

# Targeting the gut-bone axis through exercise: A novel approach to osteoporosis prevention and treatment (Review)

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**Abstract.** Osteoporosis is a metabolic bone disease marked by decreased bone mineral density and deterioration of bone microarchitecture. Its development involves complex interactions between genetic factors, nutrition, hormones and lifestyle factors. As the global population is aging, osteoporosis has become a public health concern. Although drug treatments such as bisphosphonates and hormone replacement therapy are available, these options are limited by high costs and adverse side effects, highlighting the need for alternative approaches. The gut microbiota is a regulator of bone metabolism through its metabolites, effects on immune function and role in maintaining intestinal barrier integrity, endocrine signaling and nutrient absorption. Exercise, beyond its role in promoting bone strength through mechanical loading, enhances calcium absorption, thereby modulating gut microbiota composition. Within this context, exercise-based strategies may provide a promising avenue for both osteoporosis prevention and treatment by targeting the gut-bone axis, however, the underlying molecular mechanisms remain incompletely understood and additional clinical evidence is required. The present review summarizes how exercise-induced changes in gut microbiota may influence bone health, also discussing the relevance of these to the management of osteoporosis.

## Contents

1. Introduction
2. Gut microbiota

3. Gut microbiota and osteoporosis
4. Exercise-mediated regulation of gut microbiota
5. Potential role of exercise-mediated gut microbiota in improving bone metabolism
6. Conclusion

## 1. Introduction

Osteoporosis is a systemic skeletal disease characterized by decreased bone mass, degradation of bone microstructural integrity, increased bone fragility and a heightened risk of fracture (1). Its onset and progression are influenced by a range of factors, including genetic predisposition, sex, aging, physical inactivity and dietary deficiency, especially an inadequate intake of calcium and vitamin D (2,3). As global life expectancy is increasing, age-associated osteoporosis has become a growing public health concern (4,5).

Current treatment strategies primarily rely on pharmacological agents, such as bisphosphonates, calcitonin and selective estrogen receptor modulators (6,7). However, these therapies are often associated with high cost and marked side effects, leading to reduced patient adherence and limited long-term efficacy (8-10). Consequently, there is need to explore safer, more effective and economically viable alternative therapies, including non-pharmacological interventions such as exercise.

Gut microbiota are a key player in various metabolic disorders, including osteoporosis (11,12). Increasing evidence suggests that gut microbiota and its metabolites contribute to bone health through diverse mechanisms, including immune modulation, endocrine regulation and nutrient absorption (13,14). Notably, individuals with osteoporosis have distinct gut microbiota compositions compared with healthy controls (15) and microbial dysbiosis may disrupt host metabolism and immune homeostasis, which has a negative impact on bone turnover (16,17).

Interventions targeting the gut microbiota, including probiotic supplementation, microbial colonization and exercise, have promise in modulating bone health (18-22). In particular, exercise has been recognized for its ability to mitigate bone loss through by mechanical loading on the skeleton, thereby enhancing calcium absorption and regulating bone-associated signaling

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pathways (5,23-25). Attention has turned to the gut-bone axis, with studies suggesting that exercise-induced changes in gut microbiota may mediate part of these bone-protective effects (3,10,13,17,20,26).

Despite these advances, however, the underlying mechanisms that link gut microbiota, exercise and bone metabolism remain incompletely understood. Moreover, clinical and translational studies in this area are limited. The present review summarizes how exercise influences the gut microbiota, and how these changes affect bone metabolism, with the goals of informing future research and developing potential therapeutic strategies for osteoporosis. A conceptual overview of how different exercise modalities influence bone metabolism via the gut microbiota is shown in Fig. 1.

## 2. Gut microbiota

Gut microbiota constitute a complex and dynamic microbial ecosystem, comprising primarily bacteria alongside archaea, fungi, viruses and other microorganisms (27). Throughout human evolution, the gut microbiota has formed a mutually beneficial relationship with the host, serving essential roles in physiological processes, such as maintaining intestinal barrier integrity, regulating immune responses and contributing to metabolic functions (28,29).

The composition and function of the gut microbiota are influenced by internal and external factors, including diet, genetics, age, physical activity and exposure to environmental agents (30). Alterations in microbial composition, commonly referred to as 'dysbiosis', have been implicated in the pathogenesis of numerous types of disease, including neurodegenerative and metabolic disorders, as well as osteoporosis (31).

Exercise is a non-pharmacological intervention capable of modifying gut microbiota composition and diversity. Both aerobic and resistance training increase the abundance of health-promoting bacterial genera, including *Lactobacillus*, *Bifidobacterium* and *Akkermansia*, which reduces systemic inflammation (32,33). These findings suggested that exercise-induced modulation of the gut microbiota may serve as a key mechanism in the prevention and management of bone metabolic disorders.

*Composition and functions.* Gut microbiota is predominantly composed of five major bacterial phyla: Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria and Verrucomicrobia (34,35).

Firmicutes, which include the genera *Lactobacillus*, *Clostridium* and *Faecalibacterium*, are involved in carbohydrate fermentation, production of short-chain fatty acids (SCFAs) and immunomodulation (36). Bacteroidetes, featuring genera such as *Bacteroides* and *Prevotella*, are responsible for polysaccharide degradation, and contribute to energy extraction from dietary fiber (37). Proteobacteria, including families such as Enterobacteriaceae and Pseudomonadaceae, are involved in nitrogen cycling and oxidative stress regulation (38). Actinobacteria (especially the genus *Bifidobacterium*) are key probiotics that are known for their role in immune system development and vitamin production (39). Verrucomicrobia, primarily represented by the bacterium *Akkermansia muciniphila*, contribute to mucosal integrity and metabolic regulation (40).

Other gut residents include archaea, which mediate methane metabolism and modulate intestinal gas production, as well as fungi and viruses that maintain microecological balance and regulate bacterial dynamics via bacteriophage interactions (41-43).

Gut microbiota exerts physiological functions largely through the production of metabolites and interactions with host cells. SCFAs, including acetate, propionate and butyrate, which are derived from the fermentation of dietary fibers, serve key roles, modulating intestinal pH, suppressing pathogenic bacteria and maintaining epithelial integrity and immune balance (44). Certain gut microbiota species contribute to the biosynthesis of vitamins (for example, B vitamins and vitamin K) and regulate bile acid metabolism, thereby influencing lipid absorption and energy homeostasis (45). Furthermore, probiotics such as *Lactobacillus* and *Bifidobacterium* reinforce the mucosal immune barrier and suppress inflammatory cytokine production (46,47).

Exercise has been shown to exert a positive influence on gut microbiota composition and function: Voluntary wheel running in mice increases the numbers of SCFA-producing bacteria, whereas treadmill exercise in moderate treadmill exercise in Sprague-Dawley rats enhances epithelial barrier function and microbial diversity (48,49). Collectively, these findings support the role of physical activity as a key modulator of host-microbiota interactions.

