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Review Article

Unravelling the Osteo-microbiome: Gut-Bone Axis in Osteoporosis Pathogenesis and Therapeutic Options

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Abstract

The gut microbiota plays a pivotal role in maintaining bone homeostasis through nutrient absorption, immune modulation, endocrine regulation and microbial metabolite production. Dysbiosis, a disruption of this ecosystem, is increasingly recognised as a key contributor to osteoporosis, a metabolic disorder defined by low bone mineral density (BMD) and micro-architectural deterioration. Recent insights into the gut–bone axis reveal that microbial metabolites such as short-chain fatty acids (SCFAs), immune regulators like IL-17 and TNF-α, and intestinal barrier integrity profoundly influence bone remodelling. This review explores the mechanisms linking gut dysbiosis to osteoporosis, examines preclinical and clinical evidence supporting this interaction, and discusses microbiome-targeted interventions such as probiotics, prebiotics, synbiotics, and postbiotics. Emerging multi-omics and AI-driven approaches further support the translational potential of personalised, microbiome-informed osteoporosis care. Understanding and modulating the osteomicrobiome may open new avenues for prevention and precision treatment of osteoporosis.

Keywords: Osteomicrobiome; Osteoporosis; Gut–Bone Axis; Dysbiosis; Short-Chain Fatty Acids; Probiotics; Bone Metabolism

Introduction

Osteoporosis affects hundreds of millions of people across the world and remains one of the most significant health concerns in ageing populations, especially in postmenopausal women [1]. A normal bone has a fine, dense network that helps it stay strong. When osteoporosis develops, these spaces grow larger and the structure thins out, making the bone much easier to break as shown in the figure 1.

Classical risk factors—including estrogen deficiency, inadequate calcium and vitamin D intake, ageing, and reduced mechanical loading—are well established [2]. Interestingly, recent research has identified an additional contributor: the gut microbiota [3].

The emerging concept of the "osteomicrobiome" describes how intestinal microorganisms influence bone strength, mineral metabolism, and long-term skeletal stability.

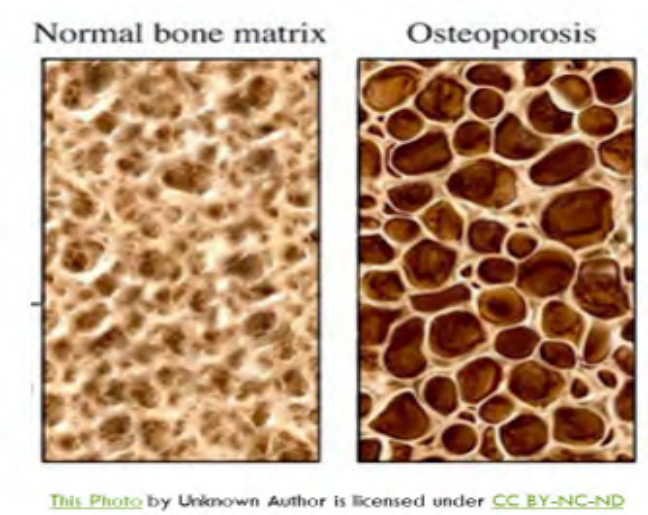

Figure 1: Showing the loss of trabecular connectivity in osteoporosis compared to normal bone: [source- Reference-4].

Figure 2: Microbial pathways influencing bone homeostasis. Schematic illustration showing how gut-derived metabolites, immune mediators, and nutrient-processing pathways regulate osteoblast and osteoclast activity.

The gut does far more than digest food; it produces a range of biologically active compounds, communicates constantly with the immune and endocrine systems, and helps regulate how nutrients are absorbed and utilised [3]. When this delicate microbial balance becomes disturbed—a state known as gut dysbiosis—several harmful processes can begin [5]. As shown in figure-2 dysbiosis triggers increased intestinal permeability, chronic low-grade inflammation, impaired mineral absorption, and altered hormonal signalling—all of which disrupt bone remodelling [5]. Because osteoporosis leads to fractures and disability, understanding the gut–bone relationship introduces new preventive and therapeutic opportunities [1,2].

The gut–bone axis: Biological framework

The connection between the gut and the skeleton operates through several major pathways: nutrient handling , immunological regulation of bone cells , and hormonal or metabolic interactions [5].

