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Review

Brain-gut-bone axis; a review of the association between gut microbiota and osteoporosis

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Abstract

The brain-gut-bone axis plays a crucial and complex role in regulating bone metabolism, particularly in the context of osteoporosis. This multidirectional communication network integrates signals from several physiological systems, including the gut microbiota, immune system, nervous system, and hormonal environment, all of which collectively influence the balance between bone formation by osteoblasts and bone resorption by osteoclasts. The gut microbiota contributes to this axis by producing metabolites such as short-chain fatty acids (SCFAs) and modulating systemic inflammation, which in turn can affect bone cell activity and mineralization processes. The immune system participates through cytokine signaling that either promotes or inhibits bone resorption and formation, linking inflammation to bone health. Meanwhile, the nervous system, via autonomic and sensory pathways, regulates nutrient absorption, bone blood flow, and directly modulates bone cell function through neuropeptides and neurotransmitters. Hormonal factors, including parathyroid hormone, sex steroids, and gut-derived hormones like serotonin, further modulate bone turnover by fine-tuning osteoblast and osteoclast activity. Disruptions in any component of this axis, such as dysbiosis of the gut microbiota, chronic inflammation, neurotransmitter imbalance, or hormonal deficiencies can lead to dysregulated bone remodeling, favoring increased bone resorption, decreased bone formation, and eventually decreased bone density. This manifests clinically as osteoporosis, characterized by fragile bones and elevated fracture risk. Therefore, understanding and targeting the brain-gut-bone axis presents promising therapeutic opportunities. Interventions such as probiotics, anti-inflammatory therapies, neuromodulation, and hormone replacement can potentially restore the balance in this axis, improving bone health and reducing osteoporosis progression. This integrative approach highlights the importance of systemic interactions and opens new avenues for precision medicine in bone metabolic disorders.

Keywords: Brain–gut–bone axis, Gut microbiota, Osteoporosis, Bone metabolism, Neuro-immune regulation, Bone mineral density

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Introduction

Osteoporosis is a systemic metabolic disorder marked by decreased bone mass and destruction of bone microstructure (1). The brain-gut-bone axis concept reveals that the brain and gut microbiota influence bone health and the progression of osteoporosis (2). The gut microbiota plays a critical role in bone metabolism by modulating nutrient absorption, immune regulation, and hormonal signals that affect bone remodeling (3). Dysbiosis in gut microbiota can lead to deterioration in bone density and increase fracture risk (4). Prior studies found that, gut bacteria produce metabolites such as short-chain fatty acids (SCFAs) that promote bone formation and inhibit bone resorption (5); while, healthy gut microbiota maintain intestinal barrier integrity, reducing systemic inflammation which leads to healthy bones (6). In this regard, the brain-gut axis contains neurotransmitters like serotonin influencing bone cell activity (7). Therefore, gut microbiota influence the balance of immune cells like Th-17 and T-reg cells, which are known to impact bone remodeling (3). In fact, hormones modulated by brain and gut signals, including those related to stress and metabolism, affect bone turnover too (8). Brain structure itself has been shown to causally influence bone mineral

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Implication for health policy/practice/research/medical education

The brain-gut-bone axis plays a crucial role in the development of osteoporosis by integrating complex interactions among neural, microbial, immune, and hormonal factors that collectively regulate bone metabolism. This axis establishes communication pathways between the brain, the gut microbiota, and the skeletal system, thereby influencing bone remodeling processes such as formation and resorption. Disruptions within any component of this axis, including gut microbiota dysbiosis or alterations in brain structure and function, can negatively impact bone health by promoting inflammatory responses, hormonal imbalances, and impaired nutrient absorption, all of which contribute to bone loss and increased risk of osteoporosis. Recent research highlights how neuroendocrine signaling and gut-derived metabolites modulate immune cell activity and bone cell function, emphasizing the integrative nature of this axis. Understanding the brain-gut-bone axis opens promising new avenues for developing targeted interventions and therapeutic strategies that address osteoporosis through modulation of gut microbiota, neural pathways, and immune mechanisms, ultimately improving bone health and reducing fracture risk.

density (BMD), emphasizing the direct link between brain and bone health in osteoporosis risk (9). It seems that, the brain-gut-bone axis contributes significantly to the development of osteoporosis through a complex network of interactions involving the nervous, immune, endocrine, and metabolic systems (7).

