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Review

Molecular pathways shaping bone function following SGLT2 inhibitor therapy; a narrative insight from metabolic and endocrine crosstalk

Parzhin Khazdoozi[1], Abnoos Mokhtariardekani[2], Mansooreh Kashefi[3], Somayeh Ghamkhari[4], Hojjat Eghbali Jelodar[5], Hanie Fooladi[6], Asaad Abass Fadhel Khalif[7*]

Abstract

A sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy promotes renal glucosuria, which triggers phosphaturia and initiates a cascade of metabolic and hormonal disturbances. The resulting hypophosphatemia stimulates secondary hyperparathyroidism, which in turn elevates fibroblast growth factor 23 (FGF23), further suppressing serum phosphate, calcitriol, and calcium levels. Concurrently, the osmotic diuresis and caloric loss induce a negative energy balance, shifting metabolism toward ketogenesis. Elevated β-hydroxybutyrate not only serves as an alternative fuel but also directly stimulates osteoclast activity while inhibiting osteoblast function. Compounding this, therapy-associated hypoinsulinemia diminishes anabolic signaling through insulin and insulin-like growth factor-1 (IGF-1), both critical for bone formation. At the heart of this skeletal disruption lies osteocyte dysfunction. Hypophosphatemia and altered hormonal milieu—particularly increased PTH and FGF23 upregulate sclerostin, a potent inhibitor of the Wnt/β-catenin pathway, thereby suppressing bone formation. Furthermore, alterations in adipokines following weight loss further modulate bone metabolism. Critically, these pathways interact synergistically: PTH enhances bone resorption and sclerostin production; FGF23 suppresses calcitriol, worsening hypocalcemia; and ketones amplify RANKL-driven osteoclastogenesis. Additionally, mechanical unloading from rapid weight loss independently increases sclerostin expression. The net effect is a profound uncoupling of bone remodeling, accelerated resorption driven by PTH, RANKL, ketones, and inflammatory cytokines, coupled with suppressed formation due to sclerostin, hypoinsulinemia, and direct ketone effects. Clinically, this manifests as rapid trabecular bone loss, deteriorated microarchitecture, and a markedly elevated fracture risk, particularly during the initial months of treatment. Therefore, SGLT2 inhibitors confer significant cardio-renal benefits; however, they may impose substantial skeletal trade-offs that warrant careful monitoring.

Keywords: SGLT2 inhibitors, Bone metabolism, Endocrine–skeletal crosstalk, Molecular pathways, Mineral homeostasis, Osteoblast–osteoclast regulation, Metabolic signaling

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Introduction

The therapeutic landscape for type 2 diabetes mellitus (T2DM) has been profoundly reshaped by sodium-glucose cotransporter-2 (SGLT2) inhibitors. These agents, by inhibiting glucose reabsorption in the proximal tubule of the kidney, promote significant glycosuria, leading to reductions in blood glucose, blood pressure, body weight, and offering robust cardio-renal protection (1). However, alongside these well-documented benefits, a concerning signal has emerged regarding skeletal health. Clinical trials and real-world evidence consistently indicate an increased risk of fractures, particularly with certain agents like canagliflozin, especially in the initial months of therapy and in vulnerable populations such as the elderly and those with pre-existing osteoporosis or renal impairment (2). The paradox of improved metabolic health juxtaposed with potential skeletal detriment, demands a deep dive into the intricate molecular pathways orchestrating bone remodeling under SGLT2 inhibition (3). Analyzing these findings require moving beyond simple caloric loss or weight reduction effects and instead resolving the complex metabolic and endocrine crosstalk triggered by the fundamental action of these drugs, detected as forced urinary glucose excretion (3). The bone, far from

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[1]School of Nursing, Gerash University of Medical Sciences, Gerash, Iran. [2]Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Science & Physiology Research Center, Kerman University of Medical Sciences, Kerman, Iran. [3]Department of Nursing, Se.C., Islamic Azad University, Semnan, Iran. [4]Department of Medical Biotechnology, Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran. [5]Department of Surgery and Orthopedic, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran. [6]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. [7]Department of Pharmacology and Toxicology, Al-Mustansiriyah University, College of Pharmacy, Baghdad, Iraq.
***Corresponding author:** Asaad Abass Fadhel Khalif Email: asaad_abbas@uomustansiriyah.edu.iq

