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Review

The Role of Gut Microbiota in Osteoporosis Triggered by High-Fat Diets: Mechanisms and Targeted Therapeutic Strategies

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Abstract

Overnutrition, and specifically a high-fat diet (HFD) in which more than 30% of energy intake is derived from fat, has been unequivocally identified as a modifiable risk factor for several major diseases including osteoporosis, cardiovascular disorders, diabetes, and metabolic syndrome. The continued rise in prevalence of osteoporosis, particularly among younger populations, along with widespread adoption of HFD, has made the underlying mechanisms and preventative strategies related to HFD-induced osteoporosis a primary focus in the field of bone metabolism research. Early studies suggested that HFD-mediated weight gain might confer protective effects on skeletal health. However, emerging evidence reveals that HFD disrupts bone metabolic homeostasis and accelerates the progression of osteoporosis through multiple pathways, including pathological expansion of adipose tissue, systemic chronic inflammation, and gut microbial dysbiosis. The gut microbiota (GM) is a crucial mediator of dietary fat absorption and is increasingly recognized as a pivotal factor in the pathogenesis of HFD-associated osteoporosis. HFD-induced alterations in gut microbial composition and metabolic function compromise intestinal barrier integrity, triggering chronic systemic inflammation and metabolic disturbances that collectively exacerbate bone loss and promote osteoporosis. Targeted microbiota interventions have shown promise in ameliorating bone deterioration, paving the way for innovative therapeutic approaches against HFD-related osteoporosis. This review systematically examines the pathways through which HFD induces osteoporosis via modulation of GM, and evaluates emerging microbiota-focused treatment strategies.

Keywords: high-fat diet; gut microbiota; osteoporosis; bone loss

1. Introduction

Osteoporosis is a prevalent skeletal disorder characterized by disruption of bone remodeling homeostasis. This metabolic bone disease manifests through reduced bone mass, deteriorated bone quality, decreased bone mineral density (BMD), and impaired microarchitecture. Fragility fractures leading to disability or mortality are the most severe clinical complication [1]. The pathogenesis of osteoporosis involves multiple factors including aging, menopause, nutritional imbalances (both deficiency and excess), and physical inactivity [2,3]. Osteoporosis poses significant challenges to healthcare systems, and substantially compromises patient quality of life. Furthermore, the adverse medical and socioeconomic consequences of osteoporosis are projected to escalate substantially with population aging [4,5].

The impact of nutritional excess on osteoporosis has attracted increasing attention from researchers. As living standards improve, health concerns have arisen regarding dietary overconsumption. High-fat diet (HFD), characterized by lipids contributing more than 30% of total energy intake, is a primary driver of overnutrition [6]. This dietary pattern has become globally prevalent, with high-fat fast food becoming increasingly popular. Conventional wisdom suggests that HFD might confer protective benefits to the skeleton through weight gain, since elevated body weight was traditionally considered advantageous for bone health [7]. However, emerging evidence demonstrates that excessive fat intake disrupts bone remodeling, accelerates skeletal aging, and constitutes a significant risk factor for osteoporosis [8].

The gut microbiota (GM) is a critical biological interface for nutrient absorption and a key regulatory factor in host health. Recent studies have focused on its role in mediating HFD-induced bone deterioration [9], with evidence that gut dysbiosis caused by HFD can disrupt the bone metabolic balance [10]. Specifically, HFD alters the composition and functionality of GM, triggering intestinal inflammation and compromising the integrity of the intestinal mucosal barrier [11,12]. This pathological cascade facilitates translocation of harmful microbial metabolites and pro-inflammatory cytokines into systemic circulation, ultimately disrupting bone remodeling and accelerating progression of osteoporosis [13].

The current review systematically examines the role of GM in HFD-induced osteoporosis, with a particular focus on HFD-mediated alterations in gut microbial ecology and intestinal barrier integrity, GM-regulated mechanisms of bone metabolism, and potential pathogenic pathways underlying these interactions. Furthermore, we critically evaluate emerging microbiota-targeted therapeutic strategies and their potential for skeletal health management. By synthesizing current evidence, this work identifies key knowledge gaps and proposes novel research directions, thereby providing theoretical foundations and innovative perspectives for preventing and treating HFD-related osteoporosis.

2. The Prevalence of HFD Consumption has Increased Markedly in Modern Lifestyles

Accelerating global industrialization has driven a marked shift away from traditional diets toward high-calorie, high-fat consumption, especially with the expansion of food processing industries and widespread adoption of fast-food culture. The Global Burden of Disease Study found the current average intake of saturated fatty acids (SFAs) worldwide contributes 11% of total energy, exceeding the World Health Organization (WHO) recommended limit of <10%. Moreover, anti-inflammatory and cardioprotective polyunsaturated fatty acids (PUFAs) account for only 5% of energy, below the recommended range of 6–11% [14]. This SFA/PUFA imbalance shows a clear correlation with rising incidences of chronic diseases such as obesity, insulin resistance, and abnormal bone metabolism, highlighting the importance for public health of optimizing dietary fat composition [15,16].

An international study across 29 countries reported that total trans-fatty acid (TFA) intake ranged from 0.3–4.2% of total energy intake, with seven countries surpassing the WHO's 1% threshold [17]. Although the average TFA intake in China (0.39 g/day, 0.16% energy) remains below this limit, certain urban student populations exceed 1%. China's dietary patterns show a pronounced increase in fat consumption, with total fat energy contribution rising from 22% to 29.8% over 1992–2002, and animal-derived foods increasing from 9.3% to 13.7% [18]. Furthermore, the proportion of population with fat intake >30% of total energy, and daily cholesterol consumption >300 mg, increased significantly from 1989 to 2009 [19]. These levels approach or exceed the upper limits set by China's Dietary Reference Intakes. By 2019, increased consumption of plant oils and animal fats drove total fat energy intake to 34.6%, far exceeding both the WHO's updated 30% limit and China's dietary guidelines of 20–30% [20].

A recent U.S. dietary survey further revealed that fat-derived energy had reached 43%, while carbohydrate-derived energy fell from 57% to 45%. The prevalence of HFD-induced morbid obesity increased progressively, affecting a growing proportion of younger Americans [21]. Furthermore, studies have conclusively demonstrated that excessive fat intake, particularly SFAs, is associated with increased risks of cardiovascular diseases, metabolic syndrome, non-alcoholic fatty liver disease, and bone metabolic disorders [15,22,23]. Consequently, U.S. public health guidelines mandate a total fat intake <30% of energy, and SFAs <10% [24]. The WHO caps TFA intake at 1% and advocates replacing SFAs with unsaturated fats.

HFD typically refers to diets in which fat contributes >30% of total energy intake. However, definitions vary across studies, with some specifying 40–45% fat energy [25], others 37% total fat (15% SFAs, 12.7% monounsaturated fatty acids (MUFAs)), or even 55% fat (25% SFAs) [26,27]. These discrepancies likely reflect different experimental designs. The effects of different HFDs on the skeleton also vary depending on the proportion of energy they provide relative to total energy intake. Some studies indicate that different proportions of fat energy are dose-dependently associated with deterioration of bone density [28,29,30]. For example, an HFD with 60% energy from fat may be associated with lower bone density compared to one with 45% energy from fat. A lower-fat HFD may primarily affect bone density by inducing mild obesity and insulin resistance [31]. An extremely high-fat HFD might, in addition to these effects, induce systemic inflammation, oxidative stress, or GM dysregulation, thereby exerting more complex or even very different skeletal impacts [10,32]. Nevertheless, long-term clinical studies that directly compare HFDs with different proportions of energy intake on BMD are still lacking. It cannot be assumed that a higher proportion of energy intake from fat correlates with lower bone density.

3. How do High Fat Diets Affect Bone Metabolism?

The rising prevalence of obesity has heightened awareness among researchers of the detrimental health effects induced by HFD, particularly given the concurrent increase in osteoporosis incidence. HFD was initially thought to enhance bone mass and skeletal health due to the positive mechanical loading effects conferred by higher body weight [33]. Early studies found that obese male adolescents consuming HFD had greater muscle area and higher BMD [34]. Furthermore, an assessment of bone parameters in adolescents aged 12–19 found elevated bone mass in obese individuals, implying potential benefits of obesity on skeletal health [35].

However, emerging evidence indicates that bone health is adversely affected by HFDs [36]. Some studies have attributed the increased BMD and bone mineral content (BMC) associated with HFDs to increased mechanical loading on bone tissue, and to accumulation of adipose tissue which then increases estrogen secretion. However, the intrinsic adverse effects of HFDs outweigh these benefits [37]. Epidemiological studies report higher incidences of

osteoporosis and osteoporotic fractures among individuals with HFDs compared to those on normal diets [38]. A study of Chinese adolescents found a more pronounced negative association between HFD-induced obesity and BMC compared to those with normal weight, with BMC consistently showing an inverse relationship with fat consumption, irrespective of body fat percentage [39]. Another study demonstrated that a 7-day, high-energy HFD reduced bone formation markers [40], while a diet rich in SFAs was found to significantly impair bone regeneration and repair [15]. Studies with animal models fed an HFD showed reduced bone density and strength, as well as impaired bone marrow stem cell function [41]. Furthermore, HFD-induced obese mice exhibited reduced BMD and deteriorated trabecular bone microstructure [42]. Beyond long bones, alveolar bone studies also reported HFD-regulated osteopenia [43]. HFD-induced gut dysbiosis was linked to degradation of alveolar bone microstructure [44,45]. These findings demonstrate that the detrimental effects of HFD on bone substantially outweigh any potential benefits from weight-associated mechanical loading and enhanced estrogen secretion.

The detrimental effects of HFD on bone metabolism can be modulated by the proportion of dietary fat and by intrinsic age-related factors [46,47]. Moderate-fat diets can benefit rat bones, whereas HFD adversely affects BMD, BMC, microstructure, and osteocytes [46]. Moreover, older HFD-fed mice exhibit more severe bone loss and trabecular deterioration than younger counterparts [47]. HFD is therefore a critical risk factor for bone metabolic dysregulation, microstructural deterioration, and reduced BMD and BMC. Both the proportion of dietary fat and intrinsic age-related factors can modulate its skeletal effects. Chronic HFD consumption induces osteoporosis through multifaceted mechanisms (Fig. 1). These are discussed in the following section.

3.1 The Lipotoxic Effects of Free Fatty Acids

The buildup of lipids in abnormal locations disrupts regular organ function, a condition known as lipotoxicity. Elevated levels of free lipotoxic fatty acids in the medullary cavity promote osteoclast activity while reducing osteoblast numbers and function, ultimately contributing to osteoporosis [48]. Accumulating evidence indicates that HFD promotes accumulation of bone marrow adipose tissue (BMAT) and production of free fatty acids (FFAs). This activates peroxisome proliferator-activated receptor γ (PPARγ) in the bone marrow niche, shifting differentiation of bone marrow mesenchymal stem cells (BMSCs) toward adipocytes rather than osteoblasts, and increasing marrow adiposity while suppressing osteogenesis [41,49]. Osteoblasts are more susceptible to lipotoxicity than undifferentiated BMSCs [50]. Furthermore, *in vitro* experiments showed that co-culture of osteoclasts with adipocytes significantly enhanced osteoclast proliferation. This may represent a crucial mechanistic link, whereby HFD-induced expansion of BMAT promotes osteoclast activation [43].

