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Review

Cross-talk of bone remodeling and cardiac dysfunction; reimagining the bone-heart axis in atherosclerosis pathogenesis

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Abstract

Recent findings detected a dynamic, reciprocal relationship between bone remodeling and cardiac dysfunction, significantly influencing atherosclerosis pathogenesis. The bone-heart axis consists of bidirectional signaling of bone-derived factors and dysregulated mineral metabolism, which directly affect vascular calcification, endothelial function, and myocardial stress. Conversely, cardiac hormones and systemic inflammation modulate osteoclast/osteoblast activity. Critically, shared molecular pathways, like RANKL/RANK/OPG modulate both skeletal turnover and vascular inflammation/calcification. Pathological bone resorption releases calcium and matrix vesicles that nucleate vascular calcification, accelerating atherosclerotic plaque instability. Reimagining this axis emphasizes on osteo-immunological mechanisms with central role in cardiovascular disease progression, suggesting integrated therapeutic targets for atherosclerosis beyond traditional lipid-centric approaches.

Keywords: Bone remodeling, Osteoblasts, Osteoclasts, Cardiac dysfunction, Atherosclerosis, Vascular calcification, Endothelial dysfunction, Oxidative stress

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Introduction

Bone remodeling and cardiac dysfunction are deeply interconnected through a series of complex molecular, cellular, and systemic pathways by a concept increasingly recognized as the bone-heart axis (1). This axis plays a significant role in the pathogenesis of atherosclerosis by linking skeletal homeostasis, immune signaling, neurohormonal activity, and metabolic function to cardiovascular outcomes (2). Bone is not simply a structural tissue, but a dynamic endocrine organ that communicates with the cardiovascular system. The process of bone remodeling is controlled by balanced activities of osteoblasts and osteoclasts and is influenced by local as well as systemic signals, including inflammatory cytokines, neurohormonal mediators, and hormones like estrogen (3). Dysregulation in any of these features can elicit profound effects on cardiac structure and function, particularly when subjected to the chronic stresses underlying atherosclerosis and heart failure syndromes (4). One of the fundamental mediators in bone-cardiac cross-talk is the cytokine interleukin-10 (IL-10), which modulates inter-organ communication among the gut, bone, and cardiovascular system (5). Studies in IL-10 knockout mice show enhanced bone loss and cardiac dysfunction, highlighting how a proinflammatory environment can simultaneously impair bone mineralization and promote increased production of fibroblast growth factor 23 (FGF23) (5). Elevated FGF23 not only disrupts calcium and phosphate homeostasis but has also been directly implicated in myocardial fibrosis and dysfunction (6). Furthermore, estrogen deficiency, which commonly follows menopause exacerbates this axis by diminishing both bone density and cardiac protective mechanisms, partially through the modulation of FGF23 expression and fibrotic signaling in the heart (7). After acute insults like myocardial infarction or bone fracture, the sympathetic response extends beyond the immediately affected tissue (8). In fact, myocardial infarction

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Implication for health policy/practice/research/medical education

The cross-talk between bone remodeling and cardiac dysfunction, mediated through the dynamic bone-heart axis, is a cornerstone of atherosclerosis pathogenesis. It is not a passive association but an active, bidirectional dialogue rooted in shared molecular pathways like RANKL/RANK/OPG, Wnt/β-catenin, osteocalcin signaling, and fueled by chronic inflammation and mineral dysregulation. In fact, pathological vascular calcification, a hallmark of advanced atherosclerosis, is an active osteogenic process within the artery wall, driven by signals originating from dysregulated bone turnover and systemic factors. This calcification directly impairs cardiac function through arterial stiffening, increased afterload, reduced coronary perfusion, plaque destabilization, and procedural complications.