Implication for health policy/practice/research/medical education

Molecular pathways influencing bone function after sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy consist of renal phosphate handling, which directly affects the availability of minerals essential for bone health. Additionally, endocrine feedback loops, featuring key hormones like fibroblast growth factor 23 (FGF23), parathyroid hormone (PTH), and vitamin D, play a fundamental role in regulating calcium and phosphate homeostasis, thereby significantly impacting bone metabolism. These agents also engage with energy metabolism regulators such as AMPK and mTORC1, influencing cellular energy balance and anabolic processes vital for bone formation. The interplay with inflammatory and oxidative stress mediators, further highlights the systemic effects of these inhibitors, since chronic inflammation and oxidative stress can negatively impact bone remodeling and overall skeletal integrity. Vascular-endothelial interactions also contribute, affecting nutrient supply and waste removal in bone tissue. Finally, the net impact of SGLT2 inhibitors on bone remodeling, mineral density, and fracture risk is determined by the complex metabolic and endocrine crosstalk interacting these diverse pathways.

being a static scaffold, is a dynamic endocrine organ delicately sensitive to systemic metabolic shifts, hormonal fluctuations, and mineral homeostasis (4). Meanwhile, SGLT2 inhibitors (SGLT2i) perturb multiple pathways simultaneously, creating a unique physiological milieu that impacts osteoblasts, osteoclasts, osteocytes, and their intricate signaling networks (3).

Search strategy

For this review, we conducted a comprehensive literature search across PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase, using a combination of targeted keywords, including 'SGLT2 inhibitors', 'bone metabolism', 'endocrine–skeletal crosstalk', 'molecular pathways', 'mineral homeostasis', 'osteoblast–osteoclast regulation', and 'metabolic signaling', to identify relevant experimental, clinical, and mechanistic studies addressing the molecular pathways influencing bone function following SGLT2 inhibitor therapy.

Molecular actions of SGLT2 inhibitors

The primary trigger for the cascade affecting bone lies in the proximal tubule. SGLT2 inhibition causes profound glycosuria, resulting in significant caloric loss. However, the osmotic diuresis accompanying this glucose excretion has far-reaching consequences for mineral handling (3). The increased solute load and flow rate through the nephron, particularly impacting the proximal tubule where SGLT2 and sodium-phosphate cotransporter (NaPi-IIa/IIc) share regulatory pathways, lead to phosphaturia. This urinary phosphate wasting is a consistent finding in both preclinical models and humans treated with SGLT2 inhibitors (5). These agents exert their effects through competitive inhibition and shared regulatory pathways (3). Notably, SGLT2 inhibition may indirectly down-regulate the expression or activity of NaPi-IIa and NaPi-IIc by altered intracellular signaling cascades triggered by changes in osmotic load and tubular flow. The resulting hypophosphatemia is a potent stimulus for the parathyroid glands (6, 7). Then, the parathyroid hormone (PTH) secretion increases rapidly in response to low serum phosphate levels, a physiological response aimed at restoring phosphate by enhancing renal reabsorption, primarily in the distal tubule, beyond the SGLT2 site and stimulating bone resorption to release phosphate and calcium from the mineralized matrix. This secondary hyperparathyroidism becomes a central driver of accelerated bone turnover (5). It is postulated that, chronically elevated PTH, even if intermittent or moderate, favors osteoclastogenesis and bone resorption over formation (8). In the next step, PTH binds to its receptor (PTH1R) on osteoblasts and osteocytes, activating complex downstream signaling. This cascade includes the canonical Gαs/cAMP/PKA pathway, which stimulates receptor activator of nuclear factor kappa-B ligand (RANKL) expression while suppressing osteoprotegerin (OPG), the decoy receptor for RANKL (9). The increased RANKL/OPG ratio is a master switch promoting osteoclast differentiation, activation, and survival via RANK signaling on osteoclast precursors, leading to enhanced bone resorption and calcium/phosphate release (10). Concurrently, the phosphaturia and hypophosphatemia trigger a counter-regulatory response from bone and other tissues involving fibroblast growth factor 23 (FGF23) (11). Consequently, FGF23, which primarily secreted by osteocytes, acts on the kidneys to promote phosphaturia, through down-regulating NaPi-IIa/IIc and suppressing 1α-hydroxylase activity, thereby reducing the active form of vitamin D (12). In fact, the initial phosphaturia caused by SGLT2 inhibition creates a paradoxical situation; since, the kidneys are already wasting phosphate due to the drug's action, and prompting FGF23 secretion. In the next step, the elevated FGF23 further suppresses calcitriol synthesis (6). Hence, calcitriol is crucial not only for intestinal calcium and phosphate absorption but also for direct effects on bone cells. Calcitriol also promotes osteoblast differentiation and mineralization while exerting complex, concentration-dependent effects on osteoclasts (13). Reduced calcitriol levels; therefore, impair calcium absorption from the gut, potentially exacerbating the hypocalcemic stimulus for PTH secretion and directly hindering bone mineralization (14). Furthermore, low-calcitriol may blunt the anabolic effects on osteoblasts (15). It should remember that, following administration of SGLT2 inhibitors, the FGF23-PTH axis becomes dysregulated; while FGF23 normally suppresses PTH, in states of chronic kidney disease (CKD), this suppression can be overcome, leading to concomitant high levels of both hormones of FGF23 and parathormone, a scenario potentially relevant in diabetic patients, especially those with underlying renal dysfunction, who treated