Search strategy

For this narrative review, we conducted a comprehensive literature search across multiple databases, comprising PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords like; brain–gut–bone axis, gut microbiota, osteoporosis, bone metabolism, neuro-immune regulation and bone mineral density.

A short look at brain-gut-bone axis

The gut microbiota modulates bone metabolism by affecting the immune system and inflammatory responses (3). It regulates the trafficking of inflammatory cells such as tumor necrosis factor (TNF) + T cells and Th17 cells to the bone marrow, which influences bone remodeling and inflammatory states associated with osteoporosis (10). Gut microbiota dysbiosis is linked to decreased BMD and osteoporosis (11). This dysbiosis affects osteoclastogenesis and osteoblast function through molecular mediators like microRNAs and insulin-like growth factor 1 (IGF-1), impacting bone regeneration (12). Similarly, the brain and gut communicate bidirectionally by neural, hormonal, and immune pathways (13). Neurotransmitters and gut hormones released in response to food intake influence bone remodeling processes, including bone resorption and formation (7). Meanwhile, extracellular vesicles derived from gut bacteria act as mediators in the gut-bone axis, facilitating molecular communication that influences skeletal health and osteoporosis development (14). In parallel, gut hormones such as glucagon-like peptide 2 and peptide YY play roles in bone metabolism by regulating bone resorption and turnover, contributing to bone homeostasis (15). Meanwhile, the central nervous system directly influences skeletal metabolism by modulating neurotransmitters that affect bone cells, showing a tight integration between brain function and bone health (16).

Impact of gut microbiota on osteoclast activity

Gut microbiota influences osteoclast activity in bone remodeling through modulation of OPG/RANKL pathway, which is critical for osteoclast differentiation and activation (3). An imbalance in microbiota can disrupt this pathway, leading to increased osteoclast activity and excessive bone resorption (17). Microbial regulation of serum insulin-like IGF-1 levels affects osteoclast function, as IGF-1 plays a role in bone remodeling (18). As mentioned, gut microbes produce metabolites such as SCFAs that can inhibit osteoclast proliferation and differentiation, reduce bone resorption, and promote osteoblast activity, thereby balancing bone remodeling (19). Through immunomodulation, the gut microbiota influences the balance between pro-inflammatory and anti-inflammatory T cells (e.g., Th-17 and T-reg cells), which regulate osteoclastogenesis and bone resorption (20). Gut microbiota also supports calcium absorption in the intestines, indirectly influencing bone mineralization processes that counteract osteoclast-mediated bone degradation (21). It is possible that, gut microbiota impacts serotonin levels, which are involved in the regulation of osteoclast and osteoblast activity (22).

Focus on microbiota-derived cytokines

Microbiota-derived cytokines profoundly impact osteoclast differentiation and activity by modulating both the immune system and the bone microenvironment through multiple interconnected mechanisms (6). These mechanisms shape the balance between bone formation and resorption, critical for maintaining bone health and preventing pathological conditions such as osteoporosis (23). In fact, cytokines such as TNF, various interleukins (ILs), and interferons, whose levels and activity can be influenced by the gut microbiota, play central roles in osteoclastogenesis (24). These cytokines serve as key signaling molecules that either promote or inhibit osteoclast development and functional activity (25). By regulating the microenvironment in which osteoclast precursors reside, microbiota-induced cytokines can exert a powerful influence on bone remodeling dynamics (26, 27). A pivotal group of cytokines involved in promoting osteoclastogenesis are the pro-inflammatory mediators, including TNF-α and IL-1β (25). These cytokines enhance osteoclast differentiation and stimulate bone resorption, which can accelerate bone loss, a hallmark