Nutrient absorption and mineral metabolism

The gut microbiota plays a crucial role in determining how well minerals can influence the activity of transport proteins such as TRPV6, PMCA1b, and NCX1, which control the movement of these minerals across the intestinal lining . As illustrated in Figure 3, microbial fermentation of dietary fibres produces short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate.

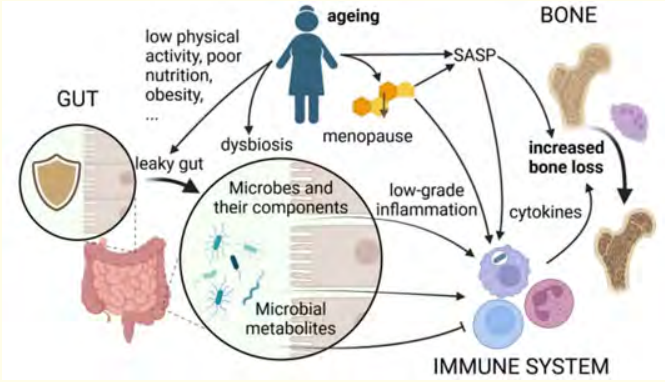

Figure 3: Intestinal barrier dysfunction and its consequences for bone health. [source: reference-4], Diagram illustrating how tight-junction disruption, microbial translocation (LPS), and systemic inflammation lead to RANKL-mediated bone resorption.

SCFAs modify luminal acidity and intestinal transporter activity, creating a biochemical environment more favourable for mineral uptake. This metabolic shift improves the efficiency of active and passive mineral transport. Gut microbes also contribute to the production of vitamin K_2 (menaquinone), which is needed for the activation of osteocalcin — a protein vital for healthy bone formation [3,5].

Immune–bone crosstalk

Bone turnover is tightly linked to immune activity [3]. Disturbances in the microbiota can stimulate Th17 cells, increasing the production of inflammatory cytokines such as IL-17, IL-6, and TNF-α . These signals activate the RANKL–RANK–NF-κB pathway, which drives osteoclast development and accelerates bone resorption. In contrast, regulatory T cells (Tregs) and anti-inflammatory cytokines like IL-10 help restrain osteoclast activity and support bone-building cells. SCFAs, especially butyrate, enhance Treg activity, promoting an anti-inflammatory environment that favours bone formation [5].

Endocrine and metabolic interactions

Gut microbes also influence key hormonal systems related to bone health [3,5]. As depicted in Figure 3, bacterial β-glucuronidase enzymes affect the recycling of oestrogens through enterohepatic circulation; disruptions in this process can modify oestrogen availability and influence bone turnover in postmenopausal women. The microbiota further interacts with hormones and growth factors such as IGF-1 and parathyroid hormone (PTH), both of which are essential for maintaining bone mass. Overall, the gut–bone axis represents a coordinated network in which nutrient absorption, immune signalling, and endocrine interactions continually regulate bone remodelling. Dysbiosis alters each of these pathways, predisposing individuals to bone loss and increased fracture risk. Microbes influence absorption and bioavailability of calcium, magnesium, and fat-soluble vitamins (D, K) and can modulate enterohepatic circulation of estrogens and bile acids — thereby indirectly affecting bone metabolism. This pathway is especially relevant in postmenopausal osteoporosis, where estrogen withdrawal unmasks inflammatory and microbial effects

Emerging concepts in the gut–bone axis

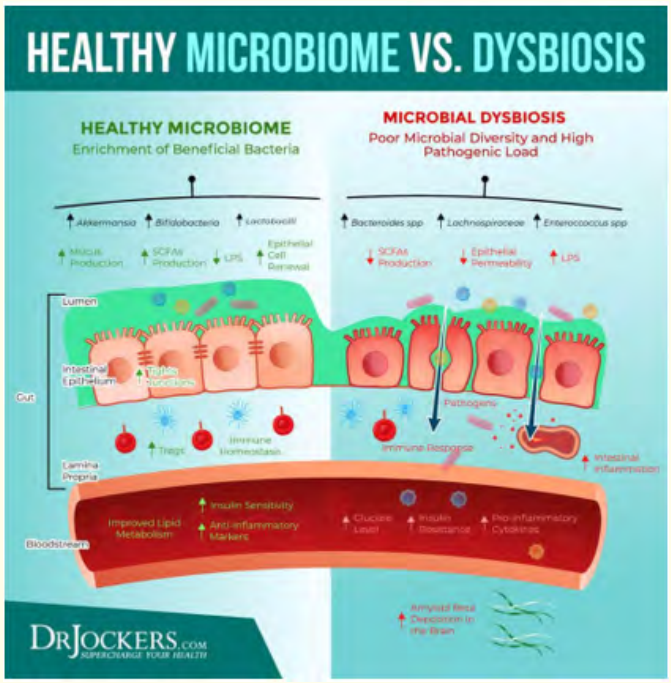

Figure 4: Commensal–pathogenic balance in the gut ecosystem [source-Reference-6, DrJockers.com (2025)].