*Gut microbiota and bone metabolism.* Accumulating evidence has suggested the gut microbiota serves a critical role in the regulation of bone metabolism, mediated via immune, metabolic and endocrine pathways (50-52). One mechanism involves the integrity of the intestinal barrier (53). Dysbiosis has been shown to increase intestinal permeability, facilitating the translocation of bacterial components, such as lipopolysaccharide (LPS), into systemic circulation (54). This activates immune responses, elevating the levels of circulating pro-inflammatory cytokines, including tumor necrosis factor (TNF)- $\alpha$ , IL-6 and IL-1 $\beta$ , which leads to the promotion of osteoclast differentiation and bone resorption (55,56). SCFAs, a major group of microbial metabolites, serve an important role in bone homeostasis. By acting through G protein-coupled receptors, SCFAs decrease inflammation, support intestinal integrity and promote osteoblast differentiation, while inhibiting osteoclastogenesis (57-60). The gut microbiota also regulates bone metabolism through endocrine and metabolic pathways. For example, bile acids, which serve metabolic roles, also act through receptors such as the farnesoid X receptor (FXR) and the G protein-coupled receptor TGR5, which are involved in endocrine signaling, which enhances osteoblast differentiation and mineralization (61,62). Furthermore, gut microbiota influence circulating levels of insulin-like growth factor-1 (IGF-1), a key hormone for bone formation and remodeling. Dysbiosis is associated with decreased expression of IGF-1, which impairs osteogenesis and contributes to bone loss (63).

A previous study (64) highlighted the role of gut microbiota in regulating bone marrow mesenchymal stem cells (BMSCs), which differentiate into osteoblasts, adipocytes or chondrocytes. Dysbiosis-induced oxidative stress has also been shown to promote premature senescence and the

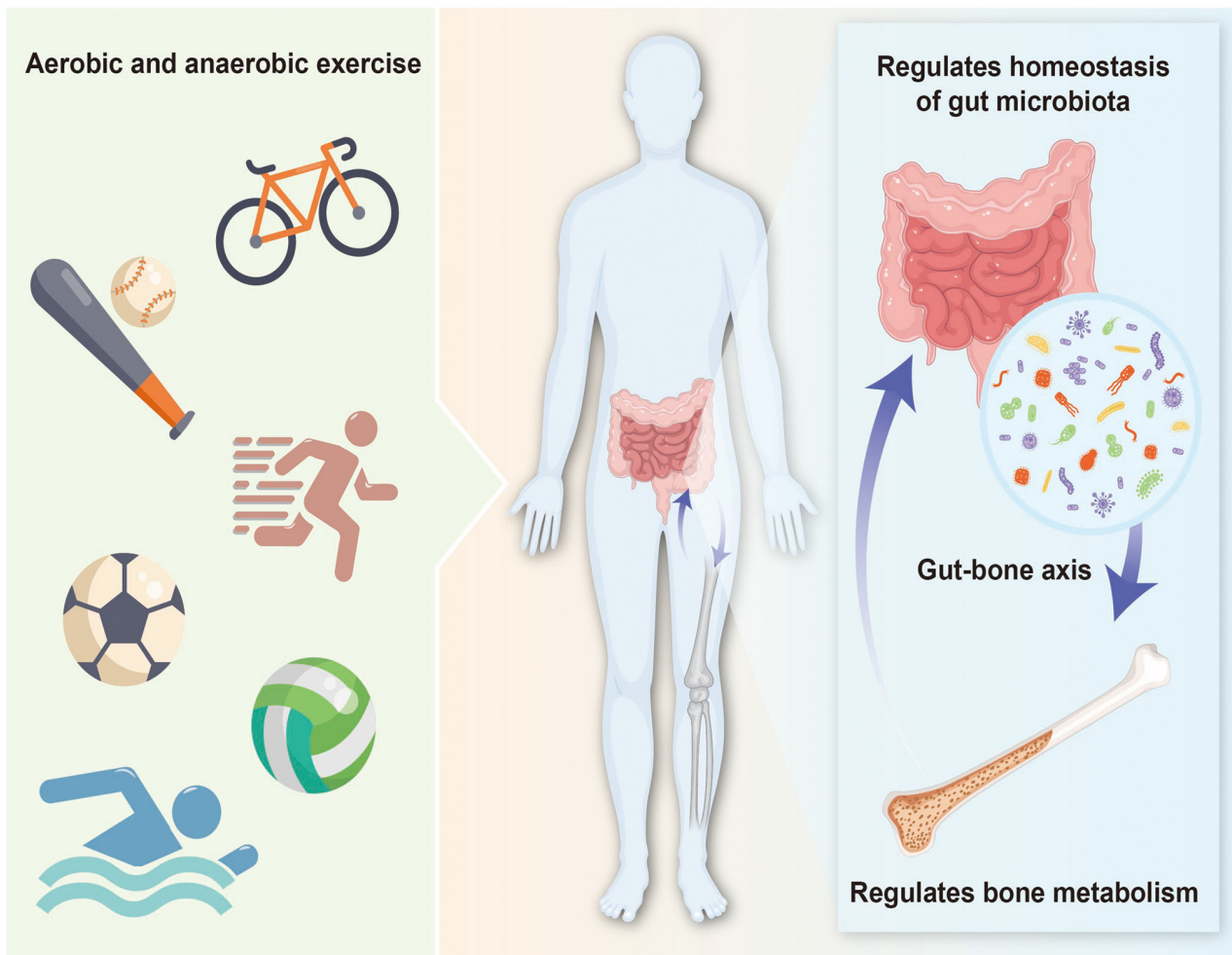


Figure 1. Aerobic and anaerobic exercise modulate the gut-bone axis. Based on the gut-bone axis, different exercise modalities regulate bone metabolism by modulating gut microbiota composition and promoting beneficial bacterial proliferation.

adipogenic differentiation of BMSCs, thereby inhibiting bone formation (65,66).

In addition, the gut microbiota modulates immune cell subsets involved in bone remodeling, especially regulatory T cells (Tregs) and T helper 17 (Th17) cells. Tregs secrete anti-inflammatory cytokines that suppress osteoclast activity, whereas Th17 cells release pro-inflammatory mediators that promote osteoclastogenesis. An imbalance in the Treg/Th17 ratio, typically associated with gut microbiota dysbiosis, may therefore disrupt bone homeostasis (67-69). Exercise may help to restore this balance, both by enhancing gut microbiota diversity and SCFA production, thereby improving barrier function, and by modulating the immune system. Mechanistically, exercise-induced mechanical loading has been shown to activate key osteogenic signaling pathways, including the Wnt/ $\beta$ -catenin and morphogenetic protein (BMP)/Smad signaling pathways, which promote osteoblast differentiation and bone formation (24). Additionally, exercise upregulates the expression of IGF-1 and activates the PI3K/Akt and MAPK/ERK pathways, enhancing osteoblast proliferation and activity (63,70). Through gut microbiota-mediated mechanisms, exercise has also been shown to increase levels of circulating SCFAs, which activates signaling pathways mediated via the G protein-coupled receptors GPR41 and

GPR43 (60), whereas secondary bile acids produced by gut microbes activate TGR5- and FXR-mediated signaling pathways; all of these effects contribute to enhanced osteoblast function and bone mineralization (61,62,71-73). Collectively, these findings demonstrate that regular physical activity supports bone health through integrated direct mechanical and gut microbiota-mediated endocrine mechanisms.

