL and its receptor RANK are key therapeutic targets for OP, with denosumab, a monoclonal antibody against RANKL, widely implemented in clinical practice (189). RANKL inhibition by denosumab may also confer beneficial effects on glucose metabolism, highlighting its potential relevance beyond skeletal outcomes (190). TRAF6 has recently been identified as a key adaptor protein within the RANK signaling cascade (191). By regulating the RANKL/OPG balance, TRAF6 influences bone homeostasis and insulin sensitivity, positioning it as a molecular target with translational potential (80).

Inhibition of TRAF6. Small-molecule inhibitors targeting TRAF6, including compounds such as 6877002, have been shown to suppress NF-κB activation and osteoclastogenesis in *in vitro* and *ex vivo* studies (192-194). Furthermore, *in vivo* rodent models demonstrate that these inhibitors decrease joint inflammation and arthritis severity (192,195,196). However, these inhibitors demonstrate limited effectiveness in improving bone mass or microarchitecture in osteolytic or OP models (192,197), indicating that TRAF6-targeted monotherapy may be insufficient to fully prevent local or systemic bone loss and may need to be combined with conventional antiresorptive therapies, such as bisphosphonates.

Upstream regulators of TRAF6, notably the mTORC2 subunit Rictor, exert a more notable influence on osteoclast biology than pharmacological inhibition with small-molecule inhibitors. Rictor deficiency diminishes TRAF6 expression, suppresses osteoclast formation and increases bone mass (198). Mechanistically, Rictor deficiency destabilizes TRAF6 through ubiquitin-mediated degradation and perturbs autophagic processes, highlighting the superior effectiveness of genetic modulation over pharmacological inhibition in controlling osteoclast activity (199).

Beyond skeletal effects, TRAF6 serves as a critical molecular interface linking inflammation and insulin resistance (200,201). Following IR activation, TRAF6 facilitates Akt1 ubiquitination, impairing insulin signaling and decreasing cellular insulin sensitivity (202). In high-fat diet-induced obese mouse models, TRAF6 is upregulated and contributes to hepatic lipid accumulation and metabolic dysregulation via the enhancer of zeste homolog 2/miR-429/PPARα axis (203,204). However, its role in adipose inflammation and insulin resistance requires further investigation. Additionally, TRAF6 activates NF-κB and interacts with RAGE to promote macrophage infiltration and chronic adipose tissue inflammation (205). Targeted suppression of TRAF6-driven inflammation via AMPK activation enhances systemic insulin sensitivity (206). Collectively, TRAF6 represents a key node linking chronic inflammation to metabolic dysfunction, underscoring its potential as a dual-targeted therapeutic approach.

AGE/RAGE signaling

RAGE antagonists. The interaction of AGEs with RAGE constitutes a fundamental mechanism connecting hyperglycemia to skeletal impairment. RAGE activation triggers NF-κB-mediated inflammation and oxidative stress, exacerbating both T2DM and OP progression (207). Pharmacological inhibition of RAGE restores osteogenic gene expression, improves bone metabolic function and alleviates insulin resistance and diabetic complications (208). RAGE antagonists represent a promising therapeutic strategy targeting this pathway. Metformin, a widely prescribed antidiabetic agent, improves bone microarchitecture in diabetic models by obstructing the RAGE/JAK2/STAT1 pathway (17,209,210). This promotes osteogenic differentiation of MSCs, evidenced by increased RUNX2, Col1a1 and OCN expression, while simultaneously downregulating proinflammatory cytokines TNF-α and IL-6 (17). By attenuating RAGE-mediated inflammation, metformin achieves a dual benefit, improving both bone remodeling and glucose homeostasis.

AGE inhibitors. Persistent hyperglycemia accelerates AGE formation, which accumulates in bone tissue and exerts multifactorial detrimental effects. Non-enzymatic AGE cross-links compromise collagen flexibility and mechanical strength, impairing osteoblast differentiation and mineralization (211). Simultaneously, AGE-RAGE interactions activate NF-κB and other proinflammatory pathways, increasing TNF-α and IL-6 levels, stimulating osteoclast activity and promoting bone resorption (212).

