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The Microbiome and Epigenetic Regulation in Bone Metabolism: Implications for Osteoporosis

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Abstract

Introduction:

Osteoporosis is a common metabolic disorder associated with aging, characterized by a progressive loss of bone mass and microarchitectural deterioration, leading to an increased risk of fractures and diminished quality of life, particularly among the elderly. Epidemiological data indicate that the disease affects women more often, with prevalence estimates suggesting a four times higher incidence in females compared to males. The underlying pathophysiology of osteoporosis involves a disruption in the tightly regulated bone remodeling cycle, wherein osteoclasts' bone resorption precedes osteoblasts' bone formation. This process is modulated by multiple factors, including hormones, nutrition, and environmental exposures. Emerging evidence has identified the gut microbiota as a novel regulator of bone homeostasis, implicating intestinal microbial populations in the etiology of osteoporosis and bone metabolism. Understanding the pathways through which the gut microbiome influences skeletal integrity is crucial for advancing targeted strategies in the prevention and management of osteoporosis.

Aim of Study:

The aim of this study is to summarize current knowledge regarding the role of the gut microbiome in the regulation of bone metabolism and its impact on the development and progression of osteoporosis. The review explores the mechanisms through which microbiota

influence skeletal homeostasis, evaluates their contribution to osteoporosis susceptibility, and examines the consequences of microbiome changes on bone integrity.

Materials and Methods:

A literature search was conducted across PubMed. Keywords included “osteoporosis,” “bone metabolism,” “gut microbiome,” “microRNAs,” “epigenetics,” and “bone remodeling.” Articles were selected based on relevance, study design, and accessibility.

Conclusion:

Osteoporosis is increasingly understood as a condition influenced not only by hormonal and nutritional factors but also by the gut microbiota and epigenetic regulators such as microRNAs. These components modulate bone remodeling by affecting osteoblast and osteoclast activity through metabolic and immune pathways. The gut-bone axis and microbiota-miRNA interactions represent a dynamic regulatory network contributing to bone health and disease. Dysbiosis and miRNA dysregulation may disrupt this balance, increasing susceptibility to osteoporosis. Recognizing these mechanisms broadens the pathophysiological understanding of osteoporosis and highlights new opportunities for biomarker discovery and microbiome- or miRNA-targeted therapies.

Keywords: osteoporosis, bone metabolism, gut microbiota, miRNA, epigenetics, bone remodeling

Introduction:

Osteoporosis affects over 200 million people worldwide and remains a significant cause of morbidity, especially in postmenopausal women and the elderly (1). The condition arises from an imbalance between bone resorption by osteoclasts and formation by osteoblasts, resulting in weakened skeletal architecture and increased fracture risk (2). Hormonal deficiencies (e.g., estrogen), chronic inflammation, and nutritional insufficiencies are well-established contributors (3). In recent years, the role of gut microbiota in modulating systemic immunity, nutrient bioavailability, and bone cell signaling has attracted attention (4). Additionally, non-coding RNAs, particularly microRNAs (miRNAs), have emerged as critical epigenetic

regulators influencing osteoblast and osteoclast differentiation (5). Investigating microbiota and miRNA activity's molecular and epigenetic axis may offer new diagnostic and therapeutic insights into osteoporosis.

Osteoporosis and Bone Remodeling:

Osteoporosis is a systemic skeletal disorder marked by decreased bone mass and deterioration of bone microarchitecture, leading to increased fracture risk. It is particularly prevalent among postmenopausal women and the elderly due to hormonal shifts and cumulative metabolic changes. (2). At the core of osteoporosis lies a disruption in the dynamic process of bone remodeling, wherein bone-resorbing osteoclasts and bone-forming osteoblasts typically work in a tightly regulated balance. Osteoclasts degrade old or damaged bone, clearing space for new matrix production by osteoblasts. (6). This remodeling process is continuously influenced by hormones, cytokines, and transcription factors responding to systemic and local cues. This balance can be disrupted under certain physiological or pathological conditions, such as elevated glucocorticoid levels, fluctuations in parathyroid hormone (PRH) levels or alterations in serum calcium levels and changes in growth hormone levels. (7). Importantly, estrogen plays a central role in maintaining the balance by inhibiting osteoclastogenesis and suppressing the production of pro-inflammatory cytokines. Its deficiency, particularly during menopause, results in elevated levels of IL-1, IL-6, and TNF-α, potent stimulators of osteoclast differentiation and bone resorption. In addition to hormonal changes, oxidative stress and chronic inflammation contribute significantly to the pathophysiology of osteoporosis. Reactive oxygen species (ROS) impair osteoblast function and survival while promoting osteoclast activity. This shift favors net bone loss and accelerates skeletal weakening. (8). Moreover, pro-inflammatory mediators and oxidative damage are known to interfere with the Wnt signaling and P13/AKT pathways, which are critical for osteoblastogenesis and bone formation. (9). As a result, osteoporosis is not solely a disease of mineral imbalance but a multifactorial condition deeply embedded in immune, hormonal, and metabolic dysregulation. Understanding these mechanisms provides a foundation for exploring how gut microbiota and epigenetic regulators, including microRNAs, further modulate this balance and potentially contribute to the progression or prevention of osteoporosis. (10).

The Gut–Bone Axis: How Microbiota Influence Bone Health:

The concept of the gut-bone axis refers to the complex and bi-directional relationship between intestinal microbiota and skeletal health. Gut bacteria break down dietary fibers into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. These SCFAs influence the organism in various molecular pathways, modulating immune cells, reducing inflammation, and stimulating osteoblast differentiation while suppressing osteoclast activity. Particularly, butyrate promotes regulatory T cell (Treg) development, which has been shown to suppress pro-osteoclastogenic cytokines such as TNF-α and IL-6 (10)(11). Bile acids, modified by gut microbiota in a process of conversion from primary bile acids into secondary bile acids, also regulate vitamin D and lipid absorption, both essential for bone metabolism. Disruptions in the microbial processing of bile acids can lead to reduced nutrient absorption and negatively contribute to bone demineralization (12). Furthermore, these secondary bile acids interact with the membrane-bound G protein-coupled bile acid receptor TGR5. Activation of TGR5 has been shown to stimulate osteoclast differentiation via the AMP-activated protein kinase (AMPK), which indicates a crucial role of gut microbiota in osteoclastogenesis and, consequently, bone homeostasis (13). Moreover, gut microbiota shapes the host's immune system. Dysbiosis increases gut permeability and permits microbial-derived pro-inflammatory molecules such as lipopolysaccharides to enter circulation. This chronic low-grade inflammation promotes osteoclastogenesis and suppresses osteoblastic bone formation (10). Additionally, the microbiota helps in nutrient absorption, including magnesium, calcium, and vitamin D – key components of mineralization (14). Certain probiotic strains can enhance calcium uptake and have been associated with increased bone density in experimental models. Animal studies provide strong support for the microbiota's role in homeostasis. Germ-free mice – raised without microbial exposure – exhibit increased bone mass and altered expression of genes involved in bone formation. Surprisingly, recolonization with a conventional microbiota leads to bone loss, suggesting that specific microbial populations modulate bone turnover via immune and endocrine pathways (15). Clinical data proves accordingly. Postmenopausal women with osteoporosis often present reduced gut microbial diversity and unfavorable compositional shifts. These changes are associated with increased inflammatory markers and altered SCFA production (10). Additionally, reduced intestinal microbiota diversity has been implicated in diminished circulating estrogen levels, particularly through the activity of β-glucuronidase – an

enzyme responsible for converting estrogen into its biologically active form (16). Furthermore, studies show that probiotic supplementation in osteoporotic patients can modestly increase bone mineral density and reduce resorption markers (17).

