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Review

The Gut-Bone Axis: Molecular Mechanisms and Therapeutic Perspectives in Skeletal Homeostasis

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Abstract

The gut–bone axis represents a paradigm shift in our understanding of skeletal biology, revealing how the gastrointestinal system and its microbial inhabitants profoundly influence bone homeostasis through complex bidirectional communication. This comprehensive review synthesizes recent high-impact research to elucidate the multifaceted mechanisms underlying gut–bone crosstalk, including microbial metabolite signaling, gut barrier integrity, immune modulation, and endocrine regulation. We examine how short-chain fatty acids (SCFAs), tryptophan metabolites, and bile acid derivatives modulate bone remodeling through epigenetic, immunologic, and hormonal pathways. The translational implications of these findings for the management of osteoporosis, osteoarthritis, and inflammatory bone disorders are critically evaluated, with particular emphasis on microbiome-targeted interventions, gut hormone-based therapies, and innovative approaches such as engineered microbial therapeutics. Furthermore, we explore the roles of farnesoid X receptor (FXR) signaling, G protein–coupled receptor activation, and mitochondrial function in bone cells as modulated by gut-derived factors. This review provides a framework for developing novel diagnostic and therapeutic strategies that target the gut–bone axis, highlighting the transition from traditional calcium-centric bone health paradigms toward integrated microbiome-targeted approaches that address the systemic nature of bone metabolism regulation.

Keywords: gastrointestinal microbiome; osteoporosis; short-chain fatty acids; bone remodeling; metabolic bone diseases; homeostasis; metabolome

1. Introduction

Bone remodeling is an exquisitely regulated process that maintains skeletal integrity through the balanced activities of osteoblasts and osteoclasts [1]. Traditional paradigms of bone homeostasis have emphasized hormonal regulation, mechanical loading, and nutritional status as primary determinants of bone mass [2]. However, the discovery that germ-free mice exhibit significant alterations in bone density first suggested that microbial colonization influences skeletal development [3]. Subsequent research has established the gut-bone axis as a critical regulatory system integrating gastrointestinal and skeletal health through complex bidirectional communication [4].

The clinical relevance of this axis is underscored by the high prevalence of osteoporosis and fractures in patients with inflammatory bowel disease (IBD), celiac disease, and other gastrointestinal disorders [5]. Meta-analyses have quantified these associations, revealing that IBD patients have a 40% increased risk of osteoporosis (relative risk [RR] 1.40, 95% CI 1.25–1.56) and a 60% higher overall fracture risk (RR 1.60, 95% CI 1.30–1.97) compared to matched controls. The risk is particularly elevated for vertebral fractures (RR 2.48, 95% CI 1.97–3.12). Similarly, individuals with celiac disease exhibit a 2.1-fold increased odds of osteoporosis (odds ratio [OR] 2.1, 95% CI 1.7–2.6) and a 1.4-fold higher risk of any fracture (hazard ratio [HR] 1.4, 95% CI 1.2–1.7). These associations cannot be fully explained by malabsorption or nutritional deficiencies alone, suggesting direct mechanistic links between gut health and bone metabolism [6]. Furthermore, age-related changes in gut microbiota composition correlate with bone loss, implicating microbial dysbiosis in the pathogenesis of senile osteoporosis [7].

However, these classical frameworks fail to fully account for the skeletal manifestations observed in various gastrointestinal and metabolic disorders, nor can they adequately explain the significant bone density alterations identified in germ-free animal models. This conceptual gap has been bridged by the emerging paradigm of the

gut-bone axis, which reveals how extra-skeletal factors—particularly the gut microbiota and its diverse metabolic output—profoundly influence bone remodeling through integrated immune, endocrine, and neural pathways. The gastrointestinal system, far from being merely a digestive organ, thus emerges as a critical regulator of skeletal homeostasis, orchestrating systemic responses that complement traditional calcium-centric and mechanical loading paradigms.

This manuscript provides a comprehensive analysis of the molecular mechanisms underlying gut-bone communication, with particular emphasis on recent advances published in high-impact journals. We examine how microbial metabolites influence bone cell function through receptor-mediated signaling and epigenetic modifications, how gut barrier integrity affects skeletal health, and how immune cells serve as intermediaries between intestinal and bone compartments (Fig. 1). Therapeutic implications for microbiome-modulating interventions are discussed in depth, with a critical appraisal of current evidence and future directions for research and clinical translation. These interventions encompass several promising approaches, including specific probiotic strains (e.g., Lactobacillus and Bifidobacterium species), prebiotic supplements (e.g., inulin, fructooligosaccharides), targeted dietary modifications (e.g., high-fiber, Mediterranean diets), fecal microbiota transplantation (FMT), and emerging synthetic biology approaches such as engineered microbial therapeutics. Accumulating evidence from preclinical models and preliminary clinical studies has demonstrated the efficacy of these strategies in ameliorating bone loss, improving bone microarchitecture, and reducing fracture risk, highlighting their translational potential for managing metabolic bone disorders [6,7].