Pharmacological blockade of AGE formation offers a strategic intervention. Aminoguanidine (AG), a prototypical AGE inhibitor, prevents non-enzymatic glycation, decreases AGE accumulation and limits activation of downstream AGE/RAGE signaling. AG not only lowers AGE levels but also modifies abnormal collagen cross-linking and preserves the collagen-mineral interface, maintaining trabecular architecture and bone strength (211). AGE inhibition improves insulin sensitivity and attenuates diabetes-associated inflammation, offering a dual protective effect against both metabolic dysfunction and bone deterioration (213).

Glyoxalase-1 (Glo-1). Glo-1, a key rate-limiting enzyme in the detoxification of AGEs, serves a key role in maintaining intracellular glycation balance (214). Hyperglycemia-induced AGE accumulation impairs osteogenic differentiation of BMSCs, decreases osteoblast functionality and exacerbates insulin resistance and inflammatory responses (215). Pharmacological activation or upregulation of Glo-1 clears intracellular AGEs, diminishes AGE/RAGE binding and suppresses downstream oxidative and inflammatory signaling, thereby restoring BMSC osteogenic potential (216). *In vivo,* Glo-1 activation is associated with RAGE downregulation, improved bone microarchitecture and enhanced systemic glucose regulation. Natural compounds such as morroniside demonstrate dual protective effects via Glo-1

activation, highlighting its potential as a therapeutic target for the simultaneous management of DM and OP (216,217).

Wnt/β-catenin signaling pathway and targets

β-catenin regulation and GSK-3β inhibition. β-catenin serves as a key effector of Wnt signaling, with its stability and nuclear translocation determining the efficiency of osteogenic differentiation. GSK-3β, a serine/threonine kinase involved in multiple intracellular pathways, negatively regulates canonical Wnt/β-catenin signaling by promoting cytoplasmic β-catenin degradation and preventing its nuclear translocation (218). Pharmacological inhibition of GSK-3β enhances osteogenic differentiation through β-catenin activation and glucose metabolism by modulating insulin signaling. For example, extracts from *Lactobacillus paracasei* L30 activate the p38 MAPK/AKT/GSK-3β pathway, facilitate β-catenin nuclear translocation and promote osteogenic differentiation of human MSCs (219). Similarly, in Duchenne muscular dystrophy models, tideglusib-mediated GSK-3β inhibition restores β-catenin levels, ameliorating both insulin resistance and OP (220,221).

Transmembrane 9 superfamily member 4 (TM9SF4) deficiency. Under diabetic conditions, hyperglycemia, AGE accumulation and chronic inflammation suppress Wnt signaling, resulting in impaired osteogenic differentiation, defective bone remodeling and a preferential shift of BMSCs toward adipogenesis (115,222,223). These alterations collectively contribute to decreased bone mass and heightened skeletal fragility (224). A study has identified TM9SF4, a transmembrane protein, as a key regulator of osteogenesis (225). Furthermore, a genome-wide association study linked TM9SF4 to bone mineral density, suggesting its potential role in skeletal metabolism (226). TM9SF4 deficiency promotes osteogenic differentiation and inhibit adipogenic commitment of BMSCs in *in vitro* studies, while also preserving bone mass in ovariectomy-induced *in vivo* models (225,227). Mechanistically, these effects may be mediated by activation of the mTORC2/Akt/β-catenin axis and enhanced Wnt/β-catenin signaling (225). This may partially counteract the pathological alterations in diabetes-associated bone disease.

Targeting TM9SF4 may counteract diabetes-induced deficit in bone formation. By restoring Wnt/β-catenin activity and mTORC2/Akt signaling, TM9SF4 modulation may improve bone microarchitecture and overall skeletal integrity (225,228). Moreover, given the role of Wnt/β-catenin in systemic energy metabolism and insulin sensitivity, TM9SF4 intervention may confer secondary benefits on glucose homeostasis (229).