Gut barrier and mucosal immunity

The intestinal barrier plays a central role in controlling the movement of nutrients and microbial products between the gut and the rest of the body. As illustrated in Figure 4, healthy gut conditions are characterised by intact epithelial tight junctions, a robust mucus layer, and sufficient secretory IgA, all of which prevent harmful antigens from entering systemic circulation. During dysbiosis these protective layers become compromised — a condition often referred to as "leaky gut. Impaired goblet cell and Paneth cell function weakens mucosal protection, allowing lipopolysaccharides (LPS) and microbial fragments to enter systemic circulation.

Circulating microbial components provoke sustained inflammation, upregulating osteoclastogenic pathways and accelerating bone resorption. This connection positions gut barrier integrity as a central regulator linking intestinal dysbiosis to systemic skeletal decline [5].

Additional microbial metabolites in bone regulation

Although short-chain fatty acids are widely recognized for their beneficial effects on bone, several other microbiota-derived metabolites significantly influence skeletal health. Tryptophan metabolites, such as indole derivatives, activate the aryl hydrocarbon receptor (AhR), which plays a role in regulating osteoblast and immune function. Polyamines like spermidine support cell growth and may protect osteoblasts from oxidative damage. Secondary bile acids interact with receptors such as FXR and TGR5, affecting vitamin D metabolism and inflammatory responses. Altered production of these metabolites during dysbiosis shifts bone metabolism toward enhanced osteoclast activity and reduced bone formation. Expanding research into these molecules offers promising new targets for osteoporosis therapy beyond SCFAs alone [5].

To provide a clearer overview of how specific gut microbes contribute to skeletal regulation, Table-1 summarizes key bacterial species, their major metabolites, and the mechanisms through which they influence bone metabolism. The table highlights distinct groups of microbes that either support bone formation through anti-inflammatory and nutrient-enhancing pathways, or contribute to bone loss by promoting inflammation and disrupting gut barrier function. Together, these species exemplify the diverse ways in which microbial composition shapes the gut–bone axis.

Group	Microbiota/Species	Major Metabolites/ Features	Mechanisms Affecting Bone	Effect on Bone	Key Authors/ Studies
Protective (Bone-Promoting)	*Lactobacillus rhamnosus GG (LGG)*	SCFAs (butyrate), lactic acid	↓ IL-6, TNF-α; ↑ Tregs; strengthens gut barrier; ↑ Ca absorption	↑ Bone density; ↓ osteoclast activity	McCabe., *et al*. 2013; Ohlsson 2020 [7,8]
Protective (bone-promoting)	*Lactobacillus reuteri*	Butyrate, reuterin	Immune modulation; ↓ inflammation; prevents estrogen-deficiency bone loss	Prevents trabecular loss	Collins., *et al*. 2016 [9]
	Lactobacillus casei	SCFAs	Improves mineral absorption; reduces oxidative stress	Supports osteoblast activity	Xu., *et al*. 2023 [10]
	Lactobacillus helveticus	Bioactive peptides, SCFAs	Enhances calcium transport proteins	↑ BMD (experimental)	Weaver., *et al*. 2020 [11]
	Bifidobacterium longum	Acetate, lactate	Enhances mineral bioavailability; ↑ Tregs	↑ Bone mineralization	Li., *et al*. 2022 [12]
	Bifidobacterium breve	SCFAs	Anti-inflammatory; supports epithelial integrity	Protects bone mass	Xu., *et al*. 2023 [10]