Epigenetic Regulation: The Role of miRNAs in Bone Remodeling:

MicroRNAs (miRNAs) are small, non-coding RNA molecules approximately 20-25 nucleotides in length that play crucial roles in post-transcriptional gene regulation. By binding to complementary sequences on messenger RNA (mRNA) targets, they can repress translation or promote mRNA degradation, thereby modulating gene expression in a precise and time-sensitive manner. In bone biology, miRNAs act as key epigenetic regulators influencing osteoblast and osteoclast differentiation, function, and apoptosis (18)(19). Dysregulated miRNA profiles have been consistently associated with osteoporosis. Several miRNAs have been identified as regulators of osteoblast differentiation, i.e., miR-21 enhances osteogenesis by targeting negative regulators of osteoblast function, such as SPRY1 and PDCD4 (19). Similarly, miR-181a/b stimulate osteoblast differentiation by activating the PI3K/AKT pathway and influencing mitochondrial metabolism (20). Another important example, miR-103a, has been shown to inhibit Runx2 – a key transcription factor in osteoblast differentiation – thereby reducing bone formation under mechanical stress conditions (21). The balance in expression of these miRNAs is essential for healthy bone remodeling. Their dysregulation may lead to osteoblast dysfunction, contributing to the reduced bone formation observed in osteoporosis (22). On the other end of the remodeling spectrum, certain miRNAs promote or inhibit osteoclast formation and activity. miR-21 has also been implicated in osteoclastogenesis by targeting PDCD4 and promoting RANKL-induced osteoclast differentiation. Others, such as miR-29b, appear to suppress osteoclastogenesis by targeting genes involved in osteoclast fusion and survival. A complex network of miRNAs, including miR-34a, miR-124, and miR-223, have been shown to influence osteoclast differentiation by modulating transcription factors such as NFATc1 and PU.1, which are central to osteoclast lineage commitment (23). This highlights the dual role of miRNAs in maintaining the homeostasis of bone turnover. Given their cell-type specificity and stability in serum and plasma, circulating miRNAs emerge as promising non-invasive biomarkers for early osteoporosis detection (24). Differences in miRNA expression profiles have been found in osteoporotic patients compared to healthy patient controls, indicating their diagnostic potential (25). Moreover, miRNA-based therapies, including mimics to restore suppressed miRNAs and inhibitors (antagomirs) to silence

overexpressed ones, are under preclinical development. For example, delivering miR-29b mimics in osteoporotic models has shown anabolic effects while inhibiting miR-133a can enhance bone matrix production (26)(27). However, challenges remain regarding tissue-specific delivery, off-target effects, and long-term safety. Despite this, the potential of miRNAs as both biomarkers and therapeutic targets continues to draw research interest.

The Microbiota-miRNA Interconnection: A Regulatory Feedback Loop:

One of the emerging areas of interest in osteoepigenetics is the role of gut-derived microbial metabolites – particularly, as previously mentioned, SCFAs – short-chain fatty acids – in modulating host gene expression via miRNAs. These metabolites can influence the expression of miRNAs involved in bone cell differentiation and inflammatory responses by altering chromatin structure and histone acetylation. Previously described butyrate, for example, enhances the expression of anti-inflammatory miRNAs, indirectly promoting osteoblast activity while suppressing osteoclast-mediated bone resorption. (12). This illustrated a direct regulatory mechanism whereby the gut microbiota influences bone metabolism through epigenetic control, with miRNAs acting as key intermediaries in this cross-talk. Moreover, miRNAs are not only targets of microbial metabolites – they also actively shape the host's immune tolerance and responsiveness to the microbiota. Certain miRNAs modulate Toll-like receptor (TLR) signaling and cytokine expression, which are essential for distinguishing commensal from pathogenic microbes. For example, miR-146a and miR-155 regulate TLR/NF-κB pathways and impact macrophage activation, thereby indirectly affecting osteoclast differentiation. These immune-regulatory roles of miRNAs establish a feedback loop: gut microbes influence miRNA profiles, and miRNAs, in turn, determine how the immune system interacts with the gut flora – this interaction has systematic consequences, including bone metabolism (10). Evidence increasingly supports the view that dysbiosis of the gut microbiota alters circulating signatures associated with osteoporosis. For example, patients with postmenopausal osteoporosis display altered levels of several bone-related miRNAs – including miR-21, miR-29b, and miR-133a – that correlate with both inflammatory markers and microbial imbalances (28)(29). Further, the studies have shown distinct miRNA expression profiles in trabecular bone samples from osteoporotic patients compared to healthy controls, highlighting the potential diagnostic value of these miRNA changes (30). Other studies identified gender-specific serum miRNA signatures linked to genetically driven bone fragility, reinforcing the idea that miRNA expression is not only microbiota-sensitive but also clinically relevant (25).