2. Microbial Metabolites and Bone Homeostasis

2.1 Short-Chain Fatty Acids: Epigenetic Regulators of Bone Remodeling

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are produced by microbial fermentation of dietary fiber and represent key mediators of gut-bone communication [8]. Acetate, the most abundant SCFA in circulation, exerts multifaceted effects on bone homeostasis primarily through activation of its cognate receptors G protein-coupled receptor 43 (GPR43) and GPR41. In osteoblasts, acetate binding to GPR43 stimulates the Wnt/β-catenin signaling pathway, enhancing osteogenic differentiation and bone formation capacity [9]. Simultaneously, acetate suppresses osteoclastogenesis through inhibition of Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB) nuclear translocation and downregulation of Receptor activator of nuclear factor kappa-B ligand (RANKL)-induced gene expression in osteoclast precursors [10]. Beyond direct actions on bone cells, acetate modulates the bone immune environment by promoting the expansion of regulatory T cells (Tregs) and inhibiting T helper 17 cells (Th17) cell differentiation, thereby creating an anti-osteoclastogenic microenvironment [11]. In ovariectomized mouse models, dietary supplementation with acetate (5% in drinking water) significantly attenuated trabecular bone loss by approximately 35% and improved bone mechanical properties [12]. Butyrate, in particular, has demonstrated potent osteogenic properties through histone deacetylase (HDAC) inhibition [13]. At concentrations of 0.5–2 mM, butyrate enhances Runt-related transcription factor 2 (RUNX2) expression and promotes osteoblast differentiation by increasing histone acetylation at promoter regions of osteogenic genes [14]. Simultaneously, butyrate suppresses osteoclast formation through downregulation of Nuclear Factor of Activated T-cells, Cytoplasmic 1 (NFATc1), a master regulator of osteoclastogenesis, and inhibition of TNF receptor-associated factor 6 (TRAF6) ubiquitination [15]. Beyond inflammatory arthritis models, compelling evidence demonstrates the efficacy of butyrate in non-inflammatory bone loss conditions, particularly age-related osteoporosis. In aging rodent models, butyrate supplementation significantly ameliorated senile osteoporosis by enhancing mitochondrial function and reducing oxidative stress in bone tissue. The beneficial effects of butyrate on age-related bone loss were associated with activation of the nuclear factor erythroid 2–related factor 2 (Nrf2)/glycogen synthase kinase-3 beta (GSK-3β) signaling pathway and upregulation of mitochondrial biogenesis factors peroxisome proliferator–activated receptor-gamma coactivator 1-alpha (PGC-1α) and mitochondrial transcription factor A (TFAM), thereby improving osteoblast mineralization capacity and restoring bone metabolic balance. Furthermore, human study has revealed that gut microbiota-derived butyrate enhances bone mineral density in healthy individuals through exercise-dependent mechanisms, with Oscillibacter and R. torques group identified as key butyrate-producing bacteria contributing to this protective effect. Propionate activates GPR43 on osteoblasts, leading to enhanced Wnt/β-catenin signaling and increased alkaline phosphatase activity [16]. In ovariectomized murine models, dietary supplementation with inulin-propionate esters significantly increased trabecular bone volume fraction (BV/TV) by 37% and reduced osteoclast surface by 29% compared to controls [17]. These effects were abolished in GPR43-knockout mice, confirming the receptor-specific nature of propionate's osteoprotective actions [17]. The therapeutic potential of SCFAs extends to inflammatory bone loss. In collagen-induced arthritis models, butyrate supplementation reduced joint erosion by 52% and decreased Th17 cell differentiation while expanding regulatory T cell populations [18]. These immunomodulatory effects were associated with decreased production of