The gut microbiota contributes to bone metabolism by regulating immune responses, producing key metabolites and influencing endocrine factors. Specifically, microbiota-derived SCFAs modulate the Treg/Th17 cell balance to suppress osteoclastogenesis via the osteoprotegerin/receptor activator for nuclear factor  $\kappa$ B ligand (RANKL) signaling pathway (67,74,75), while also activating GPR41/GPR43 signaling to inhibit bone resorption (59,60). Secondary bile acids promote osteoblast differentiation through the TGR5 and FXR (61,62,71,72), and microbial regulation of IGF-1 enhances bone formation via the PI3K/Akt and MAPK/ERK signaling pathways (63,70). These mechanisms highlight the key role of gut microbiota in maintaining bone homeostasis.

*Key microbial metabolite signaling pathways in bone remodeling.* Mounting evidence has demonstrated that the gut microbiota shapes bone metabolism through intertwined

immune, endocrine and metabolic pathways (13,14). Alterations in microbial composition and metabolite production influence the differentiation and activity of both osteoclasts and osteoblasts, thereby modulating skeletal homeostasis. Within the framework of the gut-bone axis, several molecular routes have been identified via which gut-derived signals affect bone remodeling. Among these, the LPS/NF- $\kappa$ B osteoclast and SCFA GPR41/43 osteoblast signaling pathways are the most extensively characterized, representing key links between microbial metabolism and bone physiology (76-84).

**LPS NF- $\kappa$ B osteoclast pathway.** Microbial dysbiosis compromises intestinal barrier integrity, thereby permitting LPS from Gram-negative bacteria to enter circulation. LPS engages toll-like receptor 4 (TLR4) on immune and bone marrow-derived precursor cells, thereby activating NF- $\kappa$ B signaling and inducing pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 (55,56,76). These cytokines upregulate RANKL expression, which drives osteoclast differentiation, resulting in excessive bone resorption and microarchitectural deterioration (76-81). Sustained NF- $\kappa$ B activation amplifies inflammatory osteolysis. On the other hand, probiotics, natural compounds (such as quercetin and chondroitin sulfate) and moderate exercise restore barrier integrity, suppressing LPS-induced osteoclastogenesis (82-84). This inflammatory cascade constitutes a principal mechanism by which gut microbial imbalance contributes to osteoporosis progression.

**SCFA GPR41/43 osteoblast pathway.** By contrast with the pro-resorptive effects of LPS, SCFAs exert bone-protective effects. SCFAs enhance intestinal barrier integrity and enter the systemic circulation, where they activate GPR41 and GPR43 on osteoblasts and their precursors (67,85,86). This promotes osteoblast differentiation, mineralization and bone formation. Concurrently, SCFAs inhibit osteoclastogenesis by modulating immune responses, such as promoting Treg function and suppressing pro-inflammatory signaling pathways (60,85,87). Furthermore, SCFAs influence systemic endocrine factors, including IGF-1, thereby supporting osteoblast activity (88-94). Dietary interventions that increase SCFA levels, such as high fiber intake or specific probiotics, have also been demonstrated to support bone mass accrual and mitigate bone loss (3,95-97). This pathway underscores the beneficial role of specific microbial metabolites in maintaining bone anabolism.

Considered together, the LPS/NF- $\kappa$ B and SCFA/GPR41/43 pathways illustrate how inflammatory and anabolic signals originating from the gut microbiota converge within the bone microenvironment to orchestrate remodeling balance. These interconnected mechanisms highlight the integrative role of microbial metabolites in coupling immune and metabolic homeostasis with skeletal function, and form the molecular foundation of the gut-bone signaling axis by which intestinal microbiota dynamically influence bone health and disease.

### 3. Gut microbiota and osteoporosis

A growing body of evidence demonstrates the association between gut microbiota and osteoporosis (22,98-100). Recent findings have proposed that changes in the diversity, structure and metabolites produced by gut microbial communities,

including trimethylamine N-oxide (TMAO) and bile acids, have potential both as diagnostic biomarkers for osteoporosis and as indicators of disease severity (22,99,100). Due to its key role in the pathogenesis of osteoporosis, the gut microbiota has emerged as a promising therapeutic target.

**Diagnostic role of gut microbiota in osteoporosis.** The composition of the gut microbiota and its metabolites impact osteoporosis, serving as potential diagnostic and prognostic indicators. Although regional variations exist, previous studies have shown distinct bacterial profiles in patients with osteoporosis, with certain beneficial taxa (*Lactobacillus*, *Ruminococcus* and *Bacteroides*) typically reduced, while changes in broader groups such as Firmicutes are more variable and context-dependent (22). Beneficial gut microbes, especially those that produce SCFAs, have a positive association with bone quality (101). In metabolic terms, elevated levels of TMAO in postmenopausal patients contribute to an increased susceptibility to osteoporosis and fracture risk (102), whereas higher levels of bile acids improve bone mineral content and decrease bone degradation (as determined by the  $\beta$ -C-terminal telopeptide of type I collagen ( $\beta$ -CTX) test) (103). These gut-derived factors represent crucial elements in the gut-bone axis, offering therapeutic avenues for osteoporosis.

Estrogen deficiency has been shown to both induce gut microbiota dysbiosis and increase intestinal permeability, thereby promoting osteoclast differentiation through upregulated cytokine secretion, leading to bone loss (104). This mechanism involves gut microbiota-mediated systemic inflammation, as evidenced by the prevention of bone loss following antibiotic treatment (104). Germ-free and strain-supplemented mouse models demonstrate the key role of gut microbiota in skeletal development (105-107). Compared with conventional mice, germ-free mice exhibit impaired bone development and decreased bone mass. However, supplementation with specific probiotic strains such as *Lactobacillus*, or fecal microbiota transplantation, restores normal bone metabolism and promote skeletal development. Although studies have reported inconsistent results, potentially due to methodological differences, the majority of the accrued evidence has confirmed that a stable gut microbiota is key for normal bone homeostasis, highlighting the importance of microbial composition in regulating the gut-bone axis (22,101-107).

Variations in microbial populations, including those of *Lactobacillus* and *Ruminococcus*, and metabolites such as SCFAs, bile acids and TMAO, are associated with osteoclast activity, bone mineral density and turnover biomarkers. Profiling gut microbiota and metabolites may serve as a diagnostic strategy for osteoporosis risk assessment, however, methodological inconsistencies necessitate further multi-omics studies to clarify the underlying mechanisms and validate clinical utility (22,101-107).