To the best of our knowledge, evidence regarding TM9SF4 is largely restricted to its regulation of osteogenesis and its precise role in diabetic bone pathology remains unvalidated (225,230-232). The systemic safety of TM9SF4 knockout or inhibition requires evaluation. Therefore, while TM9SF4 represents a promising therapeutic target, its clinical translation requires preclinical validation using targeted delivery strategies and disease-relevant animal models.

Bone-pancreas endocrine axis. The bone serves as an endocrine organ that plays a key role in regulating glucose metabolism (233). Traditional bone-derived hormones, such as OCN, enhance insulin secretion and improve insulin sensitivity, though their clinical utility remains limited due to their short half-life, rapid degradation in the gastrointestinal tract and lack of specific, safe delivery systems for long-term use (234). Research has broadened the focus to include additional regulatory factors, including selective PPARγ modulators and IGF-1, which occupy key nodes within the bone-pancreas signaling network and represent promising targets for integrated therapeutic strategies addressing both bone and glucose metabolic disorder (235-237).

PPARγ promotes BMSC adipogenic differentiation, accelerating bone loss and contributing to ectopic fat deposition in diabetes (238,239). Although PPARγ agonists such as thiazolidinediones (rosiglitazone and pioglitazone) improve insulin sensitivity, their associated fracture risk highlights the need for selective modulation (240). Selective PPARγ modulators, such as the flavonoid alpinetin, selectively bind PPARγ at Ser342, block aberrant Ser273 phosphorylation, enhance PI3K/AKT signaling and promote GLUT4 translocation (235). In animal models, alpinetin improves glucose metabolism comparably to rosiglitazone while simultaneously inhibiting osteoclast differentiation, avoiding bone loss (235,236). These findings position PPARγ as a key node within the bone-pancreas axis for achieving concurrent improvements in glucose homeostasis and bone integrity.

IGF-1 is a key growth factor that promotes osteogenic differentiation and bone matrix synthesis while also enhancing insulin signaling and glucose uptake (241). Structurally analogous to IR, IGF-1 coordinates glucose metabolism and bone homeostasis (237,242). In T2DM, IGF-1 activates downstream pathways such as PI3K/AKT, improving insulin sensitivity and indirectly supporting bone formation (243). By stimulating osteoblast activity and suppressing osteoclast-mediated resorption, IGF-1 maintains the balance of bone remodeling; both deficiency and excess of IGF-1 disrupt normal bone mass and integrity (101). Epidemiological data demonstrate an association between decreased IGF-1 levels and AGE-mediated bone deterioration in patients with T2DM with increased fracture risk (232). Overall, IGF-1 serves as a key mediator bridging osteogenesis and glucose metabolism, offering therapeutic potential for the simultaneous management of T2DM and OP.

Translational challenges and future perspectives. Despite the identification of multiple therapeutic targets involved in the pathogenesis of OP and T2DM, their clinical translation remains challenging. One key limitation is the insufficient evaluation of tissue specificity and systemic safety. Numerous signaling molecules, such as TRAF6 and PPARγ, are ubiquitously expressed and participate in multiple physiological processes, raising concerns regarding off-target effects. For example, although inhibition of TRAF6 may attenuate inflammation, its direct bone-protective efficacy remains unclear (192). Similarly, pharmacological activation of PPARγ improves insulin sensitivity but is associated with increased fracture risk due to its inhibitory effects on osteoblast differentiation (244).

Another issue is the lack of targeted delivery strategies. Conventional systemic administration typically leads to suboptimal drug accumulation in bone tissue and increases the risk of adverse effects in non-skeletal organs. Therefore, the development of tissue-specific delivery systems has

emerged as a promising approach to enhance therapeutic precision (245). Nanocarrier-based systems targeting BMSCs or the bone microenvironment may enable selective modulation of osteogenesis and osteoclastogenesis while minimizing systemic toxicity (246,247).