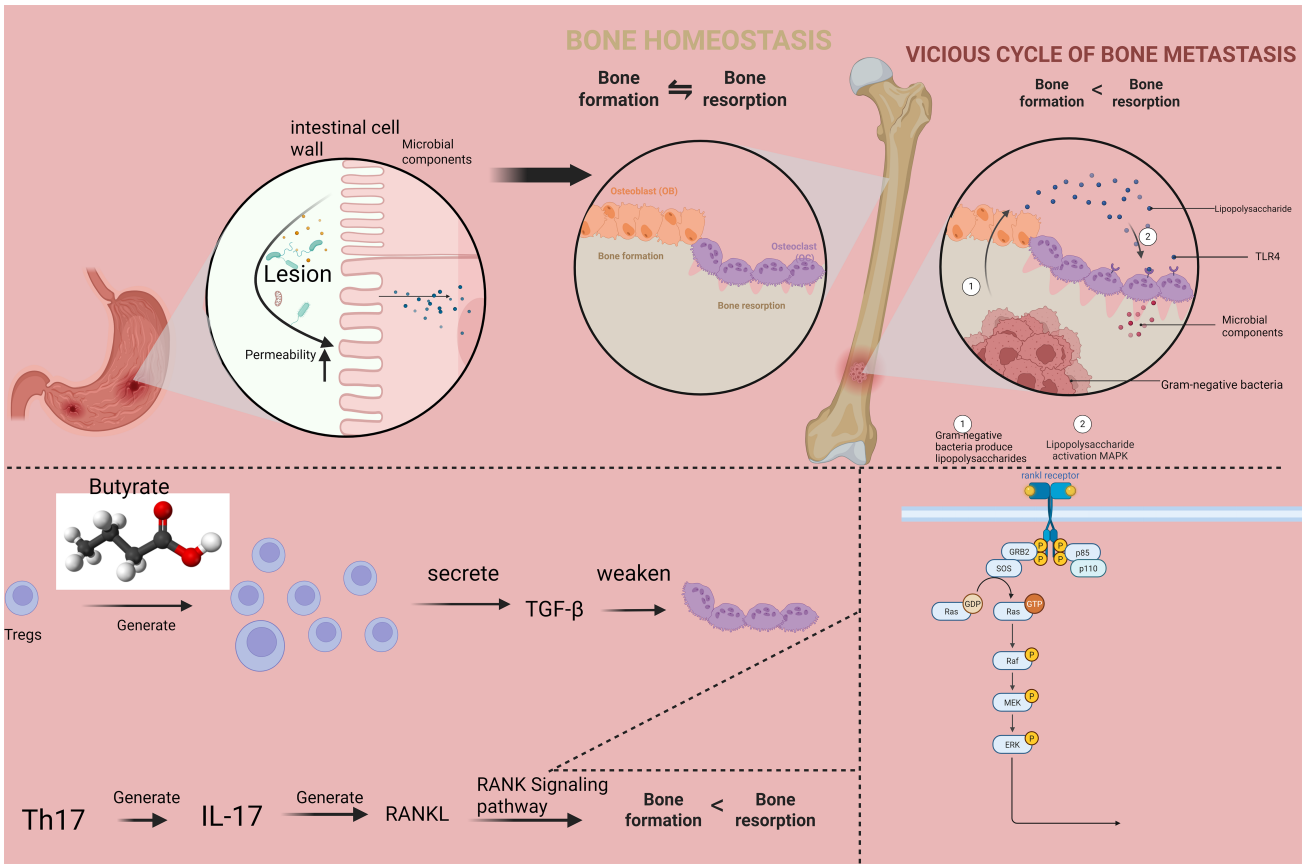

Fig. 1. The molecular interplay within the gut-bone axis linking compromised intestinal integrity to disrupted bone homeostasis. The model illustrates how altered circulating cytokine levels differentially regulate osteoblastic and osteoclastic activity, shifting the bone remodeling balance toward net resorption. TGF-β, Transforming growth factor beta; Th17, T helper 17 cells; IL-17, Interleukin-17; RANKL, Receptor activator of nuclear factor kappa-B ligand; TLR4, Toll-like receptor 4; MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular signal-regulated kinase; MEK, MAPK/ERK Kinase; ROS, Reactive Oxygen Species; GRB2, Growth factor receptor-bound protein 2. Created in BioRender. we, j. (2025) BioRender.com/8fqmz6i.

Interleukin-17 (IL-17) and RANKL, critical mediators of inflammatory bone resorption.

2.2 Tryptophan Metabolites: Aryl Hydrocarbon Receptor Modulation

Tryptophan metabolism by gut microorganisms generates numerous bioactive compounds, including indole derivatives, serotonin, and kynurenine pathway metabolites [15]. Indole-3-aldehyde and indole-3-propionic acid activate the aryl hydrocarbon receptor (AhR) in osteoblasts, promoting expression of Cytochrome P450 family 1 subfamily A member 1 (CYP1A1) and Cytochrome P450 family 1 subfamily B member 1 (CYP1B1) while enhancing osteogenic differentiation [16]. AhR activation also suppresses osteoclastogenesis by inhibiting NF-κB signaling and reducing reactive oxygen species production in precursor cells [17]. Engineering of tryptophan-producing microbial strains represents a promising therapeutic approach [18]. Transplantation of Lactobacillus reuteri engineered to overexpress tryptophan synthase increased circulating indole levels and prevented bone loss in ovariectomized mice by 78% compared to wild-type strains [18]. These effects were mediated through AhR-dependent upregulation of osteoprotegerin production by osteoblasts [19]. Notably, a recent groundbreaking study demonstrated that engineered tryptophan-producing Clostridium bacteria (Trp CB) repaired intestinal barrier function in colitis mice, resulting in a 23.6% increase in bone density and a 41.8% reduction in osteoclast numbers [20]. This intervention also increased bone formation markers (P1NP) by 1.7-fold, demonstrating the profound osteoprotective effects of targeted microbial manipulation [20,21].

2.3 Bile Acid Metabolism and FXR Signaling

Primary bile acids undergo microbial transformation into secondary bile acids, which function as signaling molecules through activation of both nuclear and membrane-bound receptors [22]. The G protein-coupled bile acid receptor TGR5 (GPBAR1) has emerged as a crucial mediator of bile acid actions on bone metabolism. Lithocholic acid (LCA) and deoxycholic acid (DCA) activate Takeda G protein-coupled Receptor 5 (TGR5)

on osteoblasts, triggering intracellular Cyclic Adenosine Monophosphate (cAMP) accumulation and subsequent protein kinase A (PKA) activation, which phosphorylates the transcription factor cAMP response element-binding protein (CREB) [22,23]. This signaling cascade promotes osteoblast proliferation, differentiation, and mineralization by upregulating key osteogenic factors including RUNX2, Osterix, and alkaline phosphatase [23]. Beyond direct effects on bone cells, TGR5 signaling exerts systemic influence on bone homeostasis through multiple pathways. TGR5 activation in intestinal enteroendocrine L-cells stimulates glucagon-like peptide-1 (GLP-1) secretion, which contributes to the postprandial suppression of bone resorption [24]. Additionally, TGR5 expression in immune cells modulates inflammatory responses, potentially influencing osteoclast differentiation and activity in inflammatory bone diseases [25]. Preclinical evidence from TGR5-deficient mouse models demonstrates accelerated age-related bone loss and impaired fracture healing, underscoring the physiological importance of this receptor in skeletal maintenance [26]. The interplay between TGR5 and farnesoid X receptor (FXR) signaling creates a sophisticated regulatory network for bile acid-mediated bone homeostasis. While TGR5 activation generally promotes bone formation through both direct and indirect mechanisms, FXR signaling exerts more complex, tissue-specific effects [23]. Intestinal-specific FXR activation appears to negatively regulate bone mass, as evidenced by the 24% increase in trabecular bone volume observed in intestinal epithelial cell-specific FXR knockout mice [27]. This effect is associated with reduced sclerostin expression and enhanced Wnt signaling in bone tissue [27]. Ursodeoxycholic acid (UDCA) and its taurine-conjugated derivative Tauroursodeoxycholic acid (TUDCA) function as dual modulators of both TGR5 and FXR signaling pathways, contributing to their osteoprotective effects [28]. In postmenopausal women with osteopenia, UDCA supplementation (15 mg/kg/day) for 12 months increased lumbar spine Bone Mineral Density (BMD) by 2.8% compared to placebo [29]. Mechanistic study indicate that UDCA reduces oxidative stress in bone marrow mesenchymal stem cells and enhances their osteogenic potential through complementary activation of both TGR5-mediated signaling and Nrf2 antioxidant pathways [30].