	Bifidobacterium adolescentis	SCFAs	Regulates gut pH; improves Ca/Mg absorption	↑ Bone strength	Zaiss., *et al*. 2021 [13]
	Faecalibacterium prausnitzii	Butyrate	Strong anti-inflammatory; inhibits IL-1β & TNF-α; ↓ osteoclasts	↑ Osteoblast differentiation	Pacifici 2021 [14]
	Roseburia species	Butyrate	Activates Wnt signaling; reduces NF-κB pathway	↑ Bone formation	Ohlsson 2020 [8]
	Eubacterium rectale	Butyrate	Regulates Treg cells; ↓ bone resorption	Improves bone turnover profile	Eastell 2022 [15]
	Akkermansia muciniphila	Mucin-degradation metabolites	Strengthens gut barrier; ↓ LPS leakage	Protects against systemic inflammation–related bone loss	Li., *et al*. 2022 [12]
	Clostridium cluster XIVa & IV (beneficial clostridia)	SCFAs	Expand Treg cells; suppress pro-inflammatory cytokines	↓ Osteoclast activity	Zaiss., *et al*. 2021 [13]
	Prevotella copri (certain strains)	SCFAs	Carbohydrate fermentation; context-dependent	May support bone via SCFA	Xu., *et al*. 2023 [10]
Harmful (Bone-Damaging)	*Clostridium difficile*	Toxins A & B	Severe inflammation; gut mucosal injury → bone loss	↑ Osteoclast activation	Khosla 2023 [16]
	Clostridium perfringens	Endotoxins	Increases systemic inflammatory load	↑ Bone resorption	Pacifici 2021 [14]
	Enterobacteriaceae (E. coli)	LPS/endotoxin	↑ IL-6, RANKL; metabolic inflammation	Rapid bone loss	Eastell 2022 [15]
	Klebsiella species	LPS	Triggers osteoclastogenesis via TNF-α	↓ BMD	Pacifici 2021 [14]
	Enterobacter species	LPS	Causes chronic inflammation → bone resorption	Linked to osteoporosis	Ohlsson 2020 [8]
	Prevotella intermedia	Proteolytic enzymes	Periodontal inflammation → promotes systemic bone loss	Harmful	Pacifici 2021 [14]

	Prevotella nigrescens	Inflammatory mediators	Stimulates IL-6, IL-17 → osteoclast activation	Negative effect	Zaiss 2021 [13]
	Ruminococcus gnavus	Pro-inflammatory polysaccharides	Associated with autoimmune activation → RA-related osteoporosis	↑ Bone destruction	Khosla 2023 [16]
	Streptococcus species (overgrowth)	Lactate/reduced SCFA output	Dysbiosis → loss of beneficial butyrate producers	↑ Osteoclastogenesis	Ohlsson 2020 [8]
	Desulfovibrio species	Hydrogen sulfide (H_2S)	Damages gut barrier → LPS leakage → bone loss	Major negative effect	Xu., *et al*. 2023 [10]
	Fusobacterium nucleatum	LPS, pro-inflammatory factors	↑ TNF-α, IL-1β → severe osteoclast activation	Strongly bone-damaging	Li., *et al*. 2022 [12]

Table 1: Key Gut Microbiota Associated with Bone Health and Osteoporosis.

Legends: SCFAs=Short Chain Fatty Acids -, LPS = Lipopolysaccharide, BMD (bone mineral density), Tregs (regulatory T cells), RA (rheumatoid arthritis), ↓ and ↑ symbols (increase/decrease).

Host genetics–microbiome–bone interactions

Bone health is influenced not only by environmental factors and microbiota composition but also by host genetics. Gene variations in vitamin D receptor (VDR), estrogen receptors, and immune regulators may alter the makeup of the gut microbiome and shape the body's response to microbial metabolites. Conversely, the microbiota can regulate expression of host genes involved in nutrient metabolism, inflammation, and osteogenesis, processes highlighted in Figure 4, which depicts how barrier dysfunction and immune activation influence systemic physiology. For example, mutations in LRP5 alter gut-derived serotonin signalling, suppressing osteoblast activity and reducing bone mass. These interactions highlight a complex genetic–microbial network, suggesting that personalized treatment must consider both the patient's genome and microbiome profile [7].

Gut–Muscle–Bone Axis (Triad Concept)

Muscle and bone are closely linked through mechanical, metabolic, and endocrine pathways — and the gut microbiome influences both systems. SCFAs improve muscle mass and mitochondrial function, while dysbiosis increases inflammation and contributes to sarcopenia. Declines in muscle integrity reduce skeletal loading, accelerating bone loss and increasing fracture susceptibility. This triad is especially relevant in ageing populations, where combined sarcopenia and osteoporosis ("osteosarcopenia") dramatically elevate fall risk. Understanding the gut–muscle–bone triad paves the way for interventions that can concurrently strengthen muscle and bone through microbiota-modulatory strategies [8].