Palmitic acid (PA) is the most prevalent saturated FFA present in plasma and is known to accumulate in the bone marrow after HFD. PA was reported to trigger BMSC apoptosis, suppress proliferation, and induce osteocyte apoptosis while impairing autophagy, thereby reducing osteocyte survival [51]. Accumulation of PA was shown to inhibit osteoblast differentiation and bone mineralization, correlating with reductions in runt-related transcription factor 2 (RUNX2) expression, alkaline phosphatase (ALP) activity, and osteocalcin levels [52]. Similarly, PA was found to significantly reduce the expression of osteogenic genes (e.g., ALP, RUNX2) and decrease vertebral BMD [53]. *In vitro* studies also confirmed reduced transcriptional activity of RUNX2 and β-catenin in PA-treated osteoblasts. While bone morphogenetic protein 2 (BMP2) enhances formation of the RUNX2-Smad complex, PA disrupts the protein expression and co-localization of these factors [54].

PA exerts lipotoxicity by inducing endoplasmic reticulum stress, activating NF-κB and ERK pathways, and disrupting autophagy [55,56]. PA also promotes pro-inflammatory responses via upregulation of Toll-like receptor 4 (TLR4), and increased secretion of IL-6, IL-8, Monocyte Chemoattractant Protein-1 (MCP-1), and Vascular Endothelial Growth Factor (VEGF). TLR4 overexpression exacerbates inflammatory responses in BMSCs, enhances osteoclast precursor differentiation, and disrupts bone formation/resorption balance [56,57]. Furthermore, the PA-induced disruption of autophagy increases osteocyte apoptosis, while concurrently reducing the expression of two key regulators of osteoblast activity and bone remodeling, dickkopf-1 (Dkk-1) and sclerostin (SOST) [51]. The decreased expression of Dkk-1 and SOST may perturb the equilibrium of osteoblastic and osteoclastic activities, potentially resulting in dysregulated skeletal homeostasis. Notably, PA-mediated osteoblast dysfunction can be rescued by parathyroid hormone (PTH) and $1,25(OH)_2D_3$ [58,59]. PTH restores osteogenic differentiation by modulating anabolic genes, preserving mitochondrial membrane potential, normalizing Bax/Bcl-2 ratios, and regulating autophagy [58]. Similarly, $1,25(OH)_2D_3$ counteracts lipotoxicity by modulating osteoblast autophagy and promoting osteogenic differentiation [59].

Beyond the lipotoxic effects of PA, HFD can disrupt bone homeostasis through several other pathways. For example, HFD increases oxidized low-density lipoprotein levels, which promotes adipogenic differentiation of BMSCs, suppresses osteoblastogenesis, and impairs the self-renewal capacity of BMSCs [60,61]. HFD causes lipid peroxidation products to accumulate in the medullary cavity, which accelerates bone resorption by activating NF-κB signaling in osteoclasts [62].

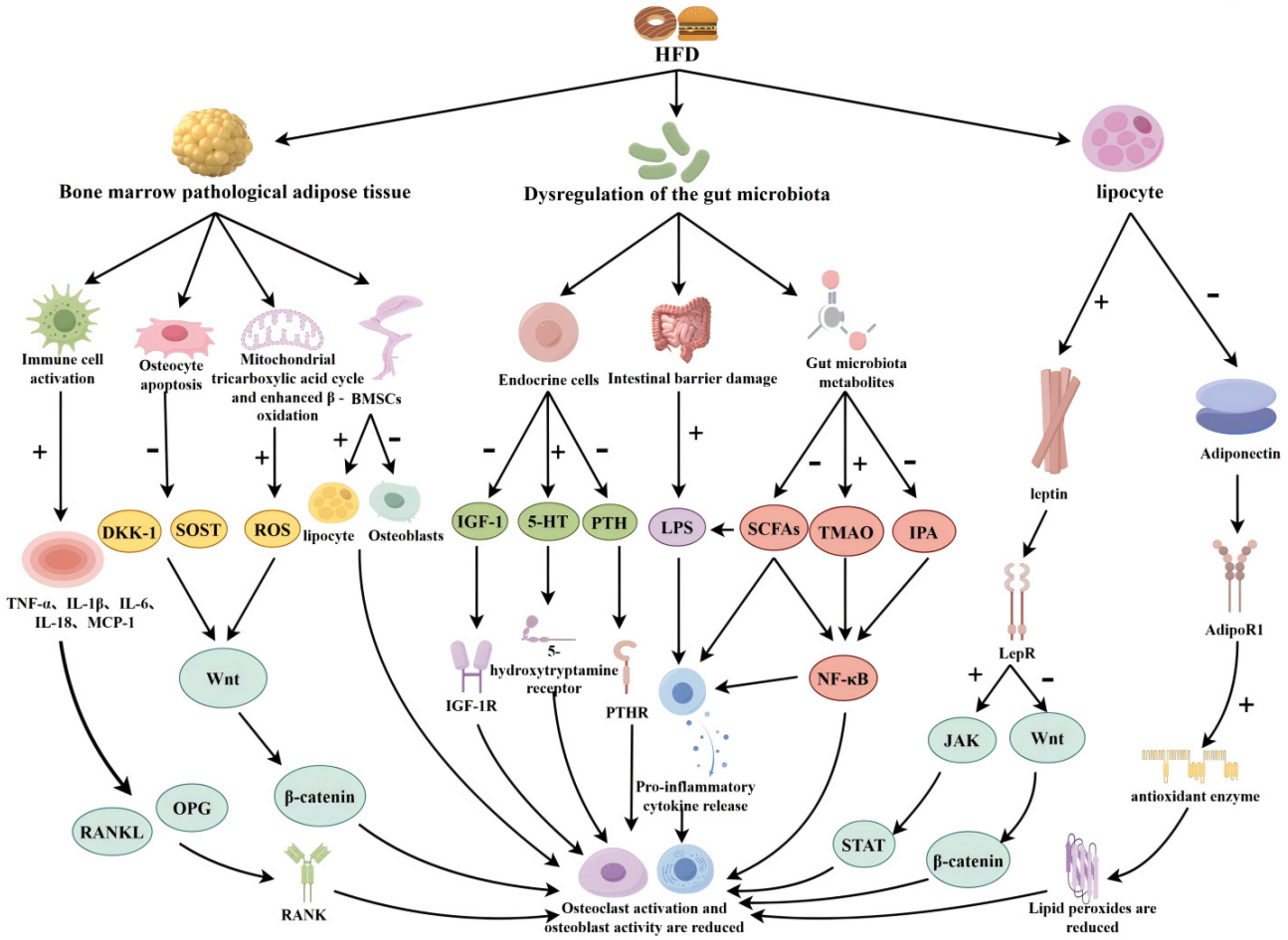

Fig. 1. Mechanistic schematic of HFD-induced osteoporosis. Firstly, a HFD triggers lipotoxic effects by promoting pathological accumulation of bone marrow adipose tissue, resulting in a state of elevated oxidative stress and heightened inflammatory response in bone tissue. Secondly, HFD induces GM dysbiosis. This disruption further compromises intestinal barrier integrity, facilitating the translocation of endotoxins (LPS) and viral antigens into systemic circulation, thereby initiating a chronic systemic inflammatory response. Moreover, gut dysbiosis interferes with the release of gut-derived endocrine hormones, promoting the secretion of bone-resorptive hormones such as serotonin, while reducing the production of osteogenic hormones like insulin-like growth factor-1 and parathyroid hormone. Concurrently, dysbiosis leads to decreased synthesis of bone-protective microbial metabolites—such as SCFAs and IPA—while enhancing the production of pro-resorptive metabolites like TMAO. In addition, HFD stimulates the secretion of bone-resorptive adipokines (leptin) and suppresses the release of osteogenic adipokines such as adiponectin. Together, these mechanisms lead to accelerated bone loss. Figure created with Figdraw.com. Abbreviations: HFD, high-fat diet; GM, gut microbiota; BMSCs, bone marrow mesenchymal stem cells; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; MCP-1, monocyte chemoattractant protein-1; RANKL, receptor activator of nuclear factor Kappa-B Ligand; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; Dkk-1, dickkopf-1; SOST, sclerostin; Wnt/β-catenin, Wingless type MMTV integration site family/β-catenin signaling pathway; ROS, reactive oxygen species; IGF-1, insulin-like growth factor-1; 5-HT, 5-hydroxytryptamine; PTH, parathyroid hormone; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; IPA, indole-3-propionic acid; NF-κB, nuclear transcription factor-κB; JAK2, janus kinase 2; Stat3, signal transducer and activator of transcription 3; LepR, leptin receptor. Note: "+" indicates promotion; "–" indicates inhibition.

3.2 Regulation of Bone Metabolism by Adipocytokines

Adipose tissue secretes various cytokines that regulate bone metabolism, including leptin, adiponectin, visfatin, and omentin [63]. Leptin is crucial in HFD-induced bone metabolic imbalance by modifying the environment of bone cells, inhibiting osteoblast function, and facilitating osteoclast activation [64,65]. The HFD-induced reduction in adiponectin also contributes to disruption of bone metabolic homeostasis [66].

Leptin is known to regulate both energy homeostasis and skeletal metabolism. A recent study found that HFD-fed mice showed significant growth of BMAT, in-

creased levels of plasma leptin, and decreased bone mass and bone formation rate [64]. Fujita et al. [65] reported a negative correlation between serum leptin and trabecular bone density in HFD-induced obese mice. However, leptin receptor (LepR) knockout mice display higher trabecular bone volume (BV/TV), enhanced bone formation, and reduced marrow adipocytes regardless of diet [67]. Furthermore, clinical investigations found that postmenopausal women with HFD-induced obesity had elevated leptin levels [68], concurrent with fewer osteoblasts and lower levels of the bone formation marker Procollagen Type I N-Terminal Propeptide (PINP) [69]. These studies indicate that leptin mediates detrimental effects on bone metabolism during exposure to HFDs. It does this through activation of Jak2/Stat3 signaling via LepR, upregulation of the adipogenic factor C/EBPα, and suppression of the osteogenic Wnt pathway [67]. Leptin also exerts inhibitory effects on osteogenesis while enhancing osteoclastogenesis and bone matrix degradation through central neuroregulation [70,71]. However, some studies reached different conclusions. Liu et al. [72] observed higher serum leptin levels alongside elevated BMD in obese children. Increased leptin levels in postmenopausal obese women were positively correlated with BMD [68]. Like estrogen, leptin exerts bone-protective effects by modulating the RANK/RANKL/OPG pathway, downregulating receptor activator of nuclear factor kappa-B Ligand (RANKL), and upregulating osteoprotegerin (OPG) to promote osteoblast differentiation. Consequently, additional studies are required to elucidate the exact effects of elevated leptin levels on skeletal homeostasis in HFD models.

HFD-induced reductions in adiponectin secretion contribute to disrupted bone homeostasis [66]. Early clinical studies linked adiponectin to lower BMD and identified it as an independent risk factor for fractures. However, recent evidence highlights its antioxidant, anti-inflammatory, and bone-protective properties. Liu et al. [73] reported that HFD-fed adiponectin-knockout mice showed decreased superoxide dismutase (SOD) activity, a reduced glutathione/glutathione disulfide ratio, and increased lipid peroxidation compared to controls. Moreover, adiponectin supplementation increased antioxidant enzyme activities and restored normal antioxidant levels [73]. Adiponectin is therefore a key factor in the attenuation of diet-mediated oxidative damage, and adiponectin deficiency exacerbates redox imbalance under HFD conditions. Furthermore, *in vitro* evidence shows that adiponectin enhances osteoblast proliferation and maturation, while suppressing osteoclast formation. Adiponectin counteracts HFD-induced bone microstructure damage by alleviating oxidative stress in the bone microenvironment [74,75]. Finally, it enhances osteogenic differentiation of BMSCs by upregulating OPG and suppressing RANKL, thereby ameliorating HFD-driven metabolic dyshomeostasis [75].