of diseases such as osteoporosis (28). They achieve these effects primarily by increasing the expression of receptor activator of nuclear factor-κB ligand (RANKL), a critical osteoclastogenic signaling molecule produced by osteoblasts, stromal cells, and immune cells (29). Elevated RANKL expression acts as a key driver for the recruitment and maturation of osteoclast precursors, facilitating increased bone degradation (30). Conversely, anti-inflammatory cytokines like IL-10 and TGF-β (transforming growth factor-beta) play protective roles by inhibiting both osteoclast formation and activity (28). IL-10 functions by suppressing pro-inflammatory cytokine production and directly impeding osteoclast precursor differentiation, thereby curbing excessive bone resorption (31). Similarly, TGF-β contributes to maintaining bone homeostasis by modulating immune responses and promoting the survival of osteoblast lineage cells (32). Together, these anti-inflammatory cytokines help preserve bone integrity by counterbalancing the effects of osteoclastogenic stimuli (31). Another critical mechanism by which gut microbiota influences osteoclast dynamics is through the creation of SCFAs, including butyrate, propionate, and acetate (19). These microbial metabolites promote the generation and activity of regulatory T cells (Tregs), a subset of immune cells that suppress inflammatory responses (33). Tregs inhibit the production of inflammatory cytokines, thereby reducing RANKL-mediated osteoclastogenesis (28). This SCFAs-driven promotion of Tregs reduces inflammation-associated bone loss, illustrating how microbial metabolism can indirectly protect bone tissue (19). Microbial-associated molecular patterns (MAMPs), like lipopolysaccharides from bacterial cell walls, and other bacterial metabolites also influence cytokine production by cells of the innate immune system, like macrophages and dendritic cells (34, 35). These interactions shape the balance between osteoclast-promoting and osteoclast-inhibiting signals by modulating local immune responses (36). For example, certain MAMPs can trigger pro-inflammatory cytokine release, which in turn drives osteoclastogenesis, while others may promote anti-inflammatory pathways that inhibit bone resorption (36). In addition, macrophage colony-stimulating factor, an essential growth factor for osteoclast precursor survival and proliferation, is regulated by microbiota-influenced immune activity (37). Macrophage colony-stimulating factor not only supports the maintenance of the osteoclast precursor pool but also synergizes with RANKL to promote their differentiation into mature osteoclasts, further highlighting the interplay of microbiota-driven factors in bone remodeling (38, 39).

Introducing osteomicrobiology

Microbial metabolites, primarily SCFAs produced from the fermentation of dietary fibers, are key regulators of bone metabolism (40). Similarly, SCFAs like butyrate and propionate can influence bone homeostasis by acting directly on bone cells or indirectly by shaping immune responses. In addition, SCFAs can inhibit osteoclast differentiation and bone resorption, and stimulate osteoblast activity (40). Butyrate stimulates osteoblast differentiation by inhibiting histone deacetylases and stimulating mineralized nodule formation and osteoprotegerin presentation (41). Other SCFAs can directly induce metabolic reprogramming of osteoclast precursors, leading to strengthened glycolysis and downregulation of essential osteoclast genes (42). Moreover, SCFAs can induce Treg cells, which suppress osteoclast differentiation (42). SCFAs also positively promote the production of serum IGF-1, an important hormone that modulates skeletal development and postnatal growth (43). The gut microbiota also influence bone health by mediating the levels of various hormones and neurotransmitters (44). Serotonin is a widely studied neurotransmitter that regulates bone metabolism (16). Gut-derived serotonin (GDS) has a negative impact on bone creation, while brain-derived serotonin has the opposite effect (45). Enterochromaffin cells in the duodenum are responsible for GDS synthesis, that is partially regulated by gut microbiota (6). The intestinal microbiome may regulate bone mass by serotonin in the gut-brain axis (6). Further, IGF-1, predominantly generated in the liver, is regulated by microbes and microbial products and plays a critical role in skeletal development and growth (46). In fact, colonization of germ-free mice with conventional microbiota augmented bone formation and resorption, as well as circulating IGF-1 (46). Besides, SCFA supplementation in antibiotic-treated mice has been shown to restore serum IGF-1 and bone mass (46). Furthermore, gut microbiota dysbiosis, such as lower diversity, may result in reduced circulating estrogens because the gut microbiota regulates estrogens through the secretion of β-glucuronidase, an enzyme that deconjugates estrogens into their active forms (47). Estrogen deficiency, which is common in postmenopausal women, stimulates osteoclast creation and bone resorption, contributing to rapid bone loss (48). Besides, the gut microbiota and its metabolites can regulate bone mass through interactions with parathyroid hormone (49). The actions of parathyroid hormone on bone require microbial metabolite activation of immune cells (49).