**Therapeutic role of the gut microbiota in osteoporosis.** Bone metabolic homeostasis relies on a coordinated equilibrium between osteoblast-mediated bone formation and osteoclast-driven bone degradation, and this is regulated by endocrine mediators such as estrogen, vitamin D, parathyroid hormone and inflammatory cytokines. An imbalance, characterized by increased osteoclast activity relative to osteoblast

function, accelerates bone resorption, consequently leading to osteoporosis (2). Gut microbiota regulate bone homeostasis through specific pathways: The LPS-NF- $\kappa$ B axis promotes osteoclastogenesis (76), whereas the SCFA-GPR41/43 axis enhances osteoblast activity and inhibits osteoclastogenesis (59,60). Additional mechanisms exist, which involve bile acids activating TGR5/FXR to stimulate osteoblast differentiation (61,62,71-73), and TMAO promoting osteoclastogenesis via the NF- $\kappa$ B signaling pathway (78-80,108). Gut microbiota dysbiosis impairs BMSC osteogenic potential through oxidative stress (109), whereas probiotics restore BMSC function (110). Gut microbiota and their metabolites influence osteoporosis progression by regulating the differentiation, proliferation and apoptosis of osteoblasts, osteoclasts and BMSCs (108-111).

**Gut microbiota and osteoclasts.** Gut microbiota dysbiosis promotes osteoclastogenesis through an increase in levels of harmful metabolites, including LPS and TMAO, which activate NF- $\kappa$ B signaling to drive osteoclast differentiation and bone resorption. Multiple interventions have demonstrated therapeutic potential in terms of suppressing osteoclast activity through distinct mechanisms (75-77,111). For example, quercetin and *Inonotus hispidus* polypeptide restore gut barrier integrity and suppress NF- $\kappa$ B activation, thereby mitigating osteoclast formation (82,84,111), whereas chondroitin sulfate, bone-strengthening granules and milk-derived extracellular vesicles increase SCFA production and rebalance the Treg/Th17 cell immune responses to inhibit osteoclast activity (75,83). These findings establish the gut-bone axis as a key regulatory pathway, where microbial metabolites differentially modulate osteoclast function. Therefore, gut microbial metabolites such as LPS and TMAO promote osteoclastogenesis and bone loss, whereas SCFAs counteract these effects through immunomodulation and the suppression of bone resorption. Therapeutic strategies that target the microbiota-metabolite axis may effectively ameliorate osteoporotic processes. Collectively, these findings highlight gut microbiota and SCFAs as critical regulators of bone-immune crosstalk, rendering them potential therapeutic targets for osteoporosis. A summary of the interventions targeting osteoclasts via the gut microbiota is shown in Table I.

**Gut microbiota and osteoblasts.** Gut microbiota influences osteoblast function through multiple pathways where an impaired intestinal barrier permits LPS translocation that inhibits bone formation, whereas gut microbiota dysbiosis dysregulate the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol levels that negatively impact osteoblast activity (112,113). Various interventions demonstrate osteogenic potential through modulation of the gut microbiota: Cinnamic acid increases microbial diversity and upregulates osteoblast-specific transcription factors through BMP/TGF- $\beta$  signaling pathway activation (114,115). Furthermore, SCFAs, notably butyrate, enhance osteoblast differentiation and function by activating the SCFA-GPR41/43 signaling axis and downstream pathways, such as the Wnt/ $\beta$ -catenin pathway, which collectively promote bone formation (87,116-118). By contrast, gut microbiota dysbiosis disrupts serotonin metabolism, elevating bone resorption, whereas inhibition of gut tryptophan hydroxylase 1 decreases levels of 5-hydroxytryptamine and promotes bone formation (119). Collectively,

these mechanisms establish the gut-bone axis as essential for maintaining osteoblast function.

In summary, gut microbiota and their metabolites regulate osteoblast differentiation and survival through inflammatory, endocrine and signaling pathways (Table II). Dysbiosis disrupts these processes, whereas restoration of the microbial balance promotes bone formation. These findings underscore the gut-bone axis as a key target for osteoporosis prevention and therapy.

**Gut microbiota and BMSCs.** BMSCs differentiate into multiple lineages, including osteoblasts, and their migration is key for bone remodeling and regeneration (120,121). Under hypoxic conditions, the adaptation of BMSCs occurs via hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) activation and exosome secretion, which modulates gut microbiota and systemic inflammation, alleviating osteopenia (122). HIF-1 $\alpha$  promotes glycolysis and angiogenesis, whereas exosomes deliver regulatory microRNAs to intestinal cells, thereby influencing microbial composition and metabolic activity. On the other hand, dysbiosis and excessive levels of TMAO activate NF- $\kappa$ B signaling, induce oxidative stress, promote premature senescence and impair osteogenic differentiation (109). Furthermore, *Lactobacillus animalis*-derived extracellular vesicles stimulate angiogenesis, enhance BMSC osteogenic differentiation and inhibit osteoblast apoptosis (110), whereas Taohong Siwu decoction was demonstrated to both regulate gut microbiota and activate osteogenic pathways (123). Collectively, these findings underscore gut microbiota modulation as a promising strategy against osteoporosis.

In summary, gut microbiota and metabolites influence BMSC function, with dysbiosis promoting senescence and impairing osteogenesis. Interventions such as probiotic vesicles and herbal formulations restore microbial balance and enhance bone formation. Maintaining gut microbiota homeostasis and regulating microbial metabolites preserve BMSC osteogenic potential, inhibit senescence and improve bone remodeling, underscoring the gut-bone axis as a promising therapeutic target. The interplay between gut microbiota, their metabolites and bone cell activity is illustrated in Fig. 2.

#### 4. Exercise-mediated regulation of gut microbiota

Aerobic and resistance exercise reshape the gut microbiota by enhancing its  $\alpha$ -diversity and enriching the relative abundance of beneficial bacterial genera such as *Lactobacillus*, *Bifidobacterium*, and *Akkermansia*. This exercise-induced microbial shift promotes the production of key metabolites like short-chain fatty acids (SCFAs), thereby supporting microbiota-mediated metabolic functions and contributing to host bone health through the gut-bone axis (124-145).

**Impact of aerobic exercise on gut microbiota.** Aerobic exercise exerts beneficial effects on gut microbiota composition and host health. Short-term voluntary wheel running significantly increase the abundance of *Lactobacillus* and *Bifidobacterium* and intestinal butyrate concentrations in mice (124). Subsequently, longer interventions, including treadmill or jump rope exercise, enhance microbial diversity, enrich beneficial taxa such as Firmicutes, Lachnospiraceae, *Butyrivimonas*, *Prevotella*, *Akkermansia* and SCFA-producing

Table I. Effects of different intervention measures on gut microbiota regulation of osteoclasts.