3.3 Oxidative Stress Triggered by HFD

Extensive research confirms that redox imbalance contributes significantly to the development of skeletal metabolic pathologies [76,77], with HFD-induced oxidative stress representing a critical pathogenic mechanism in osteoporosis. Although the HFD-oxidative stress nexus is not yet fully delineated, intrinsic oxidative damage from lipid-rich diets appears to critically influence osseous metabolic dysfunction in obese mice [78].

HFD-induced systemic oxidative stress has been shown to exacerbate oxidative reactions within the bone microenvironment. This process enhances osteoclast differentiation, suppresses osteoblast activity and triggers apoptosis, ultimately impairing bone repair and accelerating osteoporosis [73,74]. Significantly elevated levels of reactive oxygen species (ROS) were observed in HFD-induced osteoporotic mice, alongside reduced SOD and glutathione peroxidase activities [62]. Another study showed that HFD-fed rats exhibit excessive ROS production [79]. These findings suggest that HFD-induced increases in peroxide production and decreases in antioxidant enzyme activity may represent key mechanisms underlying the development of osteoporosis.

HFD generates ROS via multiple mechanisms. For example, excess FFAs increase tricarboxylic acid cycle activity, which increases NADH and flavin adenine dinucleotide (reduced form) (FADH2) production and overloads mitochondria. Coupled with diminished SOD activity, this leads to ROS accumulation [80]. Excessive lipid deposition also enhances mitochondrial β-oxidation, indirectly increasing ROS and reactive nitrogen species (RNS) levels [81]. ROS accumulation diminishes glutathione conversion efficiency, impairing osteogenesis through several mechanisms. First, by attacking the extracellular matrix in bone tissue to suppress osteoblast proliferation, differentiation, and mineralization. Second, by increasing membrane permeability to promote cytochrome C release, activating caspase signaling and inducing mitochondrial apoptosis while downregulating osteogenic markers [82]. Third, by inhibiting the Wnt/β-catenin and nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathways, thereby reducing BMP2/RUNX2 expression [83,84]. Furthermore, ROS enhances the binding of PPARγ to β-catenin, attenuating β-catenin/T-cell factor (TCF)-mediated osteoblast formation [85]. ROS also exacerbates osteocyte damage by suppressing autophagy via PI3K/protein kinase B (AKT)/mTOR [86]. Natural antioxidants (e.g., lycopene) counteract ROS by enhancing antioxidant enzyme activity, while also directly modulating bone metabolism to ameliorate HFD-induced bone loss [87].

3.4 HFD Activates Immune-Inflammatory Responses

Maintaining immune equilibrium is widely acknowledged as a pivotal determinant in sustaining bone integrity. Emerging studies reveal that HFD-mediated immune dys-

function substantially disrupts skeletal equilibrium through multiple pathological pathways. HFD promotes pathological expansion and dysfunction of adipose tissue, triggering the release of proinflammatory cytokines (tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-18, MCP-1) [88]. These activate osteoclastogenesis in the medullary cavity through the RANKL/RANK/OPG axis [89], leading to reduced BMD, decreased bone mass, and impaired bone regeneration [89,90]. Furthermore, experimental studies with animals show that IL-6 overexpression leads to degradation of trabecular and cortical bone structures through enhanced osteoclastic resorption [91]. Conversely, IL-6 deficiency confers protection against HFD-induced skeletal deterioration [92]. These findings suggest that HFD-induced release of proinflammatory factors contributes to the development of osteoporosis. HFD also induces systemic oxidative stress, leading to excessive ROS accumulation. ROS activates the NF-κB/activator protein 1 (AP-1) pathway, promoting the release of proinflammatory cytokines (TNF-α, IL-6, IL-1β) and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, thereby exacerbating osteoblast pyroptosis and osteoclast differentiation [86].

Macrophages are key mediators of immune-inflammatory responses and contribute to HFD-induced osteoporosis through multiple regulatory mechanisms [8,93]. Long-term HFD upregulates Chil3 and Fabp4 expression in bone marrow macrophages, triggering systemic chronic inflammatory responses and contributing to osteoporosis [94]. Furthermore, HFD induces macrophage infiltration into the bone marrow and stimulates IL-6 secretion, which subsequently activates RANKL/TRAF6/NFATc1 signaling to potentiate bone resorption [95]. Macrophage-derived prostaglandins also contribute to HFD-induced bone metabolic imbalance. Liu et al. [96] reported that inhibitors of prostaglandin synthesis improved trabecular bone mass and density in HFD-fed rats. Similarly, pharmacological inhibition of cyclooxygenase-2 (COX-2) significantly reduced the expression of inflammatory genes (TNF-α, IL-6, MCP-1, COX-2) in adipose depots of HFD-induced obese mice, while suppressing osteolytic factors (RANKL, matrix metalloproteinase-9 (MMP-9), cathepsin K) in the tibial microenvironment. Conversely, supplementation with arachidonic acid, a prostaglandin precursor, exacerbated osteoclastogenesis by upregulating COX-2-derived prostaglandin E_2 signaling and inflammatory cytokine expression [97]. Collectively, these findings indicate that HFD-induced macrophage activation and the subsequent release of bioactive mediators (e.g., prostaglandins) contribute to bone destruction.

4. HFD-Mediated Gut Microbial Dysbiosis and Its Regulatory Effects on Skeletal Homeostasis

The GM is primarily modulated by dietary patterns, thereby influencing physiological health through mechanisms including inflammatory immune responses, oxidative stress, and nutrient absorption [98]. Intestinal microbial imbalance (dysbiosis) contributes significantly to the disruption of skeletal homeostasis via multiple pathological pathways [99]. Recent studies confirm that HFD exerts significant adverse effects on GM not only by altering its composition, but also by compromising intestinal barrier integrity and function [11,12]. Since GM are key biological mediators of nutrient absorption, alterations can significantly influence HFD-induced osteoporosis [10,100]. Diet-induced dysbiosis in HFD-induced osteoporotic mice was found to reduce bacterial populations crucial for mucosal integrity, while promoting barrier-disrupting species. This microbial shift also showed a strong association with decreased bone mass and impaired microstructure [9,12]. HFD promotes the proliferation of pathogenic taxa (e.g., *Enterobacter*, *Klebsiella*, *Desulfovibrio*, *Vibrio cholerae*), while suppressing beneficial genera (e.g., *Lactobacillus*, *Bifidobacterium*, *Akkermansia muciniphila*) [9,10]. These alterations are accompanied by an elevated *Firmicutes*-to-*Bacteroidetes* (F/B) ratio, collectively favoring osteoporosis [101,102].

The mucin-adhering commensal bacterium *Akkermansia muciniphila* is considered a health-promoting microorganism that enhances gut barrier integrity and mitigates endotoxin translocation. HFD significantly depletes *Akkermansia muciniphila*, resulting in compromised gut barrier integrity, systemic endotoxemia, and chronic low-grade inflammation [103]. This phenomenon was identified as a potential pathogenic cascade, ultimately contributing to the development of osteoporosis [104]. *Lactobacillus* and *Bifidobacterium* spp. have well-established osteogenic properties. Under hypoxic conditions, HFD-fed mice develop gut dysbiosis characterized by diminished abundance of *Lactobacillus* and *Bifidobacterium*. This disrupts histidine metabolism (as manifested by elevated L-carnosine), exacerbates systemic inflammatory responses, and ultimately shifts bone remodeling toward net resorption through increased osteoclast activity and suppressed osteoblast function [105]. Comparative analyses of other HFD-induced osteoporosis models also revealed a significant reduction in *Lactobacillus* compared to normal-diet controls, and a positive correlation with reduced BMD [9,102]. Moreover, overgrowth of pathogenic bacteria (particularly *Klebsiella* and *Rikenellaceae*) promotes bone metabolic dysfunction through dual mechanisms of enhanced resorption and impaired formation [10,105]. Rodrigues et al. [10] reported that HFD decreases bone formation markers and osteoblast numbers, and selectively enriches *Proteobacteria* (notably *Klebsiella* spp.) within the

GM. Importantly, *Klebsiella*-derived proinflammatory extracellular vesicles (EVs) have been shown to stimulate osteoclast differentiation in bone marrow microenvironments [106].

The F/B ratio has been associated with elevated systemic inflammatory markers, while showing an inverse relationship with bone health parameters [9,107]. HFD-fed mice demonstrated increased *Firmicutes* abundance alongside decreased *Bacteroidetes* and *Actinobacteria* populations. These changes coincided with reductions in femoral BV/TV, trabecular number, and trabecular thickness [9]. Similarly, another study found a lower F/B ratio in HFD-induced bone loss models compared to controls with normal diet, accompanied by enhanced systemic inflammatory responses [45]. Collectively, these findings indicate the F/B ratio is a key modulator in HFD-induced osteoporosis. Increased F/B ratios may stimulate systemic proinflammatory responses and disrupt bone metabolic equilibrium. However, the precise mechanistic pathways remain incompletely understood, warranting further investigation of the underlying molecular and cellular mechanisms. GM diversity is another critical factor in HFD-induced osteoporosis. Qiao et al. [105] demonstrated that HFD significantly reduced GM diversity, with concomitant detrimental alterations in femoral microstructure and decreased BMD. Moreover, chronic HFD exposure was shown to decrease osteoblast numbers, increase osteoclastogenesis, reduce bone mass, and induce dysbiosis characterized by reduced α-diversity [108]. In summary, HFD-induced gut microbial dysbiosis is a critical driver of osteoporosis progression.

5. Mechanisms of GM-Mediated HFD-Induced Osteoporosis

5.1 Impairment of Intestinal Barrier Function and Metabolic Endotoxemia

Maintaining skeletal health relies heavily on intestinal barrier integrity. HFD compromises intestinal barrier function by downregulating tight junction proteins, including Claudin-1, Claudin-15, zonula occludens-1 (ZO-1), and junctional adhesion molecule A (JAM-A). This facilitates translocation of harmful microbial metabolites and pathogenic bacterial antigens into the systemic circulation, triggering bone metabolic dysregulation and contributing to osteoporosis [108]. HFD-induced intestinal barrier dysfunction involves several key mechanisms (Fig. 2), of which oxidative imbalance is known to directly compromise epithelial homeostasis. Under HFD conditions, intestinal epithelial cells actively absorb excess lipids, leading to mitochondrial respiratory chain overactivation and elevated ROS production [109]. Concurrently, HFD upregulates gut microbial functions associated with redox reactions, thereby increasing ROS generation [110]. HFD-induced ROS can directly oxidize sulfhydryl groups or tyrosine residues on critical intestinal tight junction proteins (e.g., Occludin, Claudins, and ZO-1), altering their function and compromising intestinal barrier integrity. This promotes the proliferation of pathogenic GM, including *Salmonella* and *Escherichia coli* [111]. HFD also modulates bile acid metabolism, which then exacerbates oxidative stress. Higher consumption of dietary fats is associated with increased bile acid production in the digestive system [112]. Chronic HFD increases hydrophobic bile acids (e.g., cholic acid and deoxycholic acid) [113], which intensify epithelial oxidative stress and apoptosis, thereby increasing permeability and damaging the mucosal barrier [114]. Additionally, excessive absorption of dietary fats generates substantial amounts of trivalent iron and lipid peroxides, exacerbating oxidative stress and compromising barrier function [115]. HFD also suppresses PPARγ signaling in enterocytes, degrades the mucus layer, reduces electrolyte secretion, and impairs mucosal immunity [116]. Such HFD-induced permeability defects can be reversed by treatment with the PPARγ agonist rosiglitazone, or by dietary normalization [116].