with SGLT2 inhibitors. This creates a vicious cycle as phosphaturia → hypophosphatemia → ↑PTH and ↑FGF23 → ↓calcitriol → impaired gut calcium absorption → further hypocalcemia → further ↑PTH → accelerated bone resorption (3,5). Beyond mineral disturbances, the significant metabolic shifts induced by SGLT2 inhibitors profoundly influence bone through endocrine crosstalk. The caloric loss from glycosuria creates a state of negative energy balance. While weight loss, particularly fat mass reduction, is generally beneficial for metabolic health, its impact on bone is nuanced (16). Adipose tissue is not merely inert storage; it is a major endocrine organ secreting adipokines that regulate bone metabolism (17). Leptin, secreted proportionally to fat mass, has dual effects: centrally, it can inhibit bone formation via the sympathetic nervous system (SNS), while peripherally, it may stimulate osteoblast proliferation (18). The rapid weight loss induced by SGLT2 inhibitors leads to a significant reduction in circulating leptin levels (19). The net effect on bone is complex and context-dependent, but the sudden drop may disrupt the peripheral anabolic signals and potentially alter central SNS tone, though the latter's contribution in humans under SGLT2i remains less defined (3, 18). More consistently impactful is the reduction in adiponectin. Adiponectin levels typically rise with weight loss and improved insulin sensitivity. Adiponectin directly stimulates osteoblast proliferation and differentiation via AdipoR1 receptors and AMP-activated protein kinase (AMPK) signaling, while also inhibiting osteoclast formation through suppression of RANKL signaling and induction of anti-oxidant pathways (20). The initial rapid fat loss with SGLT2 inhibitors might transiently suppress adiponectin before its eventual rise with sustained metabolic improvement, creating a window of reduced bone-protective adipokine signaling (3,21). However, the dominant metabolic shift relevant to bone is the induction of a fasting-like state and increased reliance on alternative fuels. Reduced insulin levels and increased glucagon secretion, hallmarks of SGLT2 inhibition, promote lipolysis and ketogenesis (22). Elevated levels of circulating ketone bodies, particularly β-hydroxybutyrate, are a direct consequence. While ketones serve as efficient energy substrates for many tissues, their impact on bone cells is emerging as critically important. In addition, β-hydroxybutyrate has been shown to directly stimulate osteoclast formation and bone resorptive activity (23). In-vitro, β-hydroxybutyrate enhances RANKL-induced osteoclastogenesis by promoting the expression of key transcription factors like NFATc1 and increasing reactive oxygen species (ROS) production within osteoclast precursors, creating a pro-resorptive environment (23-25). Concurrently, β-hydroxybutyrate may exert inhibitory effects on osteoblast function. Recent studies also suggested that β-hydroxybutyrate can suppress osteoblast proliferation and differentiation markers like Runx2 and Osterix, potentially by altering cellular metabolism and redox state or interfering with Wnt/β-catenin signaling, a paramount anabolic pathway for bone. This ketone-mediated shift towards resorption provides a direct molecular link between the metabolic state induced by SGLT2 inhibitors and accelerated bone loss (23,26).