2.4 Trimethylamine N-Oxide (TMAO): A Dual-Role Metabolite in Bone Homeostasis

Trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite generated from dietary precursors such as choline, L-carnitine, and betaine, has been extensively studied in relation to bone metabolism, though its role remains complex and context-dependent [29]. TMAO is produced via a two-step process: gut microbial conversion of dietary nutrients to trimethylamine (TMA), followed by hepatic oxidation via flavin-containing monooxygenase 3 (FMO3) [30]. Current evidence reveals a concentration-dependent duality in TMAO's skeletal effects. Moderate TMAO levels have demonstrated osteoprotective properties in preclinical models. In ovariectomized rats, TMAO supplementation (120 mg/kg/day) attenuated trabecular bone loss by approximately 30%, suppressing osteoclast differentiation through inhibition of NF-κB and Mitogen-Activated Protein Kinase (MAPK) signaling [31]. Furthermore, TMAO enhanced osteogenic differentiation of bone marrow mesenchymal stem cells by approximately 40% via activation of the Nrf2-mediated antioxidant pathway [32]. Conversely, chronically elevated TMAO concentrations ($\geq$300 mg/kg/day) have been associated with detrimental bone outcomes, particularly in aging and metabolic disease models. High TMAO levels exacerbated bone loss by approximately 25%, potentially through induction of systemic inflammation and oxidative stress [33]. At pathological concentrations, TMAO promotes expression of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which stimulate osteoclastogenesis and impair osteoblast function [34].

2.5 Other Microbial Metabolites: Polyamines and Vitamins

Beyond the well-characterized SCFAs, tryptophan metabolites, and bile acids, gut microbiota-derived polyamines and vitamins significantly contribute to bone homeostasis [29]. Polyamines, including spermidine and spermine, are produced by bacteria such as Bifidobacterium and Lactobacillus through enzymatic decarboxylation of amino acids [30]. These compounds enhance osteoblast differentiation and mineralization by modulating autophagy and reducing oxidative stress [29,31]. In aged murine models, dietary spermidine supplementation (3 mM in drinking water) increased trabecular bone volume by 27% and improved bone strength through upregulation of Nrf2-dependent antioxidant pathways [32]. Microbiota-synthesized vitamin K_2 (menaquinone) is essential for γ-carboxylation of osteocalcin, a process critical for bone matrix mineralization [35]. Bacteroides and Escherichia coli are primary producers of menaquinone, which activates the nuclear pregnane X receptor (PXR) in osteoblasts to promote expression of osteogenic genes [33]. Epidemiological data indicate that higher circulating menaquinone levels are associated with a 34% reduction in hip fracture risk in elderly populations [33,34]. Moreover, vitamin K_2 supplementation (45 mg/day) for 24 weeks significantly improved undercarboxylated osteocalcin levels and increased lumbar spine BMD by 1.7% in postmenopausal women with osteoporosis [36–38] (Table 1, Ref. [8–14,21–32,36,39–70]).

Table 1. Key microbial metabolites and their intricate roles in regulating bone homeostasis.