Diet patterns and lifestyle factors

Diet is one of the most powerful modulators of the gut microbiome. A high-fibre, plant-rich Mediterranean-style

diet promotes SCFA-producing bacteria and supports bone-protective immune responses. In contrast, Western-style diets high in fat, sugar, and processed foods promote dysbiosis, inflammation, and impaired calcium absorption. Fermented foods — such as yogurt, kefir, and sauerkraut — introduce beneficial microbes and enhance microbial diversity. Environmental and lifestyle variables including chronic stress, smoking, sleep deprivation, and reduced physical activity further disrupt microbial balance and indirectly impair bone health. These modifiable factors highlight the importance of holistic management strategies that support the microbiome [9].

Pharmacomicrobiomics

The emerging field of pharmacomicrobiomics explores how the gut microbiota influences the response to medications. In the context of osteoporosis, the microbiome can modify the absorption, metabolism, and effectiveness of drugs such as bisphosphonates, denosumab, and selective estrogen receptor modulators. For example, microbial enzymes may alter the breakdown of oral therapies, potentially affecting their bioavailability. Additionally, immune-modifying osteoporosis drugs may interact differently depending on the patient's microbial composition. Understanding these drug–microbiome interactions could support better therapeutic decisions — including dose optimization and combining medications with probiotics to enhance outcomes.

Microbiome-based biomarkers and diagnostic tools

Advances in microbiome science are enabling the discovery of microbial signatures that may serve as early indicators of osteoporosis. Changes in the abundance of certain species, reductions in microbial diversity, and faecal metabolite patterns have all been linked with fracture risk and bone turnover markers. Machine-learning models are increasingly capable of analyzing these microbiome data to predict which individuals may develop osteoporosis before bone loss becomes clinically evident. In the future, stool-based diagnostic approaches may complement bone density scans, offering a non-invasive method to monitor bone health and guide personalized prevention strategies [5].

Gut dysbiosis in osteoporosis pathogenesis

Mechanistic pathways

A disturbed gut microbiome can influence bone health through several interconnected mechanisms, As illustrated in Figure 5**,** one of the earliest events is the loss of intestinal barrier integrity. When dysbiosis develops, the tight-junction proteins that normally seal the gut lining — including occludin and claudin-1 become weak. This allows molecules such as LPS to leak into the bloodstream, where they provoke chronic, low-grade inflammation, which activates inflammatory cytokines. Elevated systemic levels of cytokines like TNF-α and IL-1β stimulate osteoclast development while suppressing osteoblast activity, shifting the balance of bone turnover toward excessive resorption.

Microbial imbalance also increases the generation of reactive oxygen species (ROS), which can damage osteoblasts and impair their differentiation, contributing to declines in bone mineral density through oxidative stress. Additionally, the loss of SCFA-producing bacteria particularly *Faecalibacterium prausnitzii*, *Roseburia*, and other beneficial genera highlighted on the left side of Figure 5— results in reduced SCFA production. SCFAs normally restrain osteoclastogenesis and support bone formation, so their decline favours bone degradation. Vitamin insufficiency presents another pathway: dysbiosis can reduce the intestinal production and absorption of vitamins D and K, both essential for proper bone mineralization [5].

Recent research by Weaver, and Martin, (2020) have demonstrated that these pathways form part of a much broader regulatory network linking the gut to bone metabolism. Increased gut permeability allows LPS to circulate systemically, triggering inflammatory responses driven by cytokines such as TNF-α and IL-17, which activate RANKL-mediated osteoclastogenesis — a process