can stimulate systemic osteoclast activity and bone resorption, while a bone fracture can exacerbate cardiac tissue damage and inflammation, thereby accelerating atherosclerosis (8). Both conditions activate pathways that amplify inflammation, endothelial dysfunction, and immune cell recruitment in both bone and myocardium, establishing a vicious cycle in which disease in one organ system accelerates pathology in the other (8). It seems that, reimagining the bone-heart axis in atherosclerosis pathogenesis demands a fundamental shift from viewing vascular calcification as a localized vascular disease or bone loss as an isolated skeletal disorder (1). Instead, we must conceptualize atherosclerosis as a systemic disorder of mineral and matrix homeostasis, where dysregulation of bone remodeling actively seeds and fuels vascular pathology through endocrine, paracrine, and inflammatory signals (9). The osteocyte, the master regulator embedded within the bone matrix, emerges as a key endocrine cell, sensing mechanical and biochemical cues and releasing sclerostin, FGF23, and other factors that reverberate through the cardiovascular system (10). The vascular smooth muscle cell (VSMC), far from being a passive structural cell, is revealed as a highly plastic cell capable of adopting skeletal fates under pathological duress, driven by signals like receptor activator of nuclear factor kappa-B Ligand (RANKL), bone morphogenetic proteins (BMPs), and phosphate that originate from or are amplified by bone turnover (11). Inflammation is not merely a bystander but the essential catalyst and perpetuator, creating a feed-forward loop where bone resorption releases inflammatory mediators and matrix components that activate vascular cells, whose dysfunction further exacerbates skeletal loss. This integrated view explains the epidemiological links, the paradoxical biomarker associations like high osteoprotegerin (OPG), and the unexpected cardiovascular effects of bone-targeted drugs. It positions atherosclerosis as a disease where the skeleton actively participates in its own demise, contributing to the stiffening arteries that strain the heart and the unstable plaques that trigger catastrophic events (12). In this review, we therefore sought to assess the cross-talk of bone remodeling and cardiac dysfunction; reimagining the bone-heart axis in atherosclerosis pathogenesis.

Search strategy

For this narrative review, we conducted a comprehensive literature search across multiple electronic databases, including Google Scholar, Directory of Open Access Journals (DOAJ), PubMed, Web of Science, EBSCO, Scopus, and Embase. The search was performed using a combination of controlled vocabulary (MeSH terms) and free-text keywords to maximize sensitivity and coverage. Key search terms included: bone remodeling, osteoblasts, osteoclasts, cardiac dysfunction, atherosclerosis, vascular calcification, endothelial dysfunction, and oxidative stress. Boolean operators (AND, OR) were applied to link concepts, and truncation was used where appropriate to capture variations of terms. No restrictions were placed on publication date, but only articles published in English were considered. Reference lists of relevant articles were also screened to identify additional studies. The final selection was based on relevance to the bone–heart axis and its role in the pathogenesis of atherosclerosis.

Molecular pathways of bone-heart axis

At the core of this axis lies the RANK/RANKL/OPG signaling triad, a master regulator of osteoclastogenesis and bone resorption (13). RANKL, expressed by osteoblasts and other cells, binds to its receptor RANK on osteoclast precursors, triggering their differentiation and activation, leading to bone breakdown (14). OPG, a soluble decoy receptor produced by osteoblasts and vascular cells, acts as the natural brake on this system by binding RANKL and preventing RANK activation. This elegant balance is crucial for skeletal health. However, its significance extends far beyond bone (15). RANKL is expressed by activated T-cells and endothelial cells within atherosclerotic plaques. Its binding to RANK on VSMCs and macrophages promotes a pro-inflammatory, pro-osteogenic phenotype (16). RANKL signaling in VSMCs stimulates the expression of BMPs and other osteogenic transcription factors like Runx2, driving their transformation into osteoblast-like cells that deposit hydroxyapatite crystals within the vessel wall as a process central to vascular calcification (17). Furthermore, RANKL enhances endothelial cell activation, increasing adhesion molecule expression like VCAM-1 and ICAM-1 and also promoting monocyte recruitment into the intima, causing plaque inflammation (18,19). Accordingly, macrophages exposed to RANKL exhibit increased cytokine production such as TNF-α, IL-6 and IL-1β, across with reduced efferocytosis, contributing to necrotic core expansion and plaque instability (20). Osteoprotegerin, conversely, was initially thought to be purely protective. While it inhibits RANKL-induced bone resorption and vascular calcification in-vitro, human studies present a paradox:

elevated circulating OPG levels are strongly associated with the presence and severity of atherosclerosis, coronary artery disease, and adverse cardiovascular events. This counterintuitive finding suggests OPG elevation is likely a compensatory response to excessive RANKL activity and vascular damage rather than a direct causative agent (16). The system is overwhelmed; high OPG reflects a struggle to contain rampant RANKL signaling and ongoing vascular pathology. This intricate dance between RANKL and OPG exemplifies how a skeletal regulatory pathway, when dysregulated systemically or locally within the vessel wall, becomes a potent driver of vascular inflammation, calcification, and ultimately, cardiac dysfunction stemming from impaired coronary perfusion or arrhythmogenic substrates created by stiff, calcified vessels (16, 21). Complementing the RANKL pathway, the Wnt/β-catenin signaling cascade, fundamental for osteoblast differentiation and bone formation, exerts profound influence on vascular biology (22). In healthy bone, canonical Wnt signaling stabilizes β-catenin, allowing its translocation to the nucleus to activate genes for osteoblastogenesis. This pathway is tightly regulated by inhibitors, notably sclerostin (primarily secreted by osteocytes) and Dickkopf-1 (DKK1). Sclerostin binds to LRP5/6 co-receptors, blocking Wnt signaling and thus acting as a physiological brake on bone formation (22). Intriguingly, sclerostin is not confined to bone; it circulates and is detectable in vascular tissues (23). Within atherosclerotic lesions, VSMCs exposed to pro-inflammatory cytokines and uremic toxins in chronic kidney disease (CKD), upregulate sclerostin expression. High sclerostin levels inhibit Wnt signaling in VSMCs. While this might seem anti-calcific (as Wnt promotes osteogenesis), the reality is complex (24). More significantly, sclerostin directly promotes endothelial dysfunction (25, 26). Then endothelial dysfunction reduces nitric oxide bioavailability and activity (27-29). Impaired NO signaling leads to vasoconstriction, increased leukocyte adhesion, platelet activation, and enhanced vascular permeability – all critical early steps in atherogenesis (30). Elevated circulating sclerostin levels correlate with coronary artery calcification severity, endothelial dysfunction measured by flow-mediated dilation, and future cardiovascular events. This positions sclerostin, an osteocyte-derived hormone, as a direct molecular messenger from bone to vasculature, linking impaired bone formation (high sclerostin) to accelerated vascular disease (31). The therapeutic implications are stark: monoclonal antibodies against sclerostin (romosozumab) dramatically increase bone density but carry a warning for potential increased cardiovascular risk, highlighting the delicate, often opposing, effects of modulating this pathway on bone versus heart. This clinical paradox underscores the systemic nature of the bone-heart axis and the necessity for careful cardiovascular monitoring when targeting skeletal pathways (32).