Metabolite class	Representative molecules	Primary microbial producers	Molecular targets & receptors	Signaling pathways & mechanisms	Observed effects on bone *in vivo*	Clinical & translational insights
Short-chain fatty acids (SCFAs)	Butyrate	Faecalibacterium prausnitzii, Roseburia spp., Lachnospiraceae	HDACs, GPR41, GPR43	HDAC inhibition → histone hyperacetylation → enhanced osteogenic gene transcription (e.g., *RUNX2*); GPR activation → modulation of immune cell function (Treg expansion, Th17 suppression); inhibition of osteoclastogenesis via NFATc1 downregulation.	Collagen-induced arthritis: ↓joint erosion (52%), ↓ Th17 cell differentiation.	Circulating butyrate levels correlate positively with BMD in postmenopausal women. Butyrate-producing capacity of gut microbiome is reduced in osteoporosis.
	Propionate	Bacteroides spp., Dialister spp.	GPR41, GPR43	GPR43 activation on osteoblasts → enhanced Wnt/β-catenin signaling → ↑ alkaline phosphatase activity & osteoblast differentiation.	GPR43$^{-/-}$ mice show abolished osteogenic response. Propionate ester supplementation prevents OVX-induced bone loss.	-
Tryptophan derivatives	Indole-3-propionic acid (IPA), Indole-3-aldehyde (IAld)	Lactobacillus spp., Clostridium sporogenes	Aryl Hydrocarbon Receptor (AhR)	AhR ligand binding → nuclear translocation → transcription of CYP1A1/B1; enhances osteoblast differentiation; suppresses osteoclastogenesis via NF-κB inhibition and ROS reduction; upregulates OPG production.	Engineered L. reuteri (tryptophan overproducer) prevents OVX-induced bone loss by 78%. AhR antagonism blocks protective effects.	Serum IPA levels are inversely correlated with bone turnover markers in IBD patients.
Bile acids	Ursodeoxycholic Acid (UDCA), Lithocholic Acid (LCA)	Clostridium scindens, C. hiranonis (7α-dehydroxylation)	TGR5, FXR, VDR, Nrf2	Nrf2 TGR5 (LCA, UDCA): Activation → cAMP/PKA pathway → osteoblast proliferation. FXR (CDCA, DCA): Intestinal FXR activation → FGF15/19 → suppresses bone formation; Osteoblast FXR modulation may have opposing effects. Nrf2 (UDCA): Activation → antioxidant response.	Nrf2 TGR5 (LCA, UDCA): Activation → cAMP/PKA pathway → osteoblast proliferation. FXR (CDCA, DCA): Intestinal FXR activation → FGF15/19 → suppresses bone formation; Osteoblast FXR modulation may have opposing effects. Nrf2 (UDCA): Activation → antioxidant response.	UDCA clinical trial (15 mg/kg/d): ↑ Lumbar spine BMD (2.8%) in osteopenic postmenopausal women.
Microbial polyamines	Spermidine, Spermine	Bifidobacterium spp., Lactobacillus spp.	Autophagy pathways, Nrf2	Enhancement of autophagy flux → clearance of damaged organelles & proteins; Activation of Nrf2 pathway → expression of antioxidant enzymes (HO-1, NQO1) → reduced oxidative stress in bone cells.	Enhancement of autophagy flux → clearance of damaged organelles & proteins; Activation of Nrf2 pathway → expression of antioxidant enzymes (HO-1, NQO1) → reduced oxidative stress in bone cells.	Fecal spermidine levels correlate with BMD in elderly cohorts.
Bacterial vitamins	Menaquinone (Vitamin K_2)	Bacteroides spp., Escherichia coli, Bacillus subtilis	Pregnane X Receptor (PXR), GGCX enzyme	PXR activation: Promotes osteoblast gene expression. Cofactor for GGCX: γ-carboxylation of osteocalcin → enhanced mineral binding capacity of bone matrix.	Vitamin K-deficient diets → ↑ bone fragility in rats. MK-4 supplementation restores bone quality.	High circulating MK-7 → ↓ hip fracture risk (HR 0.66). Supplementation (45 mg/d MK-4) ↑ ucOC carboxylation and BMD.
Reference	[8–13,23–29,44,55–69]	[8–11,21–27,42,43,49–59,69]	[10,28–32,41,47,70]	[8–11,21–27,42,43,49–59,69]	[36,39,40,45,46,48,58]	[11–14,45,46,48,58,69]

↑, upregulation; ↓, downregulation; $^{-/-}$, knockout; HDAC, histone deacetylases; GPR, G protein-coupled receptor; RUNX2, Runt-related transcription factor 2; OVX, Ovariectomy; BV/TV, Bone volume per tissue volume; BMD, Bone Mineral Density; FXR, farnesoid X receptor; PKA, protein kinase A; IBD, inflammatory bowel disease; HR, hazard ratio; CYP1A1, Cytochrome P450 family 1 subfamily A member 1; TGR5, Takeda G protein-coupled Receptor 5; NFATc1, Nuclear Factor of Activated T-cells, Cytoplasmic 1; VDR, Vitamin D Receptor; cAMP, Cyclic Adenosine Monophosphate; FGF, Fibroblast Growth Factor; MK, Midkine; ucOC, Under-carboxylated Osteocalcin; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, Heme Oxygenase-1; NQO1, NAD(P)H: quinone oxidoreductase 1.

3. Gut Barrier Integrity and Immune Regulation

3.1 Intestinal Permeability and Bone Health

Increased intestinal permeability permits translocation of microbial components into systemic circulation, triggering immune activation that adversely affects bone remodeling [36]. Lipopolysaccharide (LPS) from Gram-negative bacteria promotes osteoclast formation through Toll-like receptor 4 (TLR4)-mediated activation of NF-κB and MAPK signaling pathways [39]. Circulating LPS levels correlate inversely with bone mineral density in elderly populations, with individuals in the highest quartile of LPS exposure exhibiting 3.2-fold greater risk of vertebral fractures [36,40]. Beyond celiac disease, gut barrier restoration has demonstrated beneficial effects on bone health across multiple patient populations. In obese individuals with metabolic syndrome, interventions with specific probiotic strains (Lactobacillus plantarum and Bifidobacterium animalis) significantly improved intestinal barrier function, as evidenced by reduced serum zonulin levels, and concurrently decreased bone resorption markers (CTX) by 22% over 12 weeks [71]. Similarly, in elderly osteoporotic patients, a multifaceted intervention combining prebiotic fibers and barrier-strengthening nutrients (glutamine and zinc) not only enhanced gut integrity but also increased lumbar spine BMD by 2.3% compared to controls [72]. These findings suggest that gut barrier-targeted approaches may represent a viable strategy for improving skeletal health in diverse clinical contexts beyond celiac disease. Zonulin, a regulator of tight junction permeability, has emerged as a biomarker linking gut barrier function to bone health. Elevated serum zonulin levels are associated with increased CTX and decreased trabecular bone score in patients with celiac disease [73,74]. Restoration of gut barrier integrity with larazotide acetate, a zonulin antagonist, reduced bone turnover markers by 34% in these patients, independent of gluten-free diet adherence [74]. The mucus layer represents another critical component of gut barrier function [75]. Akkermansia muciniphila, a mucin-degrading bacterium, enhances mucus production and improves gut barrier integrity. Supplementation with A. muciniphila increased cortical thickness by 11% and bone strength by 19% in diabetic rats, effects associated with reduced intestinal inflammation and decreased circulating TNF-α levels [75,76].