To the best of our knowledge, most current evidence is derived from preclinical studies, and high-quality clinical trials evaluating long-term efficacy and safety are lacking (248-250). Future research should integrate molecular targeting strategies with advanced drug delivery technologies, thereby facilitating the translation of these targets into clinically viable therapies for OP and T2DM.

4. Future directions and research challenges

Despite growing insights into the mechanisms linking OP and T2DM (251,252), several critical challenges remain, highlighting avenues for future research. These challenges include the diabetic bone paradox, where conventional DXA-based bone mineral density measurements fail to capture the true fracture risk in diabetic patients (253,254), the multifactorial and heterogeneous pathophysiology of diabetic bone disease, which involves the convergence of hyperglycemia, AGE accumulation, oxidative stress, chronic low-grade inflammation and microvascular damage, rather than a single dominant pathway (115,147,151), and the current lack of dual-action therapeutics that simultaneously improve glycemic control and preserve bone integrity, as clinical management typically separates metabolic from skeletal interventions (147).

Mechanistic precision. As complex, multifactorial disorders, OP and T2DM are characterized by inflammation, oxidative stress, metabolic dysregulation and impaired bone-derived endocrine signaling (115). Future studies should leverage integrative multi-omics, including transcriptomics, proteomics, metabolomics and epigenomics, to construct comprehensive systems biology networks and identify the central molecular mediators and signaling hubs governing the bone-pancreas axis and the bone marrow microenvironment. Emerging computational tools, including artificial intelligence and machine learning, demonstrate potential for mapping these key nodes with precision (255). Particular attention should be devoted to the regulatory roles of OCN, Wnt/β-catenin signaling and bone marrow adipogenic transdifferentiation in modulating insulin secretion and systemic glucose homeostasis (256). These efforts are key for mechanistic understanding of OP-T2DM comorbidity (15,164).

Comorbidity management and precision therapy. Numerous potential targets, such as TXNIP, VNN1 and SIRT3, have demonstrated efficacy in cellular and animal models; nonetheless, robust clinical validation remains lacking (164,184,257). Future research must shift toward well-designed, multicenter cohort studies and long-term longitudinal trials to ascertain the safety, efficacy and translational feasibility of these interventions. Personalized treatment strategies should be tailored to the specific diabetes subtype (T1DM vs. T2DM), bone metabolic phenotype (high vs. low turnover) and the presence of additional comorbidities. Dual-action therapeutics that concurrently modulate glucose metabolism and bone homeostasis optimize clinical outcomes, enhance adherence and minimize adverse effects.

5. Conclusion

The interplay between OP and T2DM arises from shared molecular and cellular mechanisms, including chronic inflammation and oxidative stress, dysregulation of Wnt/β-catenin signaling, overactivation of the RANKL/RANK/OPG pathway, IGF-1 deficiency and aberrant AGE/RAGE signaling. These convergent pathways drive bidirectional dysregulation of bone and glucose metabolism, forming the mechanistic basis of the 'bone-glucose comorbidity'.

Several molecular targets, including VNN1, TXNIP and the AGE-RAGE axis, represent promising candidates for the dual modulation of bone and glucose homeostasis. Translating these targets into clinical practice requires the integration of multi-omics, rigorous mechanistic validation and well-structured translational studies to enable the development of novel therapeutics with dual benefits, advancing precision medicine for patients with coexisting OP and T2DM.

In summary, clarifying these shared pathogenic mechanisms and therapeutic targets may elucidate the pathophysiology of OP-T2DM comorbidity and deliver dual benefits, ultimately improving outcomes for individuals at elevated risk of both osteoporotic fractures and diabetes-associated metabolic complications.

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Authors' contributions

JG conceived the study. YY and LX performed the literature review. YC wrote the manuscript. FT, JG, XH and LZ edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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