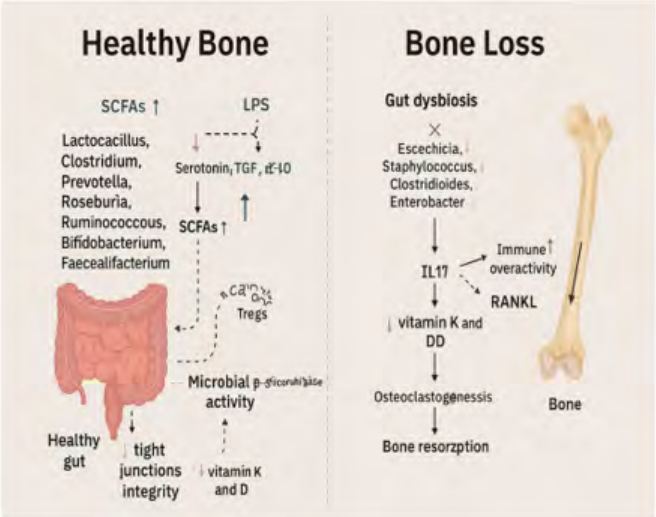

Figure 5: Integrated mechanisms linking gut dysbiosis to altered bone remodelling.

Diagram showing intestinal barrier disruption, microbial translocation (LPS), inflammatory cytokines (IL-17, TNF-α, IL-1β), SCFA depletion, oxidative stress, and serotonin-mediated suppression of osteoblast function.

illustrated on the right half of Figure 5, representing bone loss. Another emerging mechanism involves gut-derived serotonin: when intestinal serotonin synthesis increases, it inhibits osteoblast proliferation through Lrp5-dependent pathways, counteracting the bone-building actions of brain-derived serotonin [7]. Oxidative stress originating from dysbiosis further disrupts osteoblast maturation, amplifying bone loss. Simultaneously, reductions in SCFA-producing microbes — particularly *Faecalibacterium* and *Roseburia*spp. diminish Treg activation, weakening their control over inflammatory osteoclast stimulation. Together, these mechanisms illustrate how the gut acts as an integrated immune-metabolic-endocrine organ that continuously shapes bone turnover and skeletal stability.

Clinical evidence

Clinical studies strongly support these mechanistic observations. Postmenopausal women diagnosed with osteoporosis often show reduced levels of *Bifidobacterium* and *Lactobacillus*, along with an overgrowth of pro-inflammatory microbes such as *Clostridium difficile*. Large-scale metagenomic analyses have also reported associations between shifts in the Firmicutes-to-Bacteroidetes ratio and key bone turnover markers, including CTX and P1NP. A recent meta-analysis published in 2023, which evaluated 12 randomized clinical trials, found that probiotic supplementation led to measurable improvements in lumbar-spine bone mineral density and significantly lowered serum CTX concentrations. These activities reinforce the idea that gut microbial composition is closely tied to skeletal health and may represent a modifiable factor in osteoporosis prevention and management.

Therapeutic modulation of the osteomicrobiome

As the gut–bone connection becomes clearer, many therapeutic strategies aimed at modifying the intestinal microbiota have emerged as potential tools for preventing or slowing osteoporosis. These approaches range from conventional probiotics to advanced metabolite-based and microbiota-restoration therapies [20].

Probiotics

A growing body of evidence suggests that certain probiotic strains can positively influence bone metabolism . Species such as *Lactobacillus reuteri*, *Bifidobacterium longum*, and *L. rhamnosus GG* have demonstrated the ability to reduce systemic inflammation and improve calcium absorption in both preclinical models and smaller human trials [21].

One notable study — a year-long, double-blind clinical trial — showed that daily *L. reuteri* supplementation led to measurable improvements in bone mineral density among postmenopausal women [22]. These findings highlight the potential of probiotics as safe, accessible adjuncts to traditional osteoporosis therapies.

Prebiotics

Prebiotics, including inulin and fructo-oligosaccharides (FOS), act as fermentable dietary fibers that nourish

beneficial gut microbes . Their fermentation increases SCFA production and enhances the intestinal uptake of minerals like calcium and magnesium.

When prebiotics are combined with probiotics forming synbiotics, their effects can be amplified . Experimental and clinical studies show synbiotics improve trabecular bone quality, increase osteocalcin levels, and strengthen overall mineral metabolism [23].

Postbiotics and metabolite-based therapy

Unlike probiotics, which involve live microorganisms, postbiotics consist of microbial metabolites or bioactive components produced by gut bacteria. One of the most promising examples is butyrate, which promotes osteoblast maturation through pathways involving Wnt10b and Runx2, while at the same time suppressing osteoclast formation.

This metabolite-directed strategy represents an emerging therapeutic class that uses the functional outputs of the microbiome without requiring microbial colonization.