Intervention	Research subjects	Intervention duration	Research outcomes	(Refs.)
mEVs	OVX mice	8 weeks	Reshapes gut microbiota, boosts SCFAs, decreases proinflammatory cytokines and osteoclastogenic factors, thereby suppressing osteoclastogenesis	(60)
Jiangu granule	OVX rats	12 weeks	Promotes SCFA secretion, modulates Treg/Th17 balance, alters bone immune-related cytokine expression and inhibits osteoclastogenesis	(68)
High-level TMAO	C57BL/6 mice	4 days	Induces OS and exacerbates inflammatory responses, upregulates the expression of osteoclast proteins such as CTR and TRAF6 and exacerbates bone loss	(73)
Que	OVX rats	6 weeks	Regulate gut microbiota, enhance intestinal barrier, suppress LPS-induced inflammation and osteoclastogenesis, and ameliorate bone loss in castrated rats	(75)
CS	WFW rats	12 weeks	Increases gut Bifidobacterium abundance, restores microbiota homeostasis, elevates SCFAs and delays osteoclastogenesis.	(76)
LGG	OVX rats	6 weeks	Elevates the Firmicutes/Bacteroidetes ratio and gut microbiota diversity, improves Th17/Treg balance and thereby inhibits osteoclastogenesis	(79)
Baicalin	AP mice	13 weeks	Regulates gut microbiota homeostasis, enriches beneficial bacteria, promotes SCFA-producing bacteria and suppresses osteoclast activity	(80)
Gold nanospheres	OVX mice	8 weeks	Restores gut microbiota homeostasis, modulates the gut microbiota-TMAO balance and mitigates estrogen deficiency-induced bone loss	(91)
IHP	PD rats	6 weeks	Activation of the $\beta$ -catenin/NF- $\kappa$ B pathway attenuates inflammation, modulates gut microbiota, and suppresses osteoclastogenesis, thereby protecting against LPS-induced bone destruction	(102)

Que, quercetin; OVX, ovariectomized; LPS, lipopolysaccharides; IHP, *Inonotus hispidus* polypeptide; PD, periodontitis; CS, chondroitin sulfate; OS, oxidative stress; CTR, calcitonin receptor; TRAF6, tumor necrosis factor receptor-associated protein 6; WFW, weaned female Wistar; SCFA, short-chain fatty acid; Treg, regulatory T cell; Th17, T helper 17; mEV, milk-derived extracellular vesicle; LGG, *Lactobacillus rhamnosus* GG; AP, aging-periodontitis; TMAO, trimethylamine N-oxide; AP, aging periodontitis.

Table II. Role of gut microbiota and their metabolites in regulating osteoblasts.

Component	Signaling pathway	Functional effects	(Refs.)
Gut microbiota	NF- $\kappa$ B	Promotes osteoblast differentiation	(89)
	BMP/TGF- $\beta$ /Runx2	Promotes osteoblast differentiation	(94)
	SCFA/GPR41/IGF-1	Improves osteoblast function	(95)
Butyrate	5-HT	Prevents bone loss	(98)
	Wnt/ $\beta$ -catenin	Promotes osteoblast differentiation	(99)
	Treg-gp/ $\beta$ -catenin	Promotes osteoblast differentiation	(100)
Bile acid	GPR5 and FXR	Decreases estrogen-dependent bone loss in mice	(101)
	GPR5/Runx2/OCN	Promotes bone formation	(102)
	FXR/ERK/ $\beta$ -cat	Promotes osteoblast differentiation	(103)

BMP/TGF- $\beta$ /Runx2, bone morphogenetic protein/transforming growth factor  $\beta$ /osteoblast-specific transcription factor; SCFA/GPR41/IGF-1, short-chain fatty acid/G protein-coupled receptor 41/insulin-like growth factor 1; HT, 5-hydroxytryptamine; Treg-gp- $\beta$ -cat, regulatory T cell-secreted glycoprotein-catenin; FXR, farnesoid X receptor; OCN, osteocalcin.