Impact of osteocalcin on cardiovascular regulation

Osteocalcin, the most abundant non-collagenous protein in bone, synthesized by osteoblasts and incorporated into the bone matrix, undergoes carboxylation dependent on vitamin K. A small fraction of undercarboxylated osteocalcin (ucOC) is released into circulation during bone resorption (33). Initially studied for its role in energy metabolism (enhancing insulin sensitivity and secretion), ucOC has emerged as a significant player in cardiovascular regulation (34). Animal studies demonstrate that ucOC can improve endothelial function by stimulating NO production in endothelial cells, potentially via GPRC6A receptors. It may also exert direct protective effects on cardiomyocytes, reducing apoptosis under stress (35). However, the human data presents a more nuanced, sometimes contradictory, picture. While some studies associate higher ucOC levels with better endothelial function and reduced arterial stiffness, others link elevated total or ucOC to increased coronary calcification and cardiovascular mortality, particularly in populations with CKD or diabetes. This discrepancy likely reflects the complex interplay between bone turnover state, vitamin K status, renal function, and the specific forms of osteocalcin measured (36). High bone turnover states (e.g., postmenopausal osteoporosis, CKD) release more osteocalcin fragments, but the functional activity of these fragments may be altered (37). Vitamin K deficiency, common in vascular disease, impairs osteocalcin carboxylation, potentially increasing ucOC but also crippling its bone-mineral binding function and possibly altering its vascular effects. Furthermore, osteocalcin fragments generated during resorption might have different bioactivities than the intact hormone (33). The relationship appears non-linear and context-dependent. In early atherosclerosis, ucOC might exert beneficial metabolic and vasoprotective effects. However, in advanced disease with high turnover and vascular damage, the sheer quantity of released fragments, potentially coupled with impaired clearance or altered receptor sensitivity, might contribute to pathology (38). Osteocalcin exemplifies how a bone-derived factor can have pleiotropic effects, acting as a double-edged sword depending on the physiological or pathological milieu, further complicating the bone-heart dialogue (2).

Association of vascular calcification with skeletal bone formation

Vascular calcification, particularly medial calcification (Mönckeberg's sclerosis) and intimal calcification within atherosclerotic plaques, is not a passive degenerative process but an active, cell-mediated phenomenon sharing striking similarities with skeletal bone formation. This pathological ossification is a key mechanism linking bone remodeling dysregulation to cardiac dysfunction in atherosclerosis (39). Previous studies found that, VSMCs, under the influence of chronic inflammation,

hyperphosphatemia (common in CKD and aging), oxidative stress, and uremic toxins, undergo a phenotypic switch. They down-regulate contractile markers (e.g., SM22α, calponin) and upregulate osteogenic transcription factors like Runx2 and Msx2. This transformation is driven by signals originating both locally within the plaque and systemically from dysregulated bone turnover (40). Elevated phosphate levels, sensed by the sodium-dependent phosphate cotransporter Pit-1 on VSMCs, directly induce osteogenic differentiation and apoptosis (41). Apoptotic VSMCs release matrix vesicles rich in calcium and phosphate, acting as nucleation sites for hydroxyapatite crystal formation. Inflammatory cytokines (TNF-α, IL-1β, IL-6) within the plaque further amplify this process by stimulating RANKL expression, enhancing BMP signaling, and suppressing natural calcification inhibitors like matrix Gla protein (MGP) and fetuin-A (42). Crucially, MGP requires vitamin K-dependent carboxylation for full activity; vitamin K deficiency or antagonism (e.g., warfarin therapy) severely impairs its ability to inhibit calcification, creating a permissive environment (43). The source of osteogenic precursors is debated; while VSMC trans-differentiation is predominant, circulating mesenchymal stem cells or even osteoclast-like cells derived from monocytes might contribute under specific conditions. The consequence of vascular calcification for cardiac function is profound (44,45). Medial calcification causes arterial stiffening, increasing systolic blood pressure, pulse pressure, and left ventricular afterload. This condition leads to left ventricular hypertrophy, impaired diastolic filling, and reduced coronary perfusion pressure during diastole, and heart failure with preserved ejection fraction (46). Intimal calcification within coronary atherosclerotic plaques has dual effects. Spotty, micro-calcifications within the fibrous cap are associated with high plaque stress and vulnerability to rupture the event triggering most acute coronary syndromes (47). Conversely, large, sheet-like calcifications might stabilize plaques mechanically but significantly narrow the lumen, causing chronic ischemia. Furthermore, heavy calcification complicates percutaneous coronary interventions, increasing procedural failure and complication rates (48). Thus, the pathological bone-forming activity within arteries, fueled by dysregulated skeletal signaling and systemic mineral imbalances, directly translates into myocardial strain, ischemic injury, arrhythmias, and heart failure – the hallmarks of cardiac dysfunction in atherosclerosis (45).