Fecal microbiota transplantation (FMT)

Although still at an early stage for bone diseases, FMT has produced encouraging results in animal models . Transferring the gut microbiota from healthy donors into osteoporotic animals helped restore microbial balance, reduce inflammation, and normalize bone remodeling markers.

Despite these promising findings, significant challenges remain — including safety concerns, donor standardization, regulatory issues, and the unknown long-term effects of microbiota transfer — before FMT can be considered for routine clinical use in osteoporosis [25].

Emerging and integrative approaches

The therapeutic landscape is expanding well beyond probiotics and prebiotics. Postbiotics such as butyrate and propionate enhance bone formation through anabolic signalling pathways while dampening osteoclast activity. Synbiotics offer combined benefits on nutrient absorption, gut barrier strength, and mineral regulation. Nutraceuticals, particularly polyphenol-rich compounds like resveratrol and quercetin, can shift microbial ecology in favour of anti-inflammatory species and improve bone turnover markers when used alongside calcium and vitamin D [26]. Pharmacobiotic strategies, which combine established osteoporosis drugs (e.g., bisphosphonates or denosumab) with selective probiotics such as *Lactobacillus reuteri* or *Bifidobacterium longum*, have shown synergistic effects in experimental studies and early clinical observations [27]. Overall, these innovations suggest that future osteoporosis care may rely on integrated therapy, combining microbiome modulation with classic bone-targeting medications to achieve more stable, long-term skeletal protection [26,27].

Alongside emerging and integrative therapeutic approaches, non-pharmacological strategies remain a fundamental component of osteoporosis prevention and management Figure-6). These lifestyle-based interventions support bone remodeling, optimize calcium–phosphate balance, and modulate the gut–bone axis through diet, physical activity, and behavioral modifications.

Figure 6: Non-pharmacological strategies supporting bone and gut health.

The following figure summarizes the key non-pharmacological measures that play a crucial role in maintaining bone health and reducing long-term fracture risk.

Current research trends

Recent years have seen remarkable progress in understanding how the gut microbiome influences skeletal health [29]. Some of the most impactful trends include, multi-omics technologies such as metagenomics, metabolomics, and proteomics are now being used together to create detailed maps of gut–bone communication [30]. The growing awareness that commonly use medications, include antibiotics, proton-pump inhibitors (PPIs), and glucocorticoids, these can disrupt the microbiome and subtly raise osteoporosis risk [31].

Recent trends have witnessed the rising interest in next-generation probiotics, especially *Akkermansia muciniphila*, for their potential to improve metabolic bone conditions [32].

But now-a-days Artificial Intelligence (AI) and machine-learning (ML) tools are used which show the capability of analysing microbiome patterns and predicting osteoporosis susceptibility with increasing precision [33]. This drive enables the movement towards precision medicine, where gut-microbiome signatures guide personalized treatment strategies for bone disorders [34].

Emerging research frontiers

The field is accelerating rapidly as multi-omics datasets and artificial intelligence become deeply integrated into gut–bone research. Advanced metagenomic and metabolomic analyses have identified specific microbial species including *Bacteroides fragilis*, *Akkermansia muciniphila*, and *Lactobacillus rhamnosus*, whose presence or decline correlates strongly with bone mineral density and markers of bone turnover. Machine-learning models trained on large microbiome databases are now capable of predicting osteoporosis and fracture risk with notable accuracy, bringing personalized risk assessment closer to clinical reality [33]. Meanwhile, germ-free animals and antibiotic-treated models continue to provide compelling evidence that altering microbial composition can directly influence bone remodeling and that restoring a healthy microbiota can reverse these effects.

New therapeutic avenues are also emerging, for example next-generation probiotics such as *Akkermansia muciniphila*, as well as engineered postbiotic formulations, are being studied for their potential to modulate immune pathways and enhance bone formation. Looking ahead, progress will depend on combining multi-omics platforms, AI-driven analytics, and long-term human cohort studies. Together, these tools aim to transform basic mechanistic discoveries into personalized prevention and treatment strategies for osteoporosis [29,33,34].

Clinical implications and translational potential

Growing recognition of the gut–bone axis is beginning to influence clinical thinking and may reshape how osteoporosis is assessed and managed in the future. Several potential applications are emerging some are listed below.