3.2 Immunomodulation and Osteoimmunology

The gut microbiota profoundly influences the development and function of immune cells that participate in bone remodeling [76]. Regulatory T cells (Tregs) expanded by microbial metabolites such as butyrate suppress osteoclastogenesis through production of IL-10, TGF-β, and Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4)-mediated inhibition of CD40 Ligand (CD40)/CD40 Ligand (CD40L) signaling [77]. Butyrate-induced Tregs express high levels of OX40, which promotes their migration to bone marrow and enhances their suppressive capacity [76,78]. Th17 cells, in contrast, promote osteoclastogenesis through production of IL-17, which stimulates RANKL expression on osteoblasts and stromal cells [41]. Microbial dysbiosis characterized by expansion of segmented filamentous bacteria drives Th17 differentiation and accelerates bone loss in inflammatory conditions [41,79]. Inhibition of Th17 differentiation with Interleukin-23 p19 subunit (IL-23p19) monoclonal antibodies prevented inflammation-induced bone loss in murine models of rheumatoid arthritis, highlighting the therapeutic potential of targeting gut-immune-bone axis interactions [79,80]. B cells also contribute to gut-bone signaling through production of osteoprotegerin (OPG) [81]. In germ-free mice, reconstitution with Bacteroides fragilis restored OPG production by B cells and normalized bone mass. This effect was mediated through polysaccharide A-induced TLR2 signaling, which promoted B cell differentiation into OPG-producing regulatory B cells [81,82].

3.3 Inflammatory Bowel Disease and Bone Loss

The connection between IBD and osteoporosis exemplifies the clinical significance of the gut-bone axis [83]. Approximately 67% of IBD patients present with osteopenia and 57.6% with osteoporosis, indicating profound skeletal complications beyond traditional malabsorption explanations [42,83]. Recent research has identified novel epigenetic mechanisms underlying IBD-induced bone loss [42]. A groundbreaking study revealed that Fat Mass and Obesity-Associated protein (FTO) SUMOylation at sites K216, K357, and K365 regulates the differentiation of bone marrow mesenchymal stromal cells (BMSCs) in IBD-induced bone loss 4 [43,84]. SUMOylation of FTO impairs its N6-methyladenosine (m6A) RNA demethylase activity, shifting BMSC differentiation toward adipogenesis rather than osteogenesis [43]. This epigenetic modification represents a critical mechanism through which intestinal inflammation affects skeletal homeostasis [43]. Therapeutic targeting of this pathway has shown promise. Interleukin-6 receptor monoclonal antibody (tocilizumab) combined with Adeno-Associated Virus (AAV)-FTO-3KR (a mutant resistant to SUMOylation) attenuated bone loss and enhanced bone formation in IBD mice [85,86]. This approach highlights the potential of targeting specific epigenetic modifications in the treatment of inflammation-induced osteoporosis [86]. The role of microbial metabolites in IBD-related bone loss extends beyond epigenetic regulation. Butyrate deficiency in IBD patients correlates with impaired bone healing and reduced osteoblast activity [87]. Rectal administration of butyrate enemas in a dextran sulfate sodium (DSS)-induced colitis model restored osteoblast function and reduced trabecular bone loss, highlighting the therapeutic potential of metabolite replacement [88]. Additionally, microbiota-derived hydrogen sulfide (H_2S) from sulfate-reducing bacteria exacerbates bone loss

Table 2. Research models for elucidating the gut-bone axis.