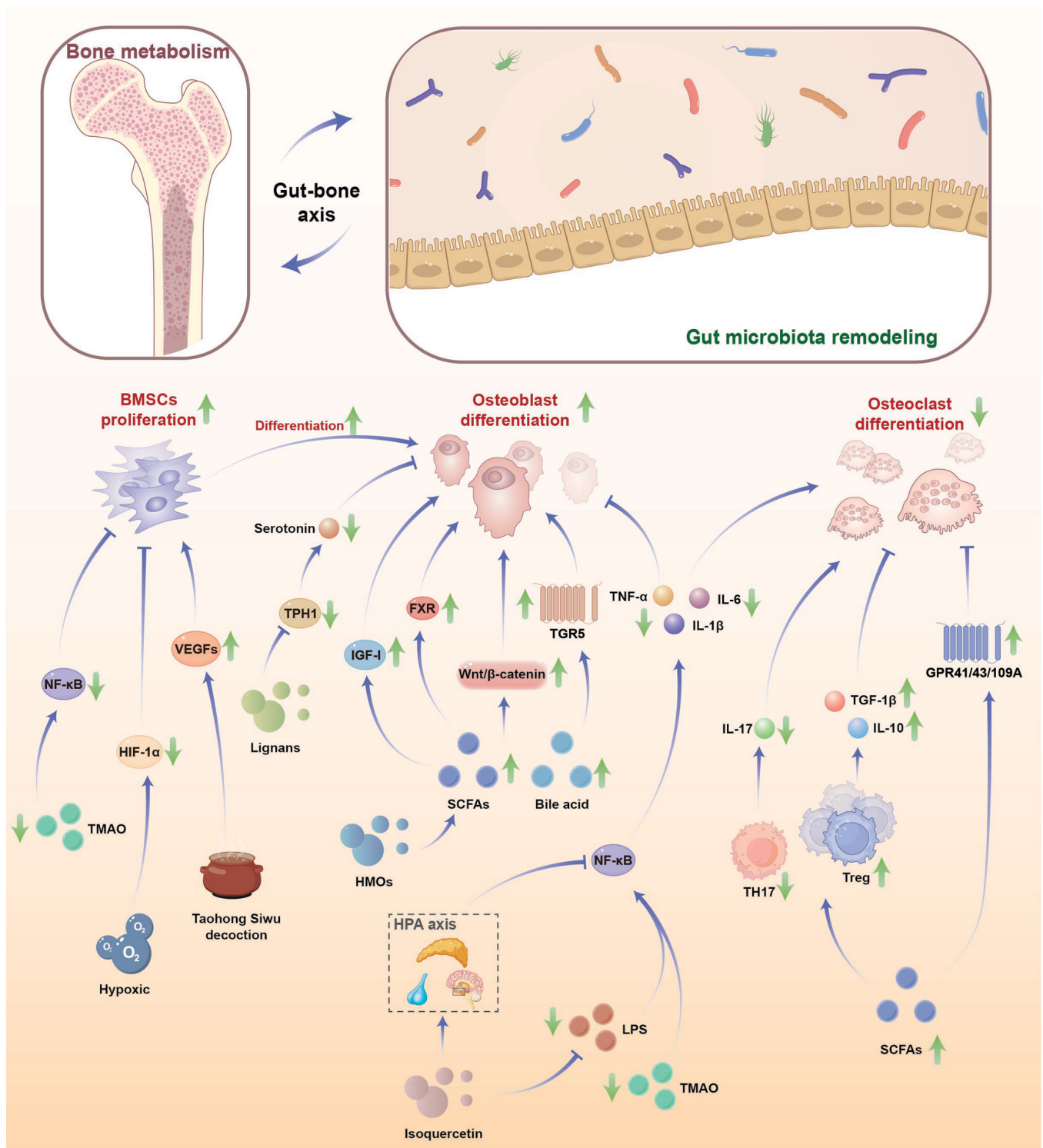


Figure 2. Therapeutic effects of gut microbiota in osteoporosis. SCFAs activate GPCR 41/43/109A, modulating the balance of Treg/Th17 and their associated cytokine IL-17, thereby regulating osteoclast differentiation. Dysbiosis of the gut microbiota leads to elevated levels of LPS and TMAO, which upregulate the NF-κB signaling and the secretion of inflammatory cytokines such as TNF-α, exacerbating OS and promoting osteoclast formation. Isoquercetin inhibits the NF-κB signaling pathway, modulating the expression of inflammatory signaling pathways and abnormal cortisol release induced by gut microbiota dysbiosis, thereby suppressing osteoblast apoptosis and promoting osteoblast differentiation. SCFAs produced by probiotic metabolism stimulate the synthesis of IGF-I through the enterohepatic circulation, forming an HMO-SCFA-IGF-I regulatory axis that promotes osteoblast differentiation. Bile acids and SCFAs activate the Wnt/β-catenin signaling pathway in osteoblasts, upregulating FXR and TGR5, thereby promoting osteoblast differentiation and preventing bone loss. Lignans inhibit serotonin synthesis by suppressing the intestinal-specific TPH1 and modulating the composition of the gut microbiota, thereby indirectly exerting skeletal protective effects. Chronic hypoxia downregulates HIF-α expression, diminishes gut microbial diversity and the abundance of *Lactobacillus* in the intestinal tract, intensifies OS and induces premature senescence in BMSCs. Taohong Siwu decoction promotes the development and differentiation of BMSCs by regulating the structure and function of the gut microbiota and upregulating the secretion of VEGFs. TMAO inhibits the osteogenic differentiation of BMSCs. SCFA, short-chain fatty acid; GPCR, G protein-coupled receptor; Treg, regulatory T cell; Th, T helper cell; LPS, lipopolysaccharide; TMAO, trimethylamine N-oxide; OS, oxidative stress; IGF, insulin-like growth factor; HMO, human milk oligosaccharide; FXR, farnesoid X receptor; TGR5, Takeda G protein-coupled receptor 5; TPH, tryptophan hydroxylase; HIF, hypoxia-inducible factor; BMSC, bone marrow-derived mesenchymal stem cell; HPA, hypothalamic-pituitary-adrenal axis.

bacteria, and modulate metabolites including L-citrulline and L-arginine, thereby promoting bone formation and metabolic health (125-129). In addition, human studies have corroborated these findings: Positive correlations were identified between cardiopulmonary fitness and microbiota diversity, with exercise increasing the numbers of Roseburia, Lactobacillaceae and Erysipelotrichaceae bacteria, while also improving insulin sensitivity, decreasing endotoxemia and preventing bone loss via microbiota-mediated mechanisms (130-134). Exercise-induced microbial alterations are dynamic, typically being reversed upon the cessation of activity, and this may vary with age, hormonal status and intervention type (131,135,136). These findings suggest that aerobic exercise promotes host health, bone metabolism by remodeling gut microbiota, highlighting its critical role in the gut-bone axis.

*Impact of anaerobic exercise on gut microbiota.* Anaerobic exercise, including resistance training and high-intensity interval training (HIIT), has been shown to significantly modulate gut microbiota diversity and function (137-144). Interventions over a period of 12 weeks enhance microbial  $\alpha$ -diversity, also adjusting the ratio of Bacteroides/Firmicutes bacteria and protecting intestinal integrity, although the effects vary according to genotype, obesity and metabolic status (137-139). In addition, human studies have confirmed that resistance training and combined HIIT improve the microbiota composition, with synergistic responses observed between bacterial and fungal communities (140,141). Furthermore, shorter or more moderate intervention yields limited effects, highlighting the importance of exercise duration and individual factors, such as baseline fitness status, body composition, age, sex and underlying metabolic conditions (142-144).

In summary, anaerobic exercise, including resistance training and HIIT, modulates gut microbiota diversity and improves beneficial microbial populations, with fungi potentially serving as biomarkers; these microbiota-mediated effects may support metabolic and bone health via the gut-bone axis.

*Translational and clinical evidence in humans.* Evidence from human studies provides support for the exercise-mediated gut-bone axis (132-134). Observational studies consistently demonstrate distinct gut microbial profiles in physically active individuals, with athletes showing enhanced microbial diversity and abundance of beneficial taxa such as Akkermansia and Faecalibacterium (132,145). Cardiorespiratory fitness levels are strongly and positively correlated with gut microbial diversity and SCFA production capacity across various populations (130). Intervention studies have further substantiated these findings, revealing that structured aerobic and resistance training regimens notably modify gut microbiota composition (129,140). These exercise-induced changes are characterized by an increased abundance of SCFA-producing bacteria and a decrease in pro-inflammatory taxa. Moreover, the observed microbial alterations are associated with improved metabolic parameters, including enhanced insulin sensitivity and decreased systemic inflammation, both of which are key mediators of bone metabolism (133,134). However, the extent to which these modifications occur may be influenced by individual characteristics, such as baseline fitness status and dietary patterns (146).

Although available evidence has established an exercise-microbiota connection in humans, only limited evidence directly demonstrates its bone-protective effects (129,146). Future longitudinal studies designed to track the complete pathway, from exercise intervention, through microbial changes, to bone health outcomes, are essential to validate the therapeutic potential of the gut-bone axis in humans.

## **5. Potential role of exercise-mediated gut microbiota in improving bone metabolism**

Regular exercise benefit skeletal health. A number of studies have shown that exercise leads to an improvement in bone health that is mediated via relevant signaling pathways, including NF- $\kappa$ B, apelin, AMPK, bile acid/SCFA-mediated, leptin/ghrelin/estrogen hormonal and Treg/Th17 immunoregulatory pathways, and various effects have been observed, including regulating the gut microbiota to inhibit osteocyte apoptosis, suppressing osteoclast differentiation, promoting osteoblast differentiation and modulating osteocyte nutrient metabolism (147-175). The potential mechanisms by which exercise-mediated changes in gut microbiota may improve bone metabolism are shown in Fig. 3 and Table III.