Beyond miRNAs: lncRNAs, circRNAs, and Bone Homeostasis:

While microRNAs have received extensive attention as epigenetic regulators of bone remodeling, other classes of non-coding RNAs – particularly long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) – have recently emerged as critical modulators of osteogenesis and bone homeostasis. These molecules often interact with miRNAs and form a part of a more extensive epigenetic network that is influenced by host-microbiome dynamics (31). One of the most studied lncRNAs in bone biology is H19, which plays a pro-osteogenic role by promoting osteoblast differentiation. Its effect is partly mediated through miR-675, which is derived from H19 and targets IGF1R, a critical factor in bone growth and remodeling. Changes in gut microbiota have been associated with altered expression of H19, linking microbial metabolites and immune signals to this epigenetic regulator. Upregulation of H19 has been shown to support osteogenesis and may offer therapeutic promise in osteoporosis settings (31)(32). On the other hand, circFOXP1, a circular RNA derived from the FOXP1 gene, enhances osteogenesis by sponging miR-33a-5p, thereby upregulating FOXP1 expression. This molecular mechanism contributes to improved bone formation and regeneration, particularly in osteoporotic models (33). The cirFOXP1-miRNA axis represents a possible link between microbial influence and host bone gene regulation, especially as microbiota-modulated inflammation can affect circRNA expression. Several other non-coding RNAs, including XIST, MALAT1, and others, act as scaffolds that bring together transcriptional machinery and signaling molecules essential for bone cell differentiation. These lncRNAs integrate into pathways like WNt/β-catenin and PI3K/AKT, both of which are influenced by gut-derived metabolites and immune modulators (31). Their interaction with the microbiome-affected epigenetic environment positions them as important factors in skeletal remodeling. Together, lncRNAs and circRNAs form a regulatory layer that integrates signals from the gut microbiota and host immune system. By interacting with miRNAs and transcription factors, they help mediate bone cell fate and contribute to either skeletal maintenance or disease progression, such as in osteoporosis (34).

Clinical Implications and Therapeutic Prospects:

Osteoporosis remains underdiagnosed until bone loss has progressed to a clinically significant stage. Thus, early and non-invasive biomarkers are needed. Circulating microRNAs show promise as diagnostic indicators due to their stability in serum and their role in regulating bone metabolism (35). Several studies have demonstrated that specific miRNA profiles – such as altered levels of miR-21, miR-29b, and miR-133a – correlate with decreased bone mineral density and can distinguish osteoporotic individuals from healthy controls (25) (26) (27). The identification of microbiota-based risk signatures could allow clinicians to stratify individuals by susceptibility and personalize interventions before clinical symptoms emerge. Growing insight into the gut-bone-epigenetic axis has inspired several novel therapeutic approaches, such as probiotic interventions, fecal microbiota transplantation (FMT), and miRNA-based therapies. Probiotic interventions, particularly with strains like *Lactobacillus reuteri***,** have shown the ability to enhance bone mass by modulating immune signaling and promoting the production of beneficial microbial metabolites (36) (37). A one year randomized controlled trial showed that supplementation with specific strain of *Lactobacillus reuteri* ATCC PTA 6745 decreased bone loss in elderly women with low bone mineral density (BMD). Good responders (indicated based on metagenomic and metabolic factors of fecal microbiota) exhibited increased gut microbiota richness and decreased inflammatory markers (38). Moreover, *Lacotbacillus reuteri* has not been an only species to be examined towards influence on bone metabolism. *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium breve* and *Bifidobacterium longum* demonstrated to modulate immune responsed promoting regulatory T cells and inhibiting osteoclastogenesis (39). Additionally, meta-analysis of 12 randomized controlled trials involving 1183 women after menopause found probiotic supplementation, particularly with doses $\geq 1 \times 10^9$ CFU/day, highly increased BMD in the hip regions and lumbar part of the spine. However, these foundings were more significant in women with osteopenia, rather than osteoporosis (40). Fecal microbiota transplantation, although still experimental in this context, is being investigated for its systemic effects on metabolism and inflammation. Early studies suggest that restoring a balanced microbiome may support bone health, especially in cases of age-related or antibiotic-induced bone loss (41). FMT from postmenopausal osteoporosis patients to antibiotic-treated mice induced bone mass loss, indicating the role of gut microbiota on bone health (42). On the epigenetic front, miRNA-based therapies are under development.