Model category	Induction method	Key gut microbiome phenotype	Key bone phenotype	Primary mechanistic insights	Successful interventions
Germ-free (GF)	Raised in sterile isolators	Complete absence of microbial colonization.	Reduced bone mass (↓ 30–50% trabecular bone), impaired skeletal growth, altered bone marrow immune cell populations.	Lack of microbial stimuli → impaired immune system development (e.g., Th17 deficiency); Absence of microbial metabolites (SCFAs).	Monocolonization studies reveal specific bacterial functions (e.g., SFB → Th17; B. fragilis → Breg/OPG).
Ovariectomy (OVX)	Surgical removal of ovaries	Reduced diversity, ↓ Firmicutes/Bacteroidetes ratio, expansion of pro-inflammatory taxa.	High-turnover osteoporosis: ↑ osteoclast activity, severe trabecular bone loss (↓ 40–60% BV/TV), increased fracture risk.	Estrogen deficiency → impaired gut barrier → metabolic endotoxemia (LPS) → systemic inflammation → osteoclast activation.	Probiotics (e.g., L. reuteri), prebiotics (inulin), SCFA supplements significantly ameliorate bone loss.
Inflammatory bowel disease (IBD)	DSS in drinking water; IL-10	Severe dysbiosis, loss of mucosal-associated bacteria, expansion of E. coli.	Systemic bone loss, inhibited bone formation, increased marrow adiposity.	Chronic intestinal inflammation → overproduction of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) → enhanced osteoclastogenesis; impaired calcium and vitamin D absorption.	Anti-TNF-α therapy; FTO overexpression; Butyrate enemas restore osteoblast function.
Aging model	Natural aging (18–24 month)	Loss of diversity, ↓ beneficial symbionts (e.g., A. muciniphila), ↑ pathobionts.	Age-related bone loss: reduced bone formation, decreased bone quality.	Inflammaging (↑ IL-1β, IL-6); ↓ SCFA production; ↑ oxidative stress.	Caloric restriction; supplementation with A. muciniphila or butyrate; senolytics.
High-fat diet (HFD)	45–60% fat diet	↑ Gram-negative bacteria, ↑ endotoxin producers, altered bile acid pool.	Increased bone fragility and decreased bone mass despite higher body weight.	Gut barrier dysfunction → metabolic endotoxemia → systemic inflammation; Altered BA/FXR signaling.	FXR antagonism; Prebiotics/probiotics to restore barrier function and SCFA production.
References	[9–12,29,39,40,71,72,81,82]	[21–34,37,38,81,82,88,89,91]	[13,29,34,37,38,42,43,84–87,93,94]	[21–34,37,38,64,88,89,91,92]	[12,37,38,41,43,79,80,84,85]

↑, upregulation; ↓, downregulation; SFB, segmented filamentous bacteria; OPG, osteoprotegerin; DSS, dextran sulfate sodium; FTO, Fat Mass and Obesity-Associated protein; BA, Bile Acids.

Table 3. Immune mediators in the gut-bone cross-talk.

Immune cell	Regulatory T cells (Tregs)	T helper 17 cells (Th17)	Regulatory B cells (Bregs)	Group 3 innate lymphoid cells (ILC3s)	Macrophages
Microbial cues	SCFAs (Butyrate via HDACi)	Segmented Filamentous Bacteria (SFB); Bile acids	B. fragilis PSA via TLR2	AhR ligands (Tryptophan metabolites)	LPS (TLR4); SCFAs (GPR43)
Functional change	Expansion, enhanced suppressive function, stability ($FoxP3^{+}CTLA\text{-}4^{+}$)	Differentiation, expansion, production of pro-inflammatory cytokines	Differentiation into IL-10 and OPG-producing cells	Production of IL-22. Maintenance of epithelial barrier integrity	Altered polarization: M1 (pro-inflammatory) vs. M2 (anti-inflammatory)
Net effect on bone	Potent inhibition of osteoclastogenesis. Potential indirect promotion of bone formation	Potent stimulation of osteoclastogenesis, leading to inflammatory bone erosion	Inhibition of osteoclastogenesis via OPG production. Maintenance of bone homeostasis	Indirect (barrier protection) and direct (STAT3 activation in osteoblasts) promotion of bone formation	M1: Pro-osteoclastogenic via TNF-α, IL-1β. M2: Anti-inflammatory, may promote repair
Key molecular mediators	IL-10, TGF-β, CTLA-4 (via CD80/86-CD28)	IL-17, IL-22, RANKL	IL-10, OPG, TGF-β	IL-22, STAT3	TNF-α, IL-1β, INOS (M1); IL-10, Arginase-1 (M2)
Therapeutic targetability	Butyrate/probiotic supplementation; Low-dose IL-2; Treg adoptive transfer	Anti-IL-17/IL-23 biologics; Depletion of SFB (e.g., via antibiotics/phages)	PSA or synthetic TLR2 agonists as immunomodulators	AhR agonists (FICZ); Recombinant IL-22	Prebiotics $\rightarrow$ SCFAs $\rightarrow$ promote M2 polarization
Reference	[8–11,14,64,107]	[8,12,41,79,80]	[70,80–82,98]	[15–19,44,77]	[8–13,36,39,40,108]

PSA, Polysaccharide A; RANKL, Receptor activator of nuclear factor kappa-B ligand; CTLA-4, Cytotoxic T-Lymphocyte-Associated protein 4.

Table 4. Human evidence and clinical associations linking gut health to bone disease.

Study type	Population/cohort	Key findings related to gut-bone axis	Implications	References
Epidemiological & observational studies	Elderly populations	• Inverse correlation between circulating LPS levels and BMD; highest quartile had 3.2x greater risk of vertebral fracture	• Systemic microbial antigen exposure is a novel risk factor for osteoporosis	[32,47,48,110,111,116–118]
		• Higher serum vitamin K_2 (menaquinone) levels associated with 34% reduction in hip fracture risk	• Microbiota-derived vitamin K_2 is crucial for bone mineralization	
	Inflammatory Bowel Disease (IBD) patients	• ~67% prevalence of osteopenia; ~58% prevalence of osteoporosis • Elevated serum zonulin (marker of gut permeability) correlated with ↑ bone turnover markers (CTX) and ↓ TBS	Bone loss in IBD is multifactorial, involving inflammation, malabsorption, and gut barrier dysfunction	[32,34,85–90]
Interventional clinical trials	Postmenopausal women with osteopenia	UDCA supplementation (15 mg/kg/day, 12 months) increased lumbar spine BMD by 2.8% vs. placebo	Repurposing bile acid drugs for osteoporosis is a viable therapeutic strategy	[27–29,55,58]
	Postmenopausal women with osteoporosis	Vitamin K_2 supplementation (45 mg/day, 24 weeks) improved ucOC levels and increased lumbar spine BMD by 1.7%	Supplemental microbial vitamins can improve bone quality	[49–53,114]
	Patients with Celiac Disease	Larazotide acetate (zonulin antagonist) reduced CTX by 34%	Restoring gut barrier integrity is a valid target for reducing bone resorption	[45,71,72,110,115,119]
Microbiome association studies	Osteoporosis vs. Healthy Controls	Distinct gut microbiota composition (dysbiosis) characterized by reduced microbial diversity, altered SCFA-producing taxa, and enrichment of pro-inflammatory species	Microbiome signatures could serve as diagnostic or prognostic biomarkers for bone disease	[7,41,79,96,120]
	Osteoarthritis (OA) patients	• Reduction of C. bolteae correlated with OA severity • GUDCA levels inversely correlated with joint degeneration via intestinal FXR inhibition	A “gut-bile acid-joint axis” exists, suggesting novel therapeutic targets for OA	[27–29,54,55,76]