Dysregulation of osteoblasts on SGLT2i therapy

The Wnt/β-catenin signaling pathway is fundamental for osteoblast differentiation, activity, and bone formation. Its dysregulation under SGLT2 inhibition represents another crucial molecular intersection (27,28). Sclerostin, as a glycoprotein predominantly secreted by osteocytes, is a potent negative regulator of Wnt signaling. It binds to low-density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors, preventing Wnt ligands from forming active receptor complexes, thereby inhibiting β-catenin stabilization and nuclear translocation (29). Elevated sclerostin levels are associated with reduced bone formation and osteoporosis (30). Clinical studies have reported increases in serum sclerostin levels following SGLT2 inhibitor initiation. The mechanisms driving this rise are multifactorial (31). The secondary hyperparathyroidism induced by phosphaturia and hypocalcemia is a key factor; PTH has been shown to stimulate sclerostin expression in osteocytes (32). Furthermore, the reduction in mechanical loading due to weight loss, while beneficial metabolically, reduces the anabolic mechanical signals that normally suppress sclerostin production (33). Adipokines may also play a role; leptin can influence sclerostin expression, and its rapid decline might contribute (34). Elevated sclerostin directly antagonizes Wnt signaling in osteoblasts, dampening their bone-forming capacity. This suppression of formation, coupled with the PTH increases in resorption, creates a powerful double-hit on bone mass: increased removal of old bone without adequate replacement with new bone (35). The net effect is rapid bone loss, particularly trabecular bone, which has a higher surface area and turnover rate (36). The interplay between mineral-regulating hormones, metabolic hormones, and local bone regulators creates a network where perturbation in one node ripples through the entire system (37). Accordingly, insulin and insulin-like growth factor-1 (IGF-1) signaling, crucial for osteoblast function and bone anabolism, are significantly altered by SGLT2 inhibition (38). Though the drugs improve insulin sensitivity peripherally, they induce a state of relative hypoinsulinemia due to reduced glucose-stimulated insulin secretion (39). Insulin receptors are expressed on osteoblasts, and insulin signaling promotes osteoblast proliferation, differentiation, and collagen synthesis. It also enhances the production of osteocalcin, an osteoblast-derived hormone involved in energy metabolism (40). Reduced insulin signaling in bone cells may therefore directly impair bone formation. Meanwhile, IGF-1, is another key anabolic factor for bone; since, its hepatic production is stimulated by growth hormone