HFD-induced intestinal immune inflammation also contributes to the impairment of gut barrier function. FFAs generated under HFD conditions directly modulate the gut immune system [117] to induce barrier-disrupting cytokines (TNF-α, IL-1β, IL-6, IFN-γ) while suppressing barrier-protective cytokines (IL-10, IL-17, IL-22) [118]. These pathological changes reduce mucus secretion and downregulate tight junction proteins, ultimately increasing intestinal permeability [119]. Lipopolysaccharide (LPS) from Gram-negative bacteria may also be a key mediator through which HFD compromises intestinal barrier integrity and subsequently induces osteoporosis [101]. Prolonged HFD exposure increases LPS levels in both ileal tissue and bone marrow. The compromised intestinal barrier allows LPS translocation into the circulation, inducing metabolic endotoxemia that disrupts bone metabolism and impairs skeletal integrity, as manifested by reduced BMD and increased trabecular separation [120]. Mechanistically, LPS binds to the CD14/TLR4 complex on intestinal epithelial cells, activating innate immunity and chronic low-grade systemic inflammation. This cascade further degrades the mucus layer and exacerbates epithelial hyperpermeability [121,122]. Additionally, LPS stimulates macrophage TLR4 to enhance pro-inflammatory cytokine release (TNF-α, IL-1β, IL-6), which upregulates RANKL expression—a critical driver of osteoclastic bone resorption.

5.2 Metabolites Regulate Bone Homeostasis

Bone homeostasis is also controlled by metabolites produced by the GM. HFD induces substantial shifts in gut microbial communities, consequently modulating the biosynthesis of bacterial metabolites. These include short-chain fatty acids (SCFAs), secondary bile acids, trimethylamine N-oxide (TMAO) and indole-3-propionic

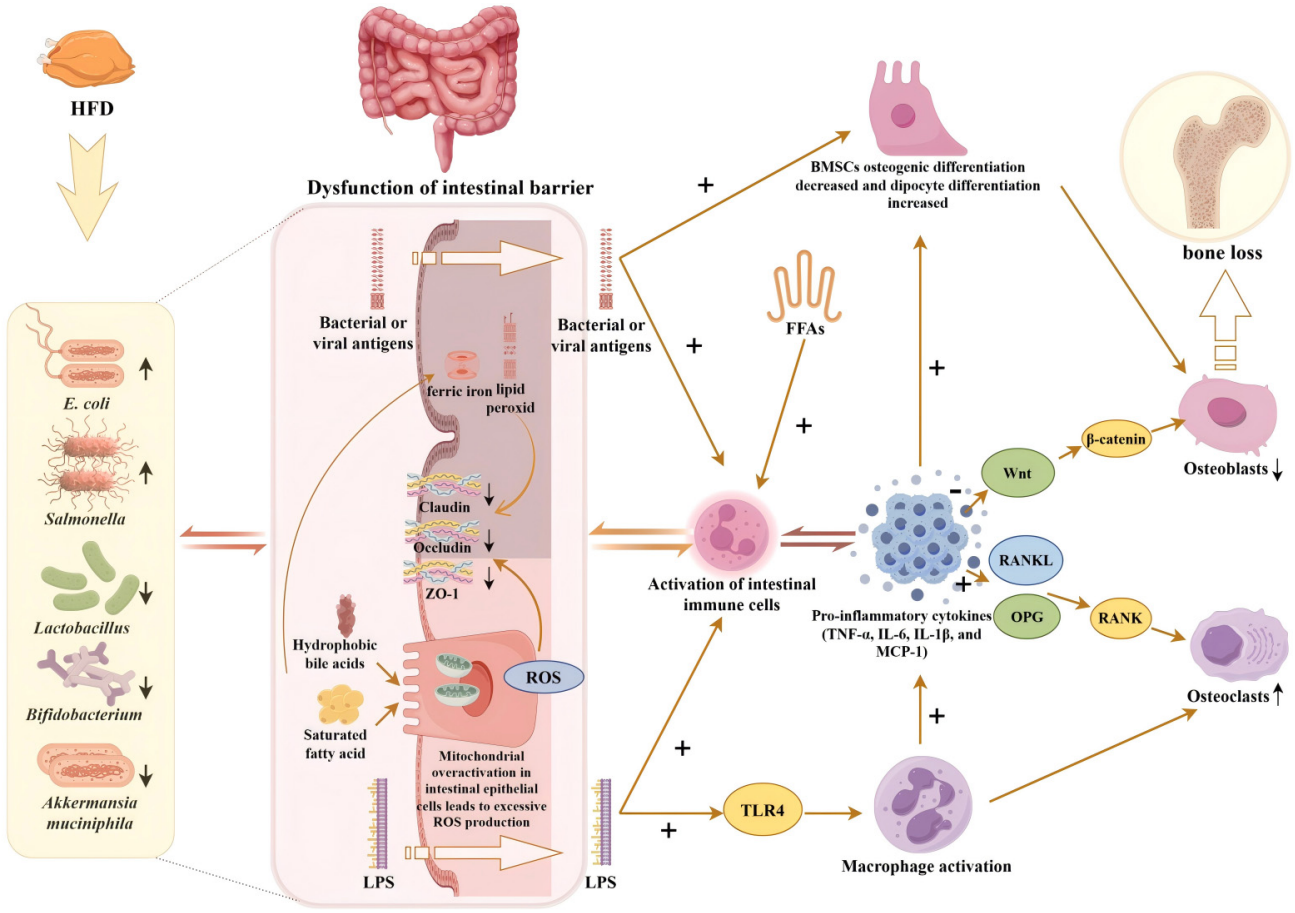

Fig. 2. Mechanisms of HFD-induced intestinal barrier impairment. A HFD increases the abundance of pathogenic GM while reducing the population of beneficial microorganisms. This shift not only promotes the production of gut-damaging bacterial endotoxins but also decreases the synthesis of protective metabolites such as SCFAs. Concurrently, HFD-induced gut dysbiosis disrupts bile acid and lipid metabolism, and stimulates intestinal epithelial cells to produce excessive trivalent iron and lipid peroxides. These changes collectively lead to mitochondrial reactive oxygen species overproduction in enterocytes, resulting in oxidative stress and accelerated impairment of intestinal barrier function. The compromised barrier facilitates the translocation of endotoxins, bacterial antigens, and viral antigens into systemic circulation, thereby triggering a chronic systemic inflammatory response. This inflammatory state accelerates bone loss and further exacerbates intestinal damage, forming a vicious cycle. Abbreviations: HFD, high-fat diet; GM, gut microbiota; ROS, reactive oxygen species; LPS, lipopolysaccharide; ZO-1, zonula occludens-1; FFAs, free fatty acids; TLR4, toll-like receptor 4; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-18, interleukin-18; MCP-1, monocyte chemoattractant protein-1; Wnt/β-catenin, Wingless type MMTV integration site family/β-catenin signaling pathway; RANKL, receptor activator of nuclear factor Kappa-B Ligand; OPG, osteoprotegerin; RANK, receptor activator of NF-κB. Note: "+" indicates promotion; "–" indicates inhibition; "↑" indicates increase; "↓" indicates decrease.

acid (IPA), which regulate bone metabolism through various pathways (Fig. 3) [108,123,124].

SCFAs are metabolic byproducts generated through fermentation of indigestible dietary fibers by GM such as *Bifidobacterium*, *Roseburia*, *Butyrivibrio*, *Ruminococcus*, *Bacteroides*, and *Akkermansia muciniphila* [125]. They exert protective effects on bone health by suppressing osteoclastogenesis and enhancing osteoblast differentiation and activity [13]. The osteoprotective properties of SCFAs are mediated through several anti-inflammatory mechanisms, including suppression of LPS-stimulated TNF-α production, inhibition of pro-inflammatory cytokine production, and attenuation of inflammatory responses by downregulating NF-κB signaling [126]. SCFAs also stimulate bone formation by upregulating insulin-like growth factor-1 (IGF-1) and glucagon-like peptide-1 (GLP-1) secretion, which indirectly influences bone metabolism [127]. Recent research further highlights the critical role of SCFAs in HFD-induced osteoporosis mediated by GM dysbiosis [128]. HFD-induced obese mouse models exhibit significantly reduced abundance of beneficial GM (e.g., *Bifidobacterium*, *Bacteroides*, *Roseburia*), resulting in decreased production of SCFAs. These alterations enhance systemic inflammation, which further suppresses osteoblast activity and