*Exercise modulates gut microbiota to inhibit osteocyte apoptosis.* Osteocyte apoptosis contributes to bone metabolic imbalance and osteoporosis, making inhibition of apoptosis key for bone health. Probiotics-fermented dairy products regulate gut microbiota, reduce serum LPS levels and normalize both NF- $\kappa$ B signaling and osteocyte apoptosis that is associated with gene expression (Bcl-2, Bax, Caspase-3), thereby mitigating osteoporosis (147). Exercise similarly modulates the gut microbiota, eliciting a range of effects, including enhancing intestinal barrier integrity, accelerating LPS clearance and suppressing the LPS/TLR4/NF- $\kappa$ B inflammatory signaling cascade, which decreases oxidative stress and osteocyte apoptosis (84,148). Furthermore, voluntary wheel running and high-intensity exercise increase the abundance of beneficial microbes such as Lactobacillus and Bifidobacterium, stabilize microbial homeostasis and enhance enzymatic and non-enzymatic antioxidant levels, collectively alleviating oxidative stress and protecting bone tissue (149-152). Therefore, exercise and probiotics decrease osteocyte apoptosis by modulating gut microbiota, thereby suppressing LPS-induced inflammation and oxidative stress. Taken together, these findings suggest that aerobic and high-intensity exercise attenuate osteocyte apoptosis via gut microbiota modulation, improving redox balance and inflammatory regulation. Although the majority of the studies that have been performed to date are preclinical, they highlight the gut-bone axis as a mechanistic pathway through which exercise supports bone health, thereby providing a promising strategy for osteoporosis prevention and therapy (84,148).

*Exercise-mediated regulation of gut microbiota to inhibit osteoclast differentiation.* Inhibiting osteoclast proliferation and differentiation is key for reducing bone resorption and preventing osteoporosis (153). Exercise modulates gut microbiota to achieve this effect through multiple mechanisms. Desai *et al* (154) found that the combination of specific

Table III. Potential role of exercise in mediating gut microbiota to improve osteoporosis.

Exercise mode	Subject	Intervention duration	Effects	(Refs.)
Treadmill exercise	Mice	8 weeks	Increases the abundance of the Firmicutes, promoting the accumulation of bile acid metabolites, thereby activating the APL signaling pathway, enhances osteogenic differentiation; and inhibits fat generation	(19)
Wheel running	Mice	4 weeks	Decreases the activation of LPS-TLR4/NF-κB inflammation pathway, alleviates obesity induced osteoarthritis and improves gut microbiota in mice	(77)
Walking	Postmenopausal patients	6 months	Improves menopause-induced bone loss by modulating gut microbiota metabolite equol	(125)
Wheel running	Mice	14 weeks	Alters GM homeostasis, while increasing BM, improving bone mechanical properties and decreasing BM	(145)
Aerobic exercise	Mice	8 weeks	Upregulates insulin sensitivity, downregulates serum leptin and endotoxin levels and improves gut microbiota dysbiosis and osteoarthritis induced by obesity	(152)
Resistance exercise	Postmenopausal patients	12 weeks	Promotes intestinal calcium absorption, increases gut microbiota diversity and improves bone health.	(159)

LPS/TLR4, lipopolysaccharide/toll-like receptor 4; APL, apelin; GM, gut microbiota; BM, bone mass.

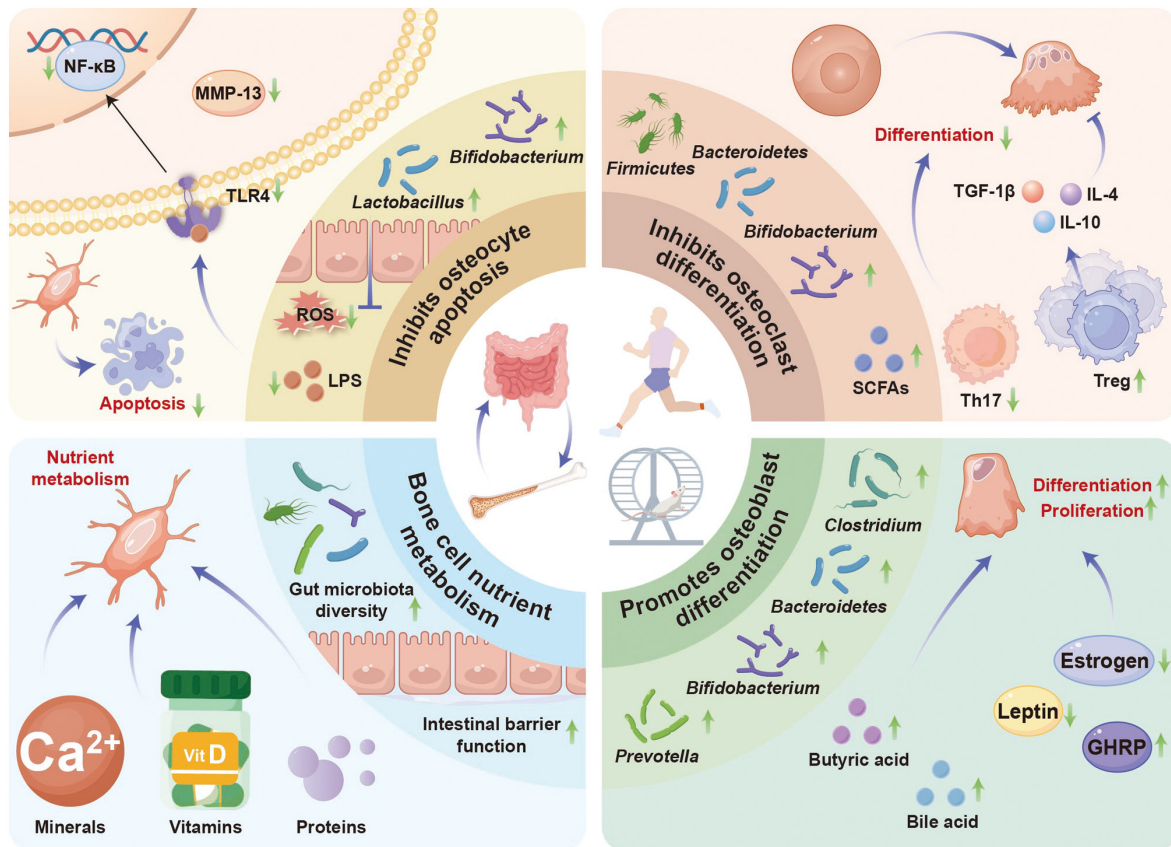


Figure 3. Potential mechanisms of exercise-mediated gut microbiota in improving bone metabolism. Exercise enhances the abundance of probiotics such as *Lactobacillus* and *Bifidobacterium*, downregulates the LPS/TLR4/NF-κB inflammatory signaling pathway and MMP-13 expression, thereby inhibiting osteocyte apoptosis. Furthermore, exercise decreases the Firmicutes/Bacteroidetes ratio, upregulates SCFA levels, suppresses Th17 cell differentiation while increasing Treg populations and promotes secretion of IL-4, IL-10 and TGF-β1, collectively inhibiting osteoclastogenesis. Additionally, exercise-mediated gut microbiota modulation exerts an effect on hormone secretion, including estrogen, leptin and ghrelin, thereby facilitating osteoblast differentiation. Exercise also increases microbial diversity, improves intestinal barrier function and enhances absorption of proteins, minerals and vitamins by bone cells, ultimately promoting skeletal health. LPS, lipopolysaccharide; TLR, toll-like receptor; SCFA, short-chain fatty acid; Th, T helper; Treg, regulatory T cell; ROS, reactive oxygen species; GHRP, growth hormone secretagogue receptor ligand.