Focus on calcium absorption

The gut microbiota plays a crucial role in enhancing calcium absorption, which is vital for maintaining bone health and various physiological processes (50). One of the key mechanisms by which gut microbiota increase calcium absorption is through the production of SCFAs (50). These SCFAs, primarily acetate, propionate, and butyrate, are generated by bacterial fermentation of dietary fibers in the lower intestine (51). Their presence lowers the pH of the gut environment, particularly in the colon, creating an acidic milieu that increases the solubility of calcium

salts (52). This acidification facilitates the release of free calcium ions, making them more readily absorbable by the intestinal epithelium (53). Preliminary studies have shown that certain prebiotic fibers, such as fructooligosaccharides (FOS) and glucomannan can beneficially modify the gut microbiota to enhance calcium bioavailability (54). These prebiotics promote the growth of beneficial bacterial species that produce SCFAs and improve calcium solubility (55). For example, supplementation with FOS and glucomannan has been associated with increased calcium content in femoral bones in animal models, highlighting their potential to bolster bone mineralization through gut microbiota modulation (56). Probiotics also play a significant role by directly interacting with the gut microbiota and host intestinal cells (57). Through this interaction, probiotics can upregulate the expression of intestinal calcium transporters, such as transient receptor potential vanilloid 6 and calcium-binding proteins (55). Enhanced expression of these transporters facilitates the active uptake of calcium from the intestinal lumen into enterocytes and subsequently into the bloodstream, improving systemic calcium availability (55). One notable example is Lactobacillus acidophilus fermenting Astragalus polysaccharides, which has been shown to favorably change the composition of the gut microbiota and increase calcium absorption (58). This fermentation process enriches populations of beneficial bacteria that support gut barrier integrity and mineral uptake, thereby enhancing calcium bioavailability (58). Beyond direct effects on calcium solubility and transport, the gut microbiota can influence bone health by modulating circulating levels of certain signaling molecules (6). One of them is GDS, which is synthesized in enterochromaffin cells (59). Serotonin produced in the gut can act on bone cells, regulating bone formation and resorption (60). The microbiota's modulation of serotonin synthesis and release represents an indirect pathway for influencing bone mass and calcium homeostasis (61). Clinical observations further support the link between gut microbiota, calcium absorption, and bone metabolism (62). As an example, increased calcium absorption has been documented in acromegaly patients, who often exhibit elevated serum calcium levels (63). This correlation suggests that systemic factors and possibly microbiota-related mechanisms enhance calcium uptake in conditions with altered hormonal profiles (64).

Conclusion

The intricate relationship between gut microbiota and bone metabolism is increasingly recognized as a crucial factor in bone health. The diverse community of microorganisms residing in the gastrointestinal tract plays a significant role in regulating both osteoclastogenesis and osteoblast activity. This delicate balance is paramount for continuous bone remodeling, which is essential for bone healing, adaptation to stress, and overall skeletal maintenance. A healthy and diverse gut microbiome fosters balanced bone remodeling processes, contributing to robust bone healing and resilience. Conversely, an imbalance in the gut microbiota, known as dysbiosis, has been strongly linked to impaired bone healing capabilities and an elevated risk of developing osteoporosis. Beyond its direct influence on bone cell activity, the gut microbiota also modulates the absorption of critical nutrients vital for bone mineralization and strength. Specifically, it influences the bioavailability of calcium and vitamin D, both of which are indispensable for maintaining bone density and preventing skeletal disorders. This indirect impact on nutrient absorption highlights another pathway through which gut health directly affects bone integrity. Furthermore, the gut microbiota exerts a profound influence on systemic immune responses and inflammation, both of which are intimately involved in bone remodeling. Dysbiosis can trigger systemic low-grade inflammation, a condition known to accelerate bone loss by promoting osteoclast activity and inhibiting osteoblast function. Beneficial microbial metabolites, particularly SCFAs like butyrate, acetate, and propionate, have been identified as key players in promoting bone formation and inhibiting bone resorption. These SCFAs act as signaling molecules that can directly impact bone cells. Given these compelling connections, interventions such as probiotics and prebiotics, which aim to restore or maintain a healthy gut microbiota, show considerable promise in improving bone density and facilitating bone repair, potentially opening new therapeutic avenues for the prevention and management of osteoporosis.

Authors' contribution

Conceptualization: Sina Salem Ahim and Sara Aghaei.
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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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