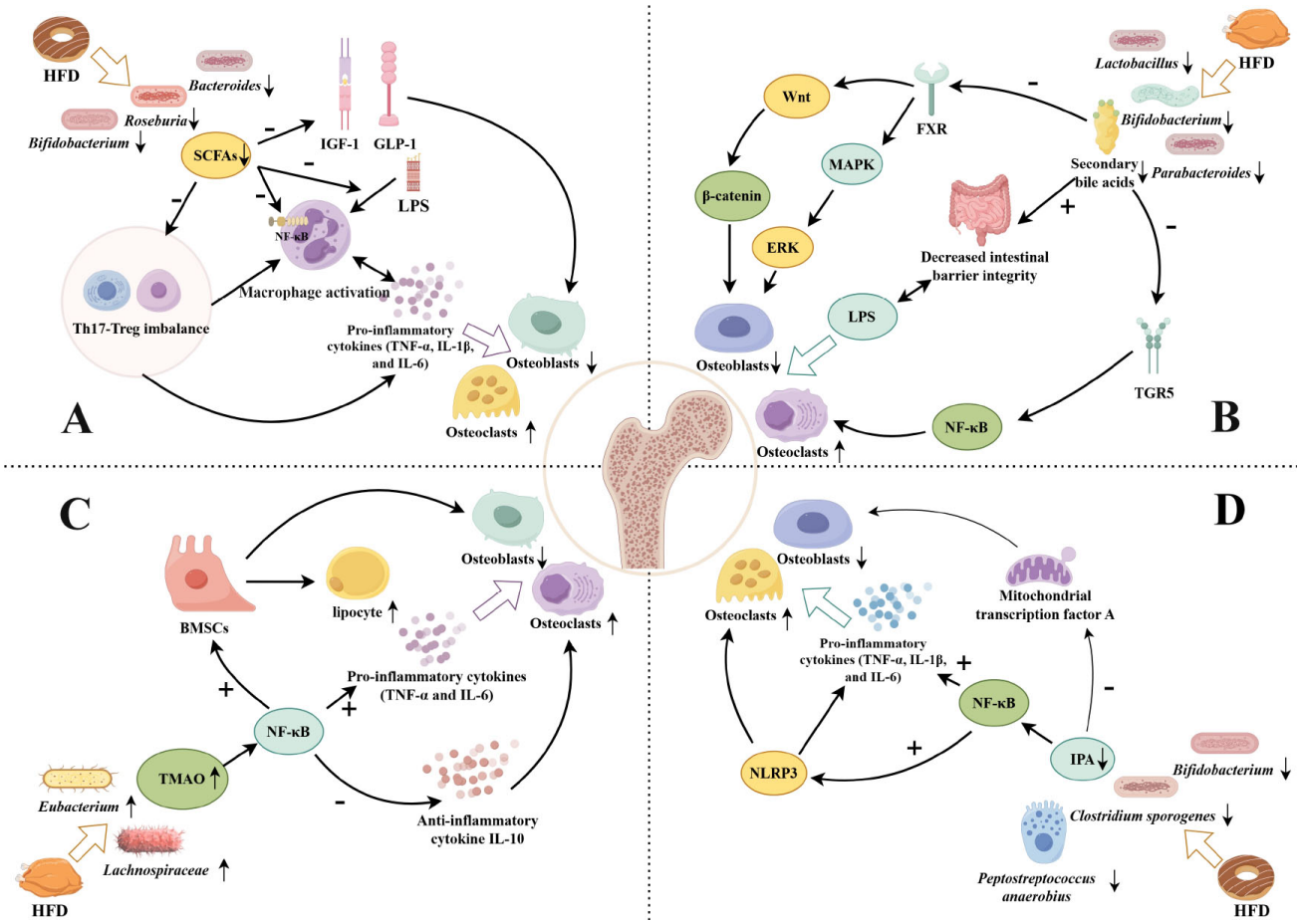

Fig. 3. Schematic diagram of HFD-induced osteoporosis via modulation of GM-derived metabolites. (A) SCFAs. HFD reduces the number of beneficial GM, leading to a decrease in SCFAs synthesis. This reduction can downregulate the secretion of insulin-like growth factor-1 and glucagon-like peptide-1, reducing stimulation for bone formation. In addition, the decrease in SCFAs diminishes their inhibitory effect on LPS-mediated systemic chronic inflammation. At the same time, the reduction of SCFAs causes an imbalance in Th17/Treg cells, accelerating the inflammatory response. These effects collectively contribute to bone loss. (B) Secondary bile acids. HFD-induced GM dysbiosis disrupts bile acid metabolism, leading to reduced production of secondary bile acids. The decrease in secondary bile acids diminishes their stimulation of corresponding receptors, weakening the activation of receptors such as FXR and TGR5 that promote bone anabolism. (C) TMAO. HFD-induced GM dysbiosis increases the synthesis of TMAO. TMAO inhibits osteogenic differentiation by activating the NF-κB signaling pathway in BMSCs and also binds to corresponding receptors on immune cells to upregulate pro-inflammatory cytokines (TNF-α and IL-6) and downregulate the anti-inflammatory cytokine IL-10. These effects collectively accelerate osteoporosis. (D) IPA. As a microbial metabolite derived from tryptophan, IPA synthesis is reduced due to HFD-induced GM metabolic disorders. The decrease in IPA weakens its inhibitory effect on inflammation mediated by the NF-κB/NLRP3 signaling pathway, while also reducing its role in promoting osteoblast differentiation through mitochondrial transcription factor A, ultimately accelerating bone loss. Abbreviations: HFD, high-fat diet; GM, gut microbiota; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; IPA, indole-3-propionic acid; IGF-1, insulin-like growth factor-1; GLP-1, glucagon-like peptide-1; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; FXR, farnesoid X receptor; TGR5, takeda G protein-coupled receptor 5; Wnt/β-catenin, Wingless type MMTV integration site family/β-catenin signaling pathway; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear transcription factor-κB; BMSCs, bone marrow mesenchymal stem cells; NLRP3, NOD-like receptor pyrin domain-containing 3; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells. Note: "+" indicates promotion; "–" indicates inhibition; "↑" indicates increase; "↓" indicates decrease.

promotes osteoclast formation, ultimately leading to bone loss [108]. A related study on periodontal health revealed that HFD reduces *Bacteroidetes* abundance, leading to decreased production of SCFAs. This exacerbates release of LPS and proinflammatory cytokines (TNF-α, IL-1β, and IL-6), ultimately accelerating bone resorption [107]. Butyrate is the predominant metabolic substrate for colonic epithelial cells and has potent anti-inflammatory activity

within the intestinal mucosal environment [129]. HFD reduces butyrate production, thereby inducing NLRP3 inflammasome hyperactivation and stimulating the release of inflammatory mediators (IL-1β, IL-6, and TNF-α), consequently aggravating osteolytic processes [102]. SCFAs also maintain bone metabolic homeostasis by regulating Th17/Treg cell balance, which is closely associated with HFD-induced osteoporosis. HFD-induced gut dysbiosis was reported to lower the total production of SCFAs (especially propionate, butyrate, and valerate), thereby disrupting Th17/Treg balance and accelerating alveolar bone loss [107]. Supplementation with SCFAs can effectively ameliorate this imbalance by targeting specific molecular receptors on Th17 and Treg cells, thereby attenuating bone loss [13].

Secondary bile acids are another important class of GM-derived metabolites that function as signaling molecules in bone metabolism regulation [130]. Primary bile acids (cholic acid, chenodeoxycholic acid) synthesized by the liver are decoupled by microbial bile salt hydrolases (BSH) to form secondary bile acids (e.g., deoxycholic acid, lithocholic acid). This biotransformation depends on microbial activity, particularly from *Bacteroides* and *Clostridium* species [131]. GM modulates both the composition and size of the bile acid pool, thereby influencing bone metabolism [132]. Current evidence indicates that HFD-induce gut dysbiosis can impair bile acid-mediated regulation of bone metabolism [133]. Earlier studies found that bile acids serve as ligands for farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) [134]. Bile acids upregulate RUNX2 through FXR activation and promote osteogenesis via the MAPK/ERK and Wnt/β-catenin signaling pathways, maintaining bone metabolic homeostasis [132]. Moreover, TGR5 activation enhances RUNX2 expression, increases ALP activity, stimulates matrix mineralization [135], and suppresses NF-κB-mediated inflammation and osteoclastogenesis through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway [136]. However, HFD-induced gut dysbiosis disrupts bile acid metabolism, inhibiting their osteogenic effects [137]. HFD-fed mice with reduced abundance of *Lactobacillus*, *Bifidobacterium*, and *Parabacteroidesdistasonis* have decreased BSH activity, leading to accumulation of conjugated bile acids and reduced secondary bile acid production [123]. This deficiency compromises FXR-FGF15 signaling, reduces FXR activation, and impairs osteoblast differentiation, ultimately leading to osteoporosis [138]. Moreover, HFD-induced bile acid dysregulation disrupts intestinal tight junction proteins, thereby increasing gut permeability and promoting LPS translocation, which may further exacerbate bone resorption [139].

Metabolites derived from other GM are also crucial in mediating HFD-induced osteoporosis. TMAO, another microbial metabolite, is generated from dietary choline, L-carnitine, and ergothioneine via microbial conversion to trimethylamine, which is subsequently oxidized by hepatic flavin monooxygenase [140]. Serum TMAO levels in osteoporosis patients show a significant negative correlation with BMD [141]. Similarly, elevated plasma TMAO levels were observed in HFD-fed mice with bone loss mediated by TMAO-related GM dysbiosis [124]. Positive associations were found between plasma TMAO and *Eubacterium*/*Lachnospiraceae* abundance, but a negative correlation with *Muribaculaceae*. TMAO activates NF-κB signaling in BMSCs to suppress osteogenic differentiation, while simultaneously binding to receptors on immune cells to upregulate pro-inflammatory cytokines (TNF-α and IL-6) and downregulate the anti-inflammatory cytokine IL-10, collectively promoting bone loss [142]. IPA, a tryptophan-derived microbial metabolite, recently emerged as a key regulator of skeletal metabolism [143]. HFD-induced obese mice show a deficiency in IPA, accompanied by significant osteoclast activation and reduced BMD [144]. However, IPA supplementation in these mice attenuates systemic inflammation, suppresses osteoclastogenesis, and improves bone mass [145]. This protective effect occurs via suppression of the NF-κB/NLRP3 signaling pathway. Specifically, IPA inhibits NF-κB phosphorylation, thereby reducing the expression of NLRP3, caspase-1, and apoptosis-associated speck-like protein, ultimately suppressing osteoclast activation [145]. IPA also promotes osteoblast differentiation by upregulating mitochondrial transcription factor A. Concurrently, it suppresses osteoclast formation and activity by inhibiting NF-κB signaling and downregulating osteoclastogenic factors, thereby reducing bone resorption and maintaining bone metabolic homeostasis [143]. Emerging evidence also suggests the potential involvement of other microbial metabolites (e.g., long-chain fatty acids (LCFAs), H_2S) in HFD-induced osteoporosis, although further investigation is needed.

5.3 Role of the Gut-Endocrine Axis in Bone Metabolism Regulation

In addition to intestinal barrier dysfunction and abnormal secretion of GM metabolites induced by GM dysbiosis, endocrine disruption also plays a critical role in HFD-mediated osteoporosis [146,147]. Specifically, HFD-induced GM dysbiosis may contribute to osteoporosis by disrupting the secretion of gut endocrine hormones [148,149].

Serotonin (5-hydroxytryptamine, 5-HT), a key hormone and neurotransmitter, mediates the effects of GM on bone metabolism. Almost all (>90%) systemic serotonin derives from intestinal enterochromaffin cells, with central nervous system (CNS) serotonergic neurons producing the remainder [150]. Specific GM can regulate peripheral serotonin synthesis through metabolite-host interactions [149]. HFD was recently found to increase intestinal serotonin production, with alterations in GM (particularly enrichment of *Turicibacter*, *Romboutsia*, and *Faecalibaculum*) playing

a pivotal role in this process [146]. HFD-induced elevation of 5-HT disrupts bone metabolic homeostasis, ultimately contributing to osteoporosis [151,152]. The precise mechanism by which GM stimulates 5-HT production is still unclear. 5-HT receptors comprise at least 14 subtypes (Htr1-7), with Htr3 being the sole ion channel receptor and the others belonging to the G protein-coupled receptor (GPCR) family. Activation of different 5-HT receptors elicits varied biological effects, with 5-HT1A, 5-HT2A, 5-HT1B and 5-HT2B receptors found on osteoblasts, and 5-HT1A, 5-HT2A, 5-HT2B, and 5-HT6 receptors on osteoclasts [153]. Gut-derived 5-HT inhibits osteoblast proliferation by activating 5-HT1B receptors on osteoblast precursors [154], while stimulation of 5-HT6 and 5-HT2B receptors on osteoclasts enhances bone resorption [155,156]. However, suppression of gut-derived 5-HT synthesis increases osteoblast activity, reduces osteoclast numbers, and ameliorates osteoporosis. Intriguingly, while gut-derived 5-HT suppresses bone formation, brain-derived 5-HT exerts bone-protective effects through activation of 5-HT2C receptors on central neurons [157].