cyclooxygenase-2 inhibitors and loaded exercise decreases joint swelling in arthritis without interfering with the bone-protective effects of loaded exercise, although this does not directly inhibit osteoclast activity or number. In other studies, resistance training suppressed osteoclast activation via the inhibition of tartrate-resistant acid phosphatase and modulation of the Fos/Fosb and calcitonin receptor pathways (155), whereas voluntary wheel running was shown to decrease the ratio of Firmicutes/Bacteroidetes bacteria, enrich the population of Bifidobacteriaceae and enhance bone biomechanical properties (156,157). In addition, exercise regulates the Treg/Th17 cell balance through multiple molecular and immunological mechanisms. Physical activity increases the numbers of circulating SCFAs, especially butyrate, which promote Treg differentiation through histone deacetylase inhibition and GPR43 signaling (74,158). Concurrently, exercise decreases the populations of pro-inflammatory cytokines, including IL-6 and IL-23, thereby suppressing Th17 cell differentiation (74,159). Additionally, exercise-induced metabolic adaptations enhance mitochondrial function in T cells, favoring Treg development over Th17 lineage commitment through AMPK-mediated metabolic reprogramming (159). These coordinated mechanisms contribute to the maintenance of immune homeostasis and bone health. Simultaneously, exercise promotes osteoblast differentiation by enhancing bile acid and butyrate production, modulating hormone secretion (for example, leptin, ghrelin and estrogen), and activating signaling pathways, such as the apelin signaling pathway (134,160-167).

In summary, exercise modulates gut microbiota to suppress osteoclastogenesis and promote osteoblast activity through immunomodulatory, metabolic and endocrine signaling pathways. Diverse exercise modalities simultaneously inhibit osteoclast differentiation and promote osteoblast activity, mediated via the gut microbiota-mediated modulation of immune, endocrine and metabolic pathways. These findings underscore the gut-bone axis as a key therapeutic target for osteoporosis prevention.

*Exercise-modulated gut microbiota promotes osteoblast differentiation.* Exercise has been shown to modulate gut microbial homeostasis and endocrine hormone secretion, thereby activating osteoblast functions and promoting proliferation (124,160-167). A 6-month walking intervention combined with isoflavone supplementation in postmenopausal patients was found to improve their body composition, lipid metabolism and osteoblast activity (133,160,161). In ovariectomized mice, 8 weeks of treadmill exercise was shown to increase the abundance of Firmicutes bacteria and levels of bile acid metabolites and to activate the apelin signaling pathway, collectively enhancing osteoblast differentiation while suppressing adipocyte formation (20). Aerobic exercise regulates leptin, ghrelin and estrogen levels, thereby restoring gut microbiota equilibrium, improving insulin sensitivity and decreasing endotoxin levels, which all contribute to bone and metabolic health (124,162,163). Microbial metabolites, including bile acids and butyrate, are also enriched by exercise; this stimulates osteoblast differentiation through SCFA-producing bacteria such as Ruminococcus and Akkermansia (131,164-167).

In summary, exercise modulates gut microbiota composition and endocrine function, thereby enhancing osteoblast activity and bone formation. Through interventions such as walking and treadmill running, exercise increases the levels of beneficial microbial metabolites such as bile acids and SCFAs, which activate osteogenic signaling pathways and suppress adipogenesis. Collectively, these findings underscore the role of exercise-induced gut microbiota modulation in promoting osteoblast differentiation, highlighting the gut-bone axis as a key mediator of skeletal health.

*Exercise-mediated regulation of gut microbiota to regulate bone cell nutrient metabolism.* Adequate intake of vitamin D and calcium is key for skeletal integrity, whereas deficiencies impair bone growth and development (168). Exercise modulates gut microbiota composition, strengthens the intestinal barrier and optimizes nutrient absorption, which is critical for osteogenesis (169). Furthermore, resistance training combined with synbiotic supplementation increases microbiota diversity, enhances SCFA production, improves immune regulation and promotes calcium uptake, thereby benefiting bone health (170). In addition, prolonged moderate-intensity treadmill or swimming exercise improves the gut microbial balance, thereby upregulating antimicrobial peptides and tight junction proteins, decreasing inflammation and mitigating intestinal barrier damage caused by high-fat diet or stress (129,171,172). SCFAs, secretion of which is promoted by exercise, increase the rate of calcium absorption by bone (132,173,174).

In summary, exercise enhances gut barrier integrity and microbiota diversity, thereby improving the absorption of key nutrients such as calcium and vitamin D. Considered altogether, these findings demonstrated that appropriately dosed exercise supports gut microbiota-mediated nutrient absorption, reinforcing bone cell function and skeletal health.

## 6. Conclusion

The gut-bone axis is a key regulator of skeletal homeostasis. Changes in gut microbial composition and metabolite output influence osteoclastogenesis, osteoblast function and MSC differentiation via intertwined immune, endocrine and metabolic pathways. Exercise modifies the intestinal microbiota and its metabolites, thereby exerting multifaceted effects on bone through the enhancement of barrier integrity, attenuation of systemic inflammation and promotion of osteogenic signaling. Nevertheless, gaps in knowledge are impeding clinical translation. Much of the mechanistic evidence has been derived from animal models and the corresponding human data are relatively sparse and heterogeneous. Inter-individual differences (for example, those associated with age, sex, diet, comorbidity and medication use) and methodological variability (for example, microbiome assay, metabolite quantification, exercise protocols and bone outcome measures) impede cross-study comparisons and causal inference. Longitudinal human cohort studies that combine metagenomics, metabolomics and immunophenotyping with validated bone endpoints should be undertaken to identify reproducible microbial and metabolite biomarkers. Randomized, well-powered intervention trials testing microbiota-directed strategies (for example, precision probiotics, prebiotics, dietary fiber intervention

and structured exercise regimens) with standardized bone outcomes and stratification by baseline microbiome features should be performed. Translational pipelines that iterate between human observational signals and mechanistic validations in controlled models to establish causality are also required. In addition, methodological harmonization and data sharing may improve reproducibility and clinical application. In short, integrating microbiome science with exercise physiology and bone biology offers a realistic route towards novel, non-pharmacological approaches for osteoporosis prevention and treatment. Focused translational research and standardized clinical testing are key to realize the therapeutic potential of the gut-bone axis.

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### Availability of data and materials

Not applicable.

### Authors' contributions

JiW and YR wrote and revised the manuscript. JuW and SZ conceived and designed the study. YL, XY, BX, YW, YS and YX revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare they have no competing interests.

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