Microbiome profiling could, in time, help identify individuals with subtle or early changes in bone metabolism, offering an additional layer of screening beyond traditional clinical risk factors, leading to improved risk assessment. Adjunctive treatment strategies that modify the gut microbiota — including probiotics, prebiotics, and postbiotic metabolites — may enhance the effectiveness of established osteoporosis medications such as bisphosphonates and denosumab. Benefit in people with chronic kidney disease, long-term glucocorticoid exposure, or gastrointestinal disorders (vulnerable groups) often experience microbiome disturbances and may gain particular benefit from gut-directed approaches [37]. As our understanding of individual microbial fingerprints expands, tailored nutritional plans, targeted probiotic regimens, and lifestyle modifications may become routine components of personalised bone-health programs [34].

Clinical and demographic perspectives

The influence of the gut microbiota on bone varies across demographic groups and clinical conditions, shaping how individuals respond to treatment. In postmenopausal women, estrogen decline disrupts gut microbial balance, lowering diversity and elevating inflammatory metabolites that intensify osteoclast activity. While male osteoporosis often reflects different drivers, including metabolic disturbances and alcohol-induced microbiome changes [38]. And in children, early exposure to antibiotics or prolonged malnutrition can interfere with microbiome maturation, resulting in suboptimal peak bone mass and greater susceptibility to osteoporosis later in life [39]. Whereas, older adults commonly experience a drop in microbial diversity, diminished SCFA production, and poorer mineral absorption factors that contribute to frailty and age-related bone loss.

Certain patient groups face unique challenges. Individuals with chronic kidney disease, chronic glucocorticoid therapy, or prolonged PPI use frequently develop medication-related dysbiosis, which further increases their fracture risk. Recognizing these demographic and clinical patterns helps support a precision-medicine approach, allowing microbiome-based strategies to be customised according to each patient's physiological, lifestyle, and disease-specific characteristics.

Limitations and challenges

Although the osteomicrobiome presents exciting clinical possibilities, several limitations must be addressed before it becomes standard practice [40]. Research methods vary widely, from differences in microbial sequencing techniques to inconsistent probiotic strains, doses, and endpoints, making comparisons difficult and limiting the ability to form unified guidelines [40,41]. Many human studies involve limited participant numbers and brief intervention periods, meaning the true causal relationship between dysbiosis and osteoporosis is not fully established [40]. Regarding regulatory and safety concerns, microbiome-based therapies face hurdles involving long-term safety, regulatory approval, potential unintended effects, and the influence of host genetics, diet, and environment. Comprehensive data on durability and real-world applicability are still needed [42].

Future directions

Several important research priorities must be addressed to advance the clinical integration of the gut–bone axis. Creating reliable, validated microbiome-based tests that can identify individuals at elevated osteoporosis risk, track treatment responses, and guide clinical decision-making. Large, long-duration randomized studies are needed to evaluate probiotics, prebiotics, postbiotics, and FMT in diverse patient populations to determine their true therapeutic potential. Importantly, understanding drug–microbiome interactions, for future work should examine how an individual's microbial composition influences the absorption, metabolism, and efficacy of bone-active drugs such as bisphosphonates. Further, examining combination therapies such as integrating microbiome modulation with dietary interventions, structured exercise programs, hormonal treatment, and standard osteoporosis medications may yield synergistic benefits. Lastly, determining precision medicine frameworks by leveraging systems biology, multi-omics platforms, and AI-driven analytics will help unravel the complexity of the gut–bone network and support personalised therapeutic strategies.

Conclusion

The concept of the osteomicrobiome, which represents the multidirectional communication between the gut microbiota and skeletal system, is reshaping how researchers and clinicians understand bone health. Evidence now shows that gut microbes influence bone through a web of immune, endocrine and metabolic pathways, whereas gut dysbiosis promotes bone loss by provoking inflammation, impairing nutrient absorption and altering the production of key microbial metabolites. Therapies aimed at restoring or enhancing the gut microbiota — including probiotics, prebiotics, postbiotics, synbiotics and emerging metabolite-

based approaches — have demonstrated early promise in improving bone mineral density and regulating bone turnover. When combined with established osteoporosis treatments, these strategies could lead to more comprehensive, personalised care that connects principles across gastroenterology, endocrinology and orthopaedics. As multi-omics technologies, AI-driven modelling and long-term clinical research continue to expand, the translation of osteomicrobiome science into routine clinical practice becomes increasingly attainable. The next decade may bring a shift toward truly integrated, microbiome-informed osteoporosis management.

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Ethical Issues

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

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