IGF-1 serves as a critical signaling molecule that mediates the regulatory effects of GM on skeletal homeostasis [158,159]. It is an essential regulator of cell survival, proliferation, and differentiation, and has long been recognized as a critical factor in bone remodeling. IGF-1 promotes osteoblast-to-osteocyte transition via the IGF-1/IGF-1R pathway, increased collagen synthesis, and differentiation of BMSC into osteoblasts, thereby increasing bone matrix deposition [160]. Additionally, IGF-1 indirectly lowers the RANKL/OPG ratio, reducing osteoclast differentiation and bone resorption. It also stimulates bone formation by modulating the secretion of PTH and growth hormone [161]. Compared to control mice, specific pathogen-free (SPF) mice exhibit less IGF-1 receptor expression in bone tissue, reduced serum IGF-1, and concomitant osteoporosis [158]. However, germ-free mice showed significantly elevated serum IGF-1 following GM transplantation [159]. It was also reported that SCFA supplementation effectively restores IGF-1 levels and bone mass in SPF mice [159], possibly by inducing hepatic IGF-1 synthesis through the activation of GPCRs on hepatocytes. These findings highlight the critical role of IGF-1 in mediating GM-regulated bone metabolism. HFD-induced bone loss is associated with decreased expression of IGF-1 [147], potentially mediated through HFD-induced GM dysbiosis. Microbiome analysis has revealed HFD-mediated changes in microbial diversity, including marked decreases in SCFA-producing taxa and IGF-1-stimulating bacterial populations [162]. This led to attenuated IGF-1-mediated osteoblastogenesis and enhanced osteoclast differentiation, ultimately contributing to osteoporosis [163].

PTH is a key regulator of bone metabolism [164]. Emerging evidence suggests that changes in GM composition can modulate the regulatory effects of PTH on bone metabolism [165]. In particular, reductions in beneficial microbiota (e.g., *Lactobacillus*, *Bifidobacterium*) may impair PTH-mediated bone anabolism [105]. HFD was reported to suppress the anabolic effects of PTH on bone metabolism, thereby contributing to osteoporosis [166]. Emerging evidence highlights the critical involvement of the GM in HFD-associated bone loss, primarily via modulation of PTH pathway activity. HFD-induced impairment of bone microstructure and BMD are closely associated with decreased serum PTH caused by GM dysbiosis [105]. This implies that gut dysbiosis triggered by HFD reduces PTH production, which is crucial to osteoporosis development. PTH-dependent osteogenic differentiation and bone matrix mineralization are modulated by butyrate, a key microbial-derived SCFA [167]. Butyrate may enhance the osteogenic effects of PTH by promoting expansion of Treg cells and stimulating Wnt10b secretion from bone marrow $CD8^+$ T cells [168]. Other gut-derived hormones, including GLP-1 [169] and ghrelin [170], may also participate in HFD-induced osteoporosis.

5.4 GM-Induced Immuno-Inflammatory Dysregulation in Bone Metabolism

GM serves as a pivotal regulator of bone metabolic balance by modulating immune-inflammatory status (Fig. 4). HFD-fed mice show reductions in beneficial gut microbes (e.g., *Lactobacillus*, *Bifidobacterium*) alongside increased abundance of potentially pathogenic bacteria (e.g., *Bacteroides*, *Rikenellaceae*). This microbial dysbiosis increases proinflammatory cytokine levels, including TNF-α, IL-6, IL-1β, and MCP-1, leading to bone loss [45,105]. Immune cells, particularly macrophages and monocytes, and their associated cytokine networks are key mediators through which HFD-induced GM dysbiosis promotes osteoporosis. Anti-inflammatory cytokines help to mitigate bone loss by suppressing osteoclast activity [171], whereas HFD-induced dysbiosis increases the release of proinflammatory cytokines that stimulate bone resorption. These cytokines promote osteoclastogenesis by inducing RANKL secretion from osteoblasts and T cells, while downregulating OPG, thereby activating RANKL/RANK signaling to drive differentiation of bone marrow-derived macrophages/monocytes into osteoclasts [8,93]. Concurrently, proinflammatory cytokines (TNF-α, IL-1β, IL-17) impair osteoblast differentiation and function by inhibiting the Wnt/β-catenin signaling pathway, collectively reducing bone formation [172]. Furthermore, chronic inflammation accelerates osteocyte apoptosis, exacerbating bone loss [173].

The Th17/Treg cell ratio is a critical factor in HFD-induced GM dysbiosis leading to osteoporosis [128,174]. Treg cells are known to maintain bone metabolic homeosta-

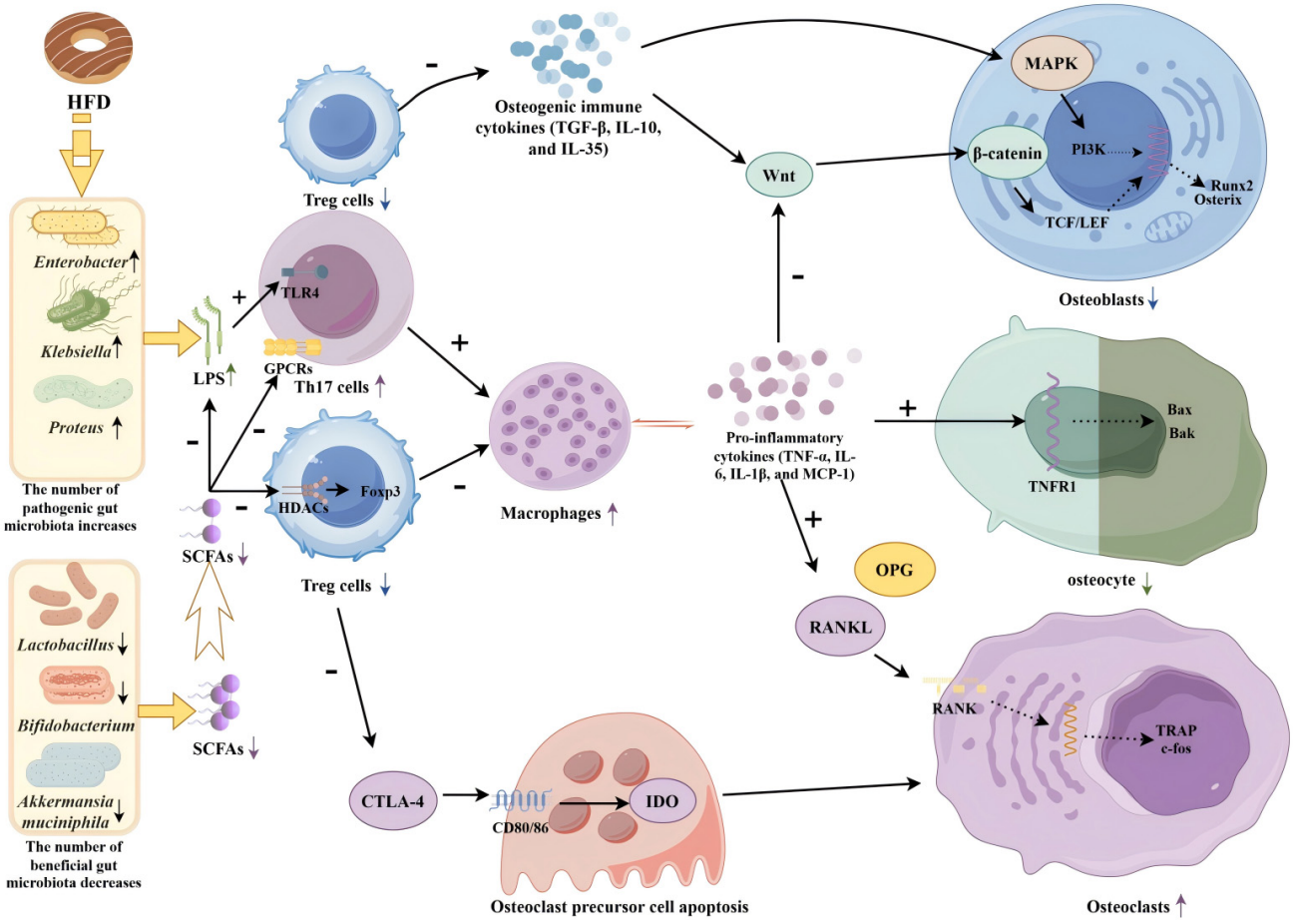

Fig. 4. Mechanisms of HFD-induced GM dysbiosis in promoting bone loss via inflammatory activation. HFD reduces the abundance of beneficial GM responsible for producing SCFAs, while enriching potentially pathogenic bacteria that generate endotoxins such as lipopolysaccharide. The consequent reduction in SCFAs undermines their dual role in suppressing LPS-induced Th17 cell activation and promoting Treg cell differentiation, leading to a Th17/Treg imbalance. This skewed immune response elevates pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, MCP-1) and represses anti-inflammatory ones (TGF-β, IL-10, IL-35). Consequently, a heightened inflammatory state pervades the bone microenvironment, which promotes osteocyte apoptosis, suppresses osteoblast formation, and enhances osteoclast activity, ultimately driving bone loss. Abbreviations: HFD, high-fat diet; GM, gut microbiota; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells; GPCR, G protein-coupled receptor; HDACs, histone deacetylases; Foxp3, forkhead box protein 3; TGF-β, transforming growth factor-β; IL-35, interleukin-35; IDO, indoleamine 2,3-dioxygenase; CTLA-4, cytotoxic T-lymphocyte antigen 4; MAPK, mitogen-activated protein kinase; Wnt/β-catenin, Wingless type MMTV integration site family/β-catenin signaling pathway; PI3K, phosphatidylinositol 3-kinase; Runx2, runt-related transcription factor 2; Bax, BCL-2-associated x protein; Bak, BCL-2 antagonist/killer 1; TNFR1, tumor necrosis factor receptor 1; TRAP, tartrate-resistant acid phosphatase; RANKL, receptor activator of nuclear factor Kappa-B Ligand; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; TCF, T-cell factor; LEF, lymphoid enhancer factor. Note: "+" indicates promotion; "–" indicates inhibition; "↑" indicates increase; "↓" indicates decrease.

sis through various immunomodulatory mechanisms. They express CTLA-4, which interacts with CD80/86 on osteoclast precursors to increase indoleamine 2,3-dioxygenase (IDO) expression. IDO activation is the rate-limiting enzyme in intracellular tryptophan degradation. The subsequent depletion of tryptophan triggers apoptosis of osteoclast precursors, thereby suppressing osteoclastogenesis and bone resorption [175]. Furthermore, Treg-derived cytokines (TGF-β, IL-10, and IL-35) enhance bone formation via MAPK and Smad signaling pathways [176,177], whereas Th17 cells exert detrimental effects on skeletal health. Th17 cells produce RANKL that binds to RANK on osteoclast precursors, promoting differentiation into mature osteoclasts and increasing bone resorption [178]. Th17-secreted cytokines (IL-17, IL-22, and IFN-γ) directly stimulate bone resorption and induce macrophages to produce proinflammatory factors (TNF-α, IL-1, and IL-6), further exacerbating bone loss [171,179]. Numerous studies have

Table 1. Probiotics and prebiotics improve HFD induced osteoporosis.