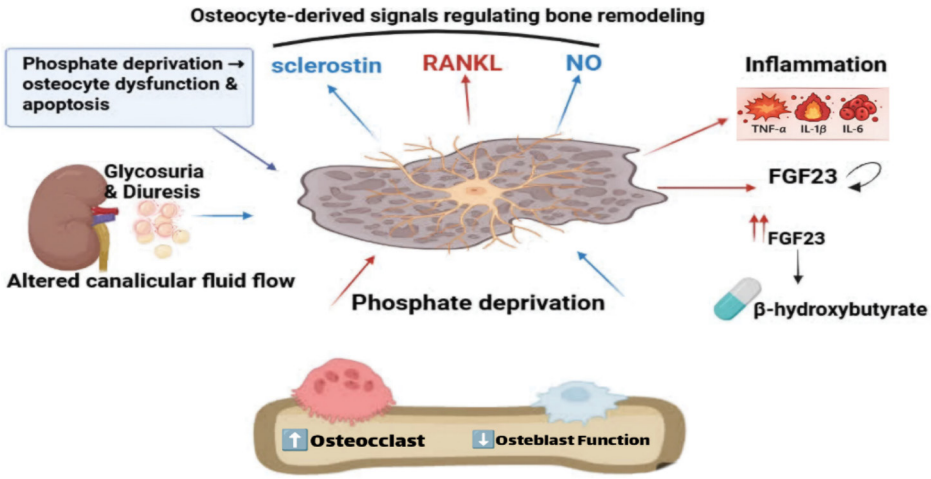

Figure 1. Proposed effects of SGLT2 inhibitors on osteocyte function and bone remodeling.

but modulated by insulin and nutritional status (41). The negative energy balance and potential alterations in growth hormone pulsatility during SGLT2 inhibition might contribute to reduced IGF-1 bioavailability. Lower IGF-1 levels further diminish the pro-formation signals on osteoblasts (3). The reduction in insulin/IGF-1 anabolic tone contrasts sharply with the persistent or enhanced catabolic signals from PTH and ketones, tilting the bone remodeling balance towards net loss (42). The endocrine crosstalk extends to the gut-bone axis (43). Previous investigations detected that, SGLT2 inhibitors induce modest increases in glucagon-like peptide-1 (GLP-1) levels, partly due to slowed gastric emptying and possibly via effects on renal DPP-4 activity (44). Recently, GLP-1 and its analogs have shown bone-protective effects in some studies, stimulating osteoblast proliferation and inhibiting osteoclast formation. However, the magnitude of GLP-1 elevation with SGLT2 inhibitors alone is likely insufficient to counteract the dominant negative pathways described above (45). The potential interaction between SGLT2i and GLP-1 receptor agonists (GLP-1 RAs), often used in combination, on bone health is an area of active investigation, with some preclinical data suggesting GLP-1 RAs might mitigate SGLT2i-induced bone loss, highlighting the complexity of endocrine interactions (46).

Impact of SGLT2 inhibitors on osteocytes

The osteocyte, embedded within the mineralized matrix, acts as the master regulator of bone remodeling, sensing mechanical strain and orchestrating the activity of osteoblasts and osteoclasts via signaling molecules like sclerostin, RANKL, and nitric oxide (47). The metabolic and mineral disturbances induced by SGLT2 inhibitors place significant stress on osteocytes. Hypophosphatemia directly impairs osteocyte function and survival (48). Osteocytes require phosphate for energy metabolism and to maintain their dendritic processes, crucial for communication and mechanosensing. Phosphate deprivation can lead to osteocyte apoptosis, creating micro-damage signals that trigger targeted bone remodeling, often resorptive (49). Meanwhile, the osmotic stress and altered fluid flow within the canalicular network due to glycosuria and diuresis might also perturb osteocyte mechanosensitivity (50,51). Furthermore, elevated FGF23, produced primarily by osteocytes in response to phosphate and vitamin D status, places an additional secretory burden on these cells. Chronic stimulation of FGF23 production may alter osteocyte gene expression profiles and viability (52). Ketone bodies like β-hydroxybutyrate can also affect osteocyte signaling (23). Therefore, the dysregulation of osteocyte function disrupts the finely tuned balance of bone remodeling signals, contributing to the uncoupling where resorption outpaces formation. Inflammation is another layer of crosstalk (53). T2DM is characterized by chronic low-grade inflammation, with elevated levels of cytokines like TNF-α, IL-1β, and IL-6. While SGLT2 inhibitors generally reduce systemic inflammation markers due to weight loss and improved glycemia, the initial phase of therapy or specific contexts might involve transient inflammatory responses (54). Pro-inflammatory cytokines are potent stimulators of osteoclastogenesis, synergizing with RANKL. TNF-α, for instance, can directly enhance RANK signaling and prolong osteoclast survival. Any residual or transient inflammation in diabetic patients on SGLT2i could further amplify bone resorption pathways (Figure 1) (55).