This includes the use of miRNA mimics to restore the function of downregulated bone-protective miRNAs and anti-miRs to silence overexpressed, bone-degrading miRNAs. Preclinical studies have shown that mimics of, previously described, miR-29b can enhance bone formation, while inhibition of miR-133a promotes matrix synthesis and mineralization. Despite the promising possibilities, several challenges remain. For miRNA-based therapy, main challenges include achieving targeted delivery to bone tissue, avoiding off-target effects, and ensuring long-term safety. Similarly, probiotic and FMT therapies require greater standardization, safety validation, and understanding of strain-specific effects before they can be broadly applied in clinical practice (41). Nonetheless, the combination of microbiome research and epigenetic regulation opens new pathways for personalized medicine in osteoporosis, meaning new diagnosis and treatment prospects.

Conclusions:

Osteoporosis is no longer understood solely as a consequence of hormonal decline and mineral imbalance but as a complex, multifactoral disease shaped by interactions among the endocrine, immune, and microbial systems. Central to this redefined view is the gut-bone axis, through which the microbiota exerts profound effects on skeletal metabolism via immune modulation, nutrient processing, and the production of signaling metabolites such as SCFAs and bile acids. In parallel, epigenetic regulators, miRNAs, lncRNAs, and circRNAs have emerged as key players in the control of bone cell fate. These non-coding RNAs modulate gene expression in osteoblasts and osteoclasts and are increasingly linked to gut microbiota-mediated signaling. The interplay between microbial metabolites and host miRNA expression forms a regulatory feedback loop that influences bone remodeling at the molecular level. Growing evidence supports the use of circulating miRNAs and gut microbiota signatures as non-invasive biomarkers for early osteoporosis detection and risk assessment. Therapeutically, probiotic supplementation, fecal microbiota transplantation (FMT), and miRNA-based interventions represent innovative strategies that target the root causes of skeletal dysregulation rather than its consequences. While challenges remain in terms of delivery specificity, long-term safety, and clinical translation, the convergence of microbiome science and epigenetics offers a promising path forward. Understanding and harnessing these interconnected systems could transform the prevention, diagnosis, and treatment of osteoporosis – ushering in a new era of precision bone medicine.

Supplementary materials:

Not applicable.

Author's Contribution

Conceptualization, Kornel Celoch, Kamil Kruk, Daniel Wojciech, Andrzej Porczyński, Jakub Bulanda, Jakub Cegielski, Jakub Ślęzak; methodology, Daniel Wojciech, Martyna Jabrzyk, Kamil Kruk, Jakub Cegielski, Jakub Ślęzak, Elżbieta Bukowczan, Kornel Celoch, software, Kornel Celoch, Jakub Bulanda, Jakub Ślęzak, Andrzej Porczyński; check, Kamil Kruk, Martyna Jabrzyk, Jakub Ślęzak, Elżbieta Bukowczan; formal analysis, Kornel Celoch, Andrzej Porczyński, Jakub Cegielski, Elżbieta Bukowczan, Martyna Jabrzyk; investigation, Jakub Bulanda, Jakub Ślęzak, Daniel Wojciech; resources, Kornel Celoch, Jakub Ślęzak, Andrzej Porczyński; data curation, Elżbieta Bukowczan, Kamil Kruk, Martyna Jabrzyk, Jakub Cegielski; writing - rough preparation, Kornel Celoch, Andrzej Porczyński, Jakub Cegielski; writing- review and editing, Elżbieta Bukowczan, Jakub Bulanda, Martyna Jabrzyk, Jakub Ślęzak, Daniel Wojciech; visualization, Kamil Kruk, Jakub Cegielski, Jakub Bulanda; supervision, Kornel Celoch, Andrzej Porczyński, Jakub Bulanda, Jakub Cegielski, Martyna Jabrzyk; project administration Kamil Kruk, Kornel Celoch, Jakub Ślęzak, Daniel Wojciech, Elżbieta Bukowczan; All authors read and agree with the published version of the manuscript.

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The data presented in this study are available upon request from the corresponding author.

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