Probiotics/Prebiotics	Main mechanisms	The impact on bones	References
Probiotics			
Lacticaseibacillus paracasei DSM13434; *Lactiplantibacillus plantarum DSM 15312* and *DSM 15313*	Regulate the composition of the GM and increase the production of SCFAs (acetate and butyrate).	Improved BV/TV score and BMD.	[184]
Lactobacillus rhamnosus GG	Enhance the production of metabolites SCFAs (butyrate) by the GM.	Leads to an increase in the secretion of the osteogenic Wnt ligand Wnt10b, ultimately enhancing BMD.	[168]
Lactobacillus plantarum LC27; *Bifidobacterium longum LC67*	Inhibit the production of endotoxins (LPS) by GM, thereby alleviating systemic chronic inflammation.	Alleviate HFD-induced osteoporosis by inhibiting NF-κB activation and enhancing AMPK signaling.	[186]
Tolypocladium sinense	Upregulate intestinal tight junction proteins (such as ZO-1, occludin, and Claudin-1) to improve intestinal barrier dysfunction.	Reduce serum LPS levels and further increase BMD.	[187]
Lactobacillus coryniformis	Reverse intestinal dysbiosis and maintain the balance of intestinal Treg/Th17 cells.	Improve HFD-induced bone loss.	[189]
Lactobacillus rhamnosus	Maintain the balance of intestinal Treg/Th17 cells.	Inhibit osteoclast formation and further increase BMD.	[190]
Lactobacillus acidophilus	Regulate the balance of intestinal Treg/Th17 cells.	Increase the BV/TV of bones and BMD.	[191]
Engineered probiotics			
Akkermansia muciniphila	Its derived EVs can restore intestinal homeostasis and improve systemic chronic inflammation induced by endotoxins.	Improve HFD-induced osteoporosis mediated by metabolic disorders.	[192,193,194]
Proteus mirabilis	Its derived EVs activates the osteoclast apoptosis pathway and induces mitochondrial dysfunction.	Inhibit bone resorption and enhance BMD.	[195]
Prebiotics			
Fructooligosaccharides; galactooligosaccharides	Increasing gut microbiome diversity and SCFAs levels reversed the hyperpermeability of the gut barrier.	Alleviated HFD-induced bone loss.	[108]
Raspberry polysaccharides	Regulated the composition of the GM and increased the levels of butyrate in the gut.	Alleviates HFD-induced oxidative stress and systemic inflammation, thereby increasing BMD.	[185]
Rosa roxburghii Tratt fruit polysaccharides	Regulate the composition of GM and enhance intestinal epithelial integrity (increase the expression of intestinal tight junction proteins occludin and ZO-1).	Inhibit endotoxin-induced systemic inflammatory cascade, thereby increasing BMD.	[188]

Abbreviations: HFD, high-fat diet; GM, gut microbiota; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; BMD, bone mineral density; BV/TV, bone volume; NF-κB, nuclear transcription factor-κB; AMPK, adenosine monophosphate-activated protein kinase; ZO-1, zonula occludens-1; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells; Wnt, wingless type MMTV integration site family; EVs, extracellular vesicles.

confirmed that HFD-induced GM disruption coincides with Th17/Treg cell imbalance, which accelerates progression of osteoporosis through the aforementioned mechanisms [13,107].

6. Therapeutic Strategies: Targeting GM to Prevent HFD-Induced Osteoporosis

Various pharmacological agents have been employed to treat osteoporosis, including bisphosphonates, calcitonin, estrogen and PTH. However, these therapies often have undesirable side effects [180]. Bisphosphonates can cause gastric discomfort and heartburn, while prolonged use of estrogen or calcitonin can increase susceptibility to malignancies. GM-directed interventions exert dual benefits on skeletal homeostasis while avoiding the adverse side effects commonly associated with standard anti-osteoporotic regimens [181]. Artificial modulation of GM was found to markedly ameliorate HFD-induced bone metabolic disorders and bone loss [108,182]. Modulation of GM ecosystems may therefore be a viable strategy to prevent HFD-associated osteopenia. The following content summarizes how emerging interventions can modulate GM composition and metabolites, thereby regulating bone homeostasis, influencing bone mass, and ameliorating HFD-induced osteoporosis.

6.1 Probiotics and Prebiotics

Probiotics are defined as beneficial live microbial communities that colonize the gut and exert specific health-promoting effects. They improve host health by modulating GM balance, inhibiting growth of pathogenic bacteria, and enhancing intestinal barrier function [183]. Prebiotics, on the other hand, are "food ingredients" that cannot be digested by the host or pathogenic intestinal bacteria, but are selectively utilized by beneficial microbiota, thereby conferring health benefits [1]. Probiotic and prebiotic interventions effectively counteract HFD-associated bone loss by modulating intestinal microbial ecology [101,182] (Table 1, Ref. [108,168,184,185,186,187,188,189,190,191,192,193,194,195]). The underlying mechanisms include selective promotion of beneficial GM to increase the production of microbial metabolites (e.g., SCFAs), restoration of intestinal barrier integrity, and modulation of immune responses to prevent systemic translocation of endotoxins, bacterial antigens, or viral components, thereby reducing chronic inflammation.

Many studies have demonstrated that HFD causes GM dysbiosis, reduces beneficial metabolites such as butyrate, and exacerbates systemic inflammation and bone loss [102]. Growing evidence suggests that probiotic and prebiotic interventions can counteract HFD-induced osteoporosis by restoring GM homeostasis and increasing bone-anabolic metabolites like SCFAs [108]. For instance, *fructooligosaccharides* and *galactooligosaccharides*, two clinically established prebiotics, were shown to increase gut microbial biodiversity and SCFA levels in HFD-fed mice when administered daily. They also reversed intestinal hyperpermeability and suppressed pro-inflammatory cytokines (TNFα, IL6, IL17) to mitigate HFD-induced bone loss [108]. Administration of a probiotic mixture containing *Lactobacillus paracasei* and *Lactobacillus plantarum* to mice significantly increased the levels of key SCFA intermediates (e.g., succinate and lactate) and SCFAs, and improved BV/TV fraction and BMD [184]. Raspberry polysaccharides (RCP), a novel class of plant-derived prebiotics, were found to modulate GM composition, diversity, and metabolic output in HFD-fed mice. RCP treatment markedly increased butyrate levels, alleviating HFD-induced oxidative stress and systemic inflammation to improve bone health [185]. Supplementation with *Lactobacillus rhamnosus GG* was found to increase intestinal butyrate production. Butyrate stimulates bone anabolism by promoting $CD8^+$ T cell-Treg cell interactions in the bone marrow, leading to increased secretion of osteogenic Wnt10b and ultimately improving bone density [168].

Probiotics and prebiotics can exert anti-osteoporotic effects by suppressing harmful microbial metabolites such as LPS. *Lactobacillus plantarum LC27* and *Bifidobacterium longum LC67* are anti-inflammatory strains that mitigate HFD-induced metabolic dysregulation by inhibiting LPS production, suppressing NF-κB activation, and enhancing AMPK signaling [186]. Probiotic, prebiotic, or synbiotic treatment of HFD-fed rats was found to reduce intestinal pro-inflammatory metabolites and the release of systemic inflammatory cytokines, thereby ameliorating HFD-induced jawbone loss [182].

Probiotics and prebiotics enhance intestinal barrier integrity, reducing the systemic translocation of endotoxins and pathogenic bacterial antigens, thereby ameliorating HFD-induced osteoporosis. *Tolypocladium sinense*, a fungus isolated from Cordyceps sinensis, produces a mycelial polysaccharide that upregulates intestinal tight junction proteins (ZO-1, occludin, and Claudin-1), improves gut barrier dysfunction, reduces serum LPS levels, and attenuates HFD-induced systemic chronic inflammation [187]. Rosa roxburghii Tratt fruit polysaccharides (RTFP) serve as effective prebiotics by remodeling the GM composition and enhancing intestinal epithelial integrity through upregulation of tight junction proteins, suppression of endotoxin biosynthesis and paracellular leakage, and attenuation of systemic inflammatory cascades, collectively preventing osteoporotic deterioration [188].

Beneficial GM are thought to enhance bone anabolism in HFD-induced obese mice through Treg cell differentiation and maintaining Treg/Th17 cell balance [196]. The *Lactobacillus coryniformis* subsp. T*orquens* (T3L), a probiotic isolated from traditional yak milk, was found to reduce bone loss by promoting Treg cell differentiation and inhibiting osteoclastogenesis. Fecal microbiota transplan-

tation from T3L-treated mice to HFD-fed mice significantly reversed gut dysbiosis and bone loss [189]. *Lactobacillus rhamnosus* was reported to maintain Treg/Th17 balance, suppress osteoclastogenic cytokines, and increase anti-osteoclastogenic cytokines, thereby inhibiting osteoclast formation and improving osteoporosis [190]. *Lactobacillus acidophilus* was shown to enhance BV/TV and BMD in osteoporotic mice by modulating Treg/Th17 equilibrium [191].

EVs produced by gut bacteria are crucial mediators in intercellular signaling and play a pivotal role in GM-bone communication. Engineered, probiotic-derived EVs were proposed as potential delivery systems for osteoporosis treatment [197]. *Akkermansia muciniphila*-derived EVs were found to restore gut homeostasis in HFD-fed mice, ameliorate chronic inflammatory states, and promote metabolic balance, potentially alleviating HFD-induced osteoporosis [192,193]. Engineered *Akkermansia muciniphila*-derived EVs can directly target bone tissue and attenuate osteoporotic phenotypes by enhancing osteogenic activity and suppressing osteoclastogenesis [194]. Furthermore, EVs from the Gram-negative bacterium *Proteus mirabilis* can inhibit osteoclast differentiation and bone resorption. miRNA and mRNA sequencing analysis revealed these EVs can activate osteoclast apoptosis pathways and induce mitochondrial dysfunction [195], thus highlighting the therapeutic potential of probiotic-derived EVs for HFD-induced osteoporosis.

Although probiotics and prebiotics demonstrate efficacy in mitigating HFD-induced osteoporosis with minimal adverse effects, several challenges remain. First, orally administered probiotics are vulnerable to gastric acid and bile salts, resulting in low survival and poor colonization in the continuously renewing intestinal mucus layer [198]. Second, their therapeutic effects may be compromised in acidic environments [199]. However, the combination of probiotics and prebiotics may enhance bacterial survival by leveraging their synergistic effects to counteract adverse environmental factors, yielding more effective therapeutic outcomes compared to the sole use of either [200]. Finally, probiotics serve as adjunctive therapies and cannot replace anti-resorptive agents (e.g., bisphosphonates) or bone-forming drugs, and have limited efficacy in severe osteoporosis cases. Since the beneficial effects of probiotics are not shared by all strains, their efficacy is highly dependent on specific strains. Therefore, research findings of a particular strain cannot be simply generalized to the entire species or to all probiotics. In future research and clinical applications, it is crucial to clearly define the identity and functional characteristics of the strains.

6.2 Potential Drugs and Natural Compounds

In addition to probiotic/prebiotic therapies, natural compounds can potentially modulate the GM to promote bone health [201] (Table 2, Ref. [128,201,202,203,204,205,206,207,208,209]). Polyphenolic natural plant extracts demonstrate significant therapeutic efficacy in alleviating osteoporosis associated with GM dysbiosis [210,211]. Punicalagin (PU), a polyphenolic compound derived from pomegranate peel, exhibits potent antioxidant, anti-inflammatory, and anti-cancer activities. PU was found to suppress RANKL-induced osteoclast formation and bone resorption [212]. Emerging evidence suggests the osteoprotective effects of PU are closely associated with GM modulation. In HFD-fed rats, PU significantly increased the abundance of beneficial bacteria (e.g., *Akkermansia* and *Ruminiclostridium_9*), which showed strong positive correlations with SCFA and serum vitamin K-2 levels. Furthermore, these microbial changes correlated with altered levels of bone metabolism markers, including procollagen type I N-terminal propeptide and RUNX2. PU stimulates osteogenesis through SCFA biosynthetic pathways and by downregulating markers of osteoclast activity. Elevated vitamin K-2 levels markedly accelerate bone mineralization and improve bone strength [128], indicating that PU mitigates HFD-induced bone loss through regulation of GM. Green tea catechins are another class of polyphenolic compounds that demonstrate antioxidant, metabolic regulatory, and antimicrobial properties [213]. They reduce systemic chronic inflammation in HFD-fed mice by modulating SCFA composition, thereby improving osteoporosis. Green tea catechins increase the abundance of *Akkermansia* and other beneficial microbiota, alleviate intestinal barrier dysfunction, and reduce the expression of intestinal inflammatory factors, ultimately exerting a bone-protective effect [202]. Anthocyanins are a class of polyphenolic compounds extracted from Butterfly pea flower. They ameliorate HFD-induced osteoporosis through modulation of the GM-bone axis. Anthocyanins increase BMD by enriching SCFA-producing bacteria (e.g., *Akkermansia*, *Butyricicocceae*), upregulating expression of intestinal tight junction proteins, and modulating Treg/Th17 cell balance [203].