Impact of SGLT2i on oxidative stress pathways

SGLT2 inhibitors may impact inflammatory and oxidative stress pathways, which are critical regulators of bone remodeling. Chronic low-grade inflammation and increased oxidative stress in diabetes contribute to altered bone turnover and fragility (16). SGLT2 inhibitors have shown anti-inflammatory and antioxidative effects in

various tissues through suppressing pro-inflammatory cytokines and reducing reactive oxygen species production (56). These molecular actions may have protective effects on bone cells by mitigating inflammation-induced osteoclastogenesis and apoptotic pathways in osteoblasts and osteocytes (49). Thus, SGLT2 inhibitors' influence on inflammation and oxidative stress adds a layer of metabolic-immune crosstalk shaping bone health (3,16). Bone remodeling is tightly coupled with vascular function and microcirculation, integrating endocrine, paracrine, and metabolic signals (57). Recent studies found that, SGLT2 inhibitors improve endothelial function and microvascular integrity, potentially enhancing bone perfusion and nutrient delivery essential for osteogenesis and matrix mineralization (21). Improved vascular health may positively affect bone remodeling dynamics, although clinical evidence linking these vascular effects directly to skeletal outcomes remains limited (58).

A short look at the insulin signaling pathway

A further aspect of endocrine crosstalk involves the insulin signaling pathway. Type 2 diabetes is characterized by insulin resistance and hyperinsulinemia, conditions that negatively influence bone quality and increase fracture risk (59). Insulin has anabolic effects on bone, promoting osteoblast proliferation and differentiation. By improving glycemic control and insulin sensitivity systemically, SGLT2 inhibitors may indirectly benefit bone metabolism (16). Nevertheless, the potential for glucose-lowering therapies, including SGLT2 inhibitors, to cause weight loss can contribute to a reduction in mechanical loading on the skeleton, which may offset metabolic advantages and lead to decreased bone mass (39). The interplay between glucose and lipid metabolism also modulates bone cell function and energy supply (60). Besides, SGLT2 inhibitors induce shifts in substrate utilization favoring lipolysis and ketone body production, altering systemic energy balance (61). Ketone bodies may serve as alternative fuel for osteoblasts, potentially promoting anabolic bone activity under certain metabolic states (62). This metabolic adaptation implicates nutrient sensing pathways such as mammalian target of rapamycin complex 1 (mTORC1) signaling, which integrates energy, nutrient, and growth factor cues to regulate bone cell growth and matrix synthesis (62, 63). Previous authors showed that, SGLT2 inhibitors' capacity to suppress aberrant mTORC1 activation in diabetic kidneys suggests a parallel mechanism may exist in bone tissue, limiting pathological remodeling and supporting skeletal integrity (3).

Conclusion

In summary, SGLT2 inhibitors affect bone function through multiple molecular pathways interconnected by metabolic and endocrine crosstalk. Their influence on renal phosphate transport triggers endocrine responses involving FGF23, PTH, and vitamin D that modulate bone remodeling. Concurrently, alterations in energy metabolic signaling by AMPK and mTORC1, antioxidant and anti-inflammatory effects, improved endothelial function, and systemic metabolic shifts contribute to the regulation of bone cell activity and skeletal homeostasis. While clinical data reflect some concerns regarding bone health, particularly fracture risk, the net effects of SGLT2 inhibitors on bone depend on a balance of these opposing molecular mechanisms within the framework of the individual's metabolic context.

Authors' contribution

Conceptualization: Parzhin Khazdoozi and Asaad Abass Fadhel Khalif.
Data curation: Hanie Fooladi, Abnoos Mokhtariardekani and Asaad Abass Fadhel Khalif.
Investigation: Parzhin Khazdoozi and Mansooreh Kashefi
Supervision: All authors.
Validation: Abnoos Mokhtariardekani and Hojjat Eghbali Jelodar
Visualization: Hojjat Eghbali Jelodar and Somayeh Ghamkhari
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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