Impact of vascular-cardiac axis on bone homeostasis

The vascular-cardiac axis, particularly in the context of long-term stress such as hypertension and chronic volume overload, also interacts with bone homeostasis. Vascular calcification, a hallmark of advanced atherosclerosis, shares key molecular drivers with bone mineralization (49). Vascular smooth muscle cells can undergo osteogenic trans-differentiation under the influence of inflammatory cytokines, high phosphate levels, and derangements in calcium metabolism, leading not only to arterial stiffness but also to altered cardiac loading conditions and increased risk of heart failure (44). The secreted factors and paracrine signals involved in this process overlap substantially with those governing osteoblast and osteoclast function, further solidifying the concept of a functional bone-heart axis (2).

Impact of neurohormonal mediators

Neurohormonal mediators, especially those involved in the stress response such as cortisol, catecholamines, and the renin-angiotensin-aldosterone system (RAAS), exert parallel deleterious effects on both bone and the cardiovascular system (50,51). Chronic RAAS activation enhances cardiac fibrosis, promotes hypertension, and increases sodium retention as the factors that aggravate atherosclerosis and heart failure (52). In the meantime, aldosterone excess and heightened sympathetic tone drive bone resorption, decrease bone mineral density, and potentiate osteoporosis, linking neurohormonal dysregulation to both organ systems (53, 54). Pharmacologic interruption of these pathways has been associated with improved outcomes in both cardiovascular and bone health (55).

A short look at the inflammaging

The inflammatory milieu is the fertile ground where bone and vascular pathologies converge and amplify each other. Chronic low-grade inflammation is a hallmark of both aging (inflammaging), atherosclerosis, and osteoporosis (56). Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are elevated in these conditions and act as potent disruptors of the bone-heart axis. TNF-α and IL-1β directly stimulate osteoclast formation and activity by RANKL-independent pathways, accelerating bone resorption (57). Simultaneously, they promote endothelial activation, monocyte recruitment, foam cell formation, and VSMC osteogenic differentiation within the vasculature (58). Then, IL-6 signaling through its soluble receptor (trans-signaling) drives hepatic production of C-reactive protein and other acute-phase reactants, further amplifying systemic inflammation (59). It also directly stimulates osteoclastogenesis and inhibits osteoblast function (60). This creates a vicious cycle: inflammation-driven bone loss releases bone-derived factors (like RANKL, sclerostin fragments, osteocalcin) and bone matrix components (like calcium, phosphate, collagen fragments) into circulation, which can further activate immune cells and vascular cells, perpetuating inflammation and vascular damage (61). Conversely, vascular inflammation and endothelial dysfunction impair blood flow to bone, potentially contributing to bone loss by reducing nutrient and oxygen delivery and altering the bone microenvironment (62). Macrophages are pivotal cellular integrators. In bone,

they can differentiate into osteoclasts under RANKL stimulation. Within atherosclerotic plaques, macrophage subsets exhibit remarkable plasticity. M1 macrophages drive inflammation and tissue destruction, while M2 macrophages promote resolution and repair (63). However, in the calcifying plaque, macrophages can also adopt osteoclast-like characteristics, attempting to resorb calcified matrix but often failing, instead contributing to a pro-calcific environment through cytokine release and defective efferocytosis (64). The failure to clear apoptotic cells (efferocytosis) is a critical link; apoptotic bodies from dead VSMCs and macrophages within plaques release pro-calcific vesicles and DAMPs (damage-associated molecular patterns), fueling further inflammation and calcification. This defective clearance is also observed in bone during high turnover states (65). Thus, shared inflammatory pathways and dysfunctional phagocytic clearance mechanisms create a self-sustaining loop connecting skeletal fragility and vascular calcification (66).