Other natural compounds also exhibit promising therapeutic effects on HFD-induced osteoporosis. Geranylgeraniol, a C20 isoprenoid from Annatto (a plant-derived natural food colorant) altered the GM composition in HFD-induced osteoporotic mice, specifically increasing the abundance of *Butyricicoccus pullicaecorum* while decreasing *Dorea longicatena* [214]. These GM changes resulted in increased serum levels of PINP (a marker of bone formation), decreased CTX-1 (a marker of bone resorption), and improved femoral cortical thickness and BMD [201]. An extract from the plant Molokhia (WM) was found to ameliorate HFD-induced metabolic disorders, including osteoporosis, by modulating GM composition [204]. Mechanistically, WM may increase *Lactobacillus* abundance while decreasing *Desulfovibrio*, thereby improving gut barrier integrity and suppressing metabolic endotoxemia [204]. These osteoprotective effects could amelio-

Table 2. Natural compounds improve HFD induced osteoporosis.

Natural compound	Target GM	Mechanisms	Main functions	References
Polyphenolic natural plant compounds				
Punicalagin	Increase the abundance of beneficial bacteria (Akkermansia and Ruminiclostridium_9).	Increase serum SCFAs concentration and vitamin K2 levels.	Stimulates osteogenesis and inhibits osteoclast activity, while accelerating bone mineralization and bone formation, ultimately increasing BMD.	[128]
Green tea catechins	Increase the abundance of GM (Akkermansia).	Increase the synthesis of SCFAs by the GM.	Alleviate systemic chronic inflammation, thereby improving HFD-induced osteoporosis.	[202]
Anthocyanins	Enrich beneficial gut bacteria (Akkermansia and Butyricicoccaceae).	Increase the production of SCFAs and the expression of intestinal tight junction proteins.	Regulate the Treg/Th17 cells balance to enhance BMD.	[203]
Other natural plant compounds				
Geranylgeraniol	Increased the abundance of Butyricicoccus pullicaecorum, while decreasing the number of Dorea longicatena.	Enhance intestinal barrier function and reduce LPS-induced inflammatory responses.	Improve cortical thickness and increase BMD.	[201]
Molokhia leaf extract	Increase the abundance of Lactobacillus while reducing the number of Desulfurococcus.	Improve the integrity of the intestinal barrier and inhibit metabolic endotoxemia.	Improving HFD-induced osteoporosis.	[204]
Genistein	Increase the abundance of beneficial bacteria g-Dubosiella and g-Blautia.	Maintain intestinal barrier function, increase SCFAs production, and inhibit metabolic endotoxemia.	Prevent HFD-induced bone loss.	[205]
Berberine; genistein; mung bean seed coat extract; phaseolamin	Enhance the activity of beneficial bacterial communities (such as Lactobacillus and Bifidobacterium) and inhibit the proliferation of potential pathogenic bacteria (such as Helicobacter pylori and Desulfovibrio).	Strengthen the intestinal barrier, reduce systemic endotoxin translocation, and collectively improve metabolic disorders.	Improving HFD-induced osteoporosis.	[206,207,208,209]

Abbreviations: HFD, high-fat diet; GM, gut microbiota; SCFAs, short-chain fatty acids; LPS, lipopolysaccharide; BMD, bone mineral density; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells.

rate HFD-induced osteoporosis. Genistein is a soy-derived isoflavone that can prevent HFD-induced bone loss by reducing GM dysbiosis, increasing the abundance of beneficial bacteria *g-Dubosiella* and *g-Blautia* in feces, and maintaining intestinal barrier function [205,206]. Additional plant-derived compounds that share similar mechanisms include berberine [207], mung bean seed coat extract [208], and non-nutritive bioactive agents such as phaseolamin from Phaseolus vulgaris L. [209]. These compounds enhance the activity of beneficial bacterial communities (e.g., *Lactobacillus*, *Bifidobacterium*), inhibit the proliferation of potential pathogenic bacteria (e.g., *Helicobacter pylori*, *Desulfovibrio*), strengthen the intestinal barrier, and reduce systemic endotoxins to collectively improve HFD-induced osteoporosis mediated by metabolic disorders. However, the doses of natural compounds used in different studies vary greatly, directly affecting the comparability and reproducibility of results.

7. Conclusions and Future Perspectives

Recent studies have elucidated the risk factors and pathogenesis of osteoporosis. With the adoption of HFDs increasing globally, HFD-induced osteoporosis has attracted growing attention. HFD has emerged as a significant etiological factor in the development of osteoporosis in contemporary populations. HFD-induced pathological expansion of adipose tissue disrupts bone metabolism homeostasis through multiple pathways, including oxidative stress, immune-inflammatory cascades, and lipotoxic-

ity. Furthermore, emerging research highlights the pivotal role of GM in HFD-induced osteoporosis. This systematic review analyzed the three-way relationship between HFD, GM, and osteoporosis, while raising possible therapeutic strategies for HFD-induced osteoporosis by targeting GM. The key mechanisms by which GM mediates HFD-induced osteoporosis were examined, including intestinal barrier dysfunction, dysregulation of microbial metabolite secretion, abnormal release of gut-derived endocrine hormones, and inflammatory cascade activation caused by microbial dysbiosis. These HFD-induced alterations were identified as potential therapeutic targets through microbiota-based interventions including probiotics, prebiotics, and natural compounds that improve HFD-induced osteoporosis.

An abundance of *Lactobacillus*, *Bifidobacterium*, and *Akkermansia muciniphila* is positively correlated with improved bone mass, whereas *Enterobacteriaceae*, *Klebsiella*, *Desulfovibrio*, *Vibrio cholerae*, and the F/B ratio are associated with HFD-induced osteoporosis. Future studies should prioritize these microbial taxa as potential interventional targets. Investigation of the optimal timing for GM-targeted interventions (e.g., subclinical stage of the disease, clinical phase, or specific age windows) is essential for the translation of microbiome modulation into effective osteoporosis management. However, for patients with severe immune deficiency, critical illness, or underlying conditions such as short bowel syndrome, probiotics may carry the risk of causing bacteremia or fungemia. Moreover, certain natural compounds may interact with conventional medications, placing a serious burden on liver and kidney function.

Current research evidence is mainly derived from mouse models, with a lack of relevant clinical research data. Although mouse models are valuable for mechanistic studies of how HFD influences bone remodeling via the GM, significant interspecies differences pose challenges for extrapolating the findings to humans. These include variations in gut microbial diversity, expression of key bacterial genera, and intestinal physiological features including transit time, luminal pH, mucus composition, and immune regulation. Fundamental differences in bone physiology and remodeling dynamics between mice and humans further complicate direct translation. To improve clinical translational relevance, future studies should incorporate humanized probiotic models and longitudinal multi-omics analyses across diverse populations covering age, sex, menopausal status, and geographic region. This should be integrated with multidimensional data from genomics, metabolomics, and immunomics analyses. Findings from such studies should inform and optimize the design of clinical trials for personalized, microbial-based therapeutics targeting HFD-induced osteoporosis, thereby increasing their likelihood of success.

Given the complexity of GM and lack of standardized assessment protocols, current research findings show considerable heterogeneity. Moreover, existing studies often overemphasize the role of individual microbial taxa in bone health rather than adopting an integrated perspective that considers diet, environment, genetics, and microbial communities. Standardized methodologies are needed for future microbiome studies, as well as randomized controlled trials in humans to validate the efficacy of GM modulation for osteoporosis management. Future studies should also prioritize multi-omics integration—including genomics, transcriptomics, and metabolomics—to achieve a comprehensive functional understanding. Considering the individual differences within populations, personalized approaches that take into account genetic background, diet, and lifestyle should be developed, along with comprehensive treatment strategies that combine dietary adjustment, exercise, microbiome transplantation, and drug therapy. In summary, the elucidation of mechanisms in the gut-bone axis and identification of novel therapeutic targets could transform osteoporosis management. Advances in microbiota-based therapies may lead to personalized interventions tailored to individual GM profiles, ultimately improving the quality of life for patients with HFD-induced osteoporosis.

Abbreviations

HFD, high-fat diet; GM, gut microbiota; BMD, bone mineral density; SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids; TFA, trans-fatty acid; MUFAs, monounsaturated fatty acids; BMC, bone mineral content; BMAT, bone marrow adipose tissue; FFAs, free fatty acids; PPARγ, peroxisome proliferator-activated receptor γ; BMSCs, bone marrow mesenchymal stem cells; ROS, reactive oxygen species; PA, palmitic acid; RUNX2, runt-related transcription factor 2; ALP, alkaline phosphatase; BMP2, bone morphogenetic protein 2; TLR4, toll-like receptor 4; NF-κB, nuclear transcription factor-κB; ERK, extracellular signal-regulated kinase; Wnt/β-catenin, Wingless type MMTV integration site family/β-catenin signaling pathway; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; IL-10, interleukin-10; IL-17, interleukin-17; IL-22, interleukin-22; IL-35, interleukin-35; IFN-γ, interferon-γ; MCP-1, monocyte chemoattractant protein-1; Dkk-1, dickkopf-1; SOST, sclerostin; PTH, parathyroid hormone; Bax, BCL2-associated X protein; Bcl-2, B-cell lymphoma-2; BV/TV, bone volume; PINP, procollagen type I N-terminal propeptide; JAK2, janus kinase 2; Stat3, signal transducer and activator of transcription 3; RANKL, receptor activator of nuclear factor Kappa-B Ligand; OPG, osteoprotegerin; PI3K, phosphatidylinositol 3-kinase; NLRP3, NOD-like receptor pyrin domain-containing 3; COX-2, cyclooxygenase-2; EVs, extracellular vesicles; JAM-A, junctional adhesion molecule A; LPS, lipopolysaccharide; ZO-1, zonula occludens-1; SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; IPA, indole-3-propionic

acid; IGF-1, insulin-like growth factor-1; GLP-1, glucagon-like peptide-1; FXR, farnesoid X receptor; TGR5, takeda G protein-coupled receptor 5; LCFAs, long-chain fatty acids; 5-HT, 5-hydroxytryptamine; GPCR, G protein-coupled receptor; SPF, specific pathogen-free; IDO, indoleamine 2,3-dioxygenase; TGF-β, transforming growth factor-β; RCP, raspberry polysaccharides; RTFP, Rosa roxburghii Tratt fruit polysaccharides; PU, punicalagin; Treg cells, regulatory T cells; Th17 cells, T helper 17 cells.

Author Contributions

XPW and LJL collected and studied the references and wrote the manuscript; KZ and WYL conceived and designed the review; YZX, RWL, and YCC assisted in the preparation of the charts and tables. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

We used ChatGPT software to improve our English. The authors checked the article, made appropriate revisions, and are responsible for the article.

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