Clinical manifestations of bone-heart axis

The clinical manifestations of this axis are increasingly recognized. Patients with severe osteoporosis, particularly postmenopausal women, exhibit higher rates of coronary artery calcification and cardiovascular mortality (67). Conversely, individuals with established atherosclerotic cardiovascular disease often have lower bone mineral density. This association is especially pronounced in specific populations; those with type 2 diabetes (where advanced glycation end products impair both bone quality and vascular function), CKD (the epicenter of mineral and bone disorder driving vascular calcification), and rheumatoid arthritis (characterized by systemic inflammation affecting both joints/bone and vasculature) (68). Therapeutic interventions targeting bone have revealed unexpected cardiovascular effects, providing causal insights. Bisphosphonates, potent anti-resorptives that inhibit osteoclasts, reduce fracture risk (55). Some studies, particularly with nitrogen-containing bisphosphonates like zoledronic acid, suggest potential cardiovascular benefits, including reduced aortic calcification progression and lower myocardial infarction risk in osteoporosis patients, possibly by reducing bone resorption and systemic inflammation (69). However, the evidence is mixed, and concerns about atrial fibrillation risk with high-dose IV zoledronic acid persist (70). Denosumab, a monoclonal antibody against RANKL, profoundly inhibits bone resorption and reduces fractures. Its impact on vascular calcification is complex: animal studies show inhibition, but human data is less clear (71). Crucially, denosumab significantly lowers serum OPG levels. Given the paradoxical association of high OPG with CVD, this reduction might be beneficial, but long-term cardiovascular outcome data is still maturing (72). The most dramatic illustration of the axis's therapeutic complexity is romosozumab, the anti-sclerostin antibody. While it powerfully builds bone by unleashing Wnt signaling, a signal imbalance emerged in clinical trials: a higher rate of major adverse cardiovascular events (MACE) was observed compared to alendronate in the ARCH trial, leading to a black box warning (73). This suggests that blocking sclerostin's inhibitory effect on Wnt signaling, while beneficial for bone, might have detrimental vascular consequences potentially by enhancing vascular Wnt signaling and promoting calcification or by other off-target effects. This condition demonstratres the peril of targeting shared pathways without fully understanding their systemic pleiotropy (73,74). Conversely, drugs developed for cardiovascular disease impact bone. Warfarin, a vitamin K antagonist, inhibits the carboxylation of osteocalcin and MGP. While effective for anticoagulation, it accelerates bone loss and promotes vascular calcification by crippling these vitamin K-dependent proteins (75). Besides, statins as the HMG-CoA reductase inhibitors used for lipid-lowering, have shown modest bone-protective effects in some studies, possibly by BMP-2 up-regulation, though clinical significance remains debated. These therapeutic observations highlight the inseparability of bone and vascular health and the critical need for integrated patient management (76).

Conclusion

In this review study, we found bone-heart axis is a dynamic process, where dysregulated bone remodeling actively fuels cardiac dysfunction and atherosclerosis. Osteoclast/osteoblast imbalances release mediators (RANKL, OPG, sclerostin and osteocalcin) that promote vascular inflammation, endothelial damage, and calcification. Conversely, cardiac stress hormones and inflammatory cytokines disrupt skeletal homeostasis. This bidirectional cross-talk explains the clinical link between osteoporosis and cardiovascular disease. Recognizing bone not merely as structural support but as an endocrine organ influencing vascular pathology redefines atherosclerosis pathogenesis. Targeting this axis through bone-modifying drugs or novel mediators offers promising therapeutic avenues to concurrently mitigate skeletal fragility and halt atherosclerotic progression, demanding integrated clinical management strategies for high-risk patients.

Authors' contribution

Conceptualization: Kianoush Saberi and Amir Heidari.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

The authors have completely observed ethical issues (including plagiarism, data fabrication, double publication).

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 accuracy and content of the publication.

Conflicts of interest

The authors declare that they have no competing interests.

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