GUDCA, glycoursodeoxycholic acid; TBS, Trabecular Bone Score.

in IBD by inducing osteocyte apoptosis through mitochondrial dysfunction [89,90]. Inhibition of H_2S production with tungstate treatment preserved bone mass in colitis models by reducing caspase-3 activation in osteocytes [90] (Table 2, Ref. [9–13,21–34,37–43,64,71,72,79–82,84–89,91–94]).

3.4 The Role of Innate Lymphoid Cells (ILCs) and Mucosal-Associated Invariant T (MAIT) Cells

Emerging research highlights innate immune cells as critical intermediaries in the gut-bone axis. Group 3 innate lymphoid cells (ILC3s) reside in the intestinal lamina propria and are educated by the local microbial milieu [95]. ILC3s produce IL-22, a cytokine that enhances gut barrier integrity by stimulating mucin production and epithelial cell regeneration [44]. Furthermore, IL-22 exerts direct osteoanabolic effects by activating Signal Transducer and Activator of Transcription 3 (STAT3) signaling in osteoblasts, increasing their proliferation and differentiation capacity [91]. Microbial dysbiosis, particularly a reduction in Lactobacillus species, diminishes IL-22 production, leading to a compromised barrier and reduced bone formation [96]. Conversely, mucosal-associated invariant T (MAIT) cells, activated by microbial vitamin B2 derivatives, can exacerbate bone erosion in inflammatory conditions by producing pro-osteoclastic cytokines like TNF-α and RANKL [97]. The balance between these innate immune cell populations is thus a pivotal determinant of skeletal health, offering novel cellular targets for immunotherapy [98].

4. Endocrine and Neural Regulation of Bone Metabolism

4.1 Gut Hormones and Bone Remodeling

Enteroendocrine hormones play a pivotal role in postprandial bone turnover regulation [99]. Glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and glucagon-like peptide 2 (GLP-2) are secreted by intestinal endocrine cells in response to nutrient intake and have demonstrated significant effects on bone remodeling processes [99,100]. At physiological concentrations, GIP appears to be the primary contributor to postprandial bone resorption suppression, while supraphysiological concentrations of gut hormones induce more potent antiresorptive effects [100]. Notably, research has revealed that GIP infusion significantly reduced bone resorption (as measured by CTX levels) by 14% at 30 minutes, while GLP-1 showed no such effect [45]. This suggests that GIP's osteoprotective actions remain intact even in conditions where its insulinotropic effects are impaired, highlighting its potential as a therapeutic target for bone disorders independent of its glycemic functions [45,99]. GLP-2 has emerged as another important regulator of bone metabolism, primarily through its effects on reducing parathyroid hormone (PTH) and enhancing intestinal calcium absorption [101]. The combined application of GIP and GLP-2 in preclinical studies has shown synergistic benefits for bone quality, suggesting potential for combination therapies targeting multiple gut hormone pathways [102].

4.2 Neural Regulation: The Gut-Brain-Bone Axis

Emerging evidence suggests that the autonomic nervous system (ANS) serves as an important conduit in gut-bone communication [103]. A Mendelian randomization and mediation analysis study revealed that specific gut microbiota taxa can influence bone density through heart rate variability (HRV), a measure of autonomic function, with mediation effects reaching up to 40% [104]. This suggests that gut microbes may modulate bone metabolism through neural pathways in addition to endocrine and immune mechanisms. The proposed "gut-nerve-bone axis" represents a novel dimension of skeletal regulation that expands our understanding of how gastrointestinal health influences bone homeostasis [103,105]. Vagal nerve stimulation and other neuromodulatory techniques may offer future therapeutic approaches for osteoporosis that leverage this neural connectivity [106] (Table 3, Ref. [8–19,36,39–41,44,64,70,77,79–82,98,107,108]).

4.3 Microbial Influence on Mineral Absorption

Gut microbiota significantly modulate calcium and magnesium absorption through acidification of the colonic lumen via SCFA production [107]. This acidic environment enhances solubility and passive absorption of minerals critical for bone mineralization [92]. Lactobacillus and Bifidobacterium strains increase expression of transient receptor potential vanilloid type 6 (TRPV6) and calbindin-D9k in intestinal epithelial cells, facilitating active calcium transport [92,107]. In ovariectomized rats, probiotic supplementation with Lactobacillus helveticus increased calcium absorption efficiency by 38% and prevented femoral bone loss by maintaining serum ionized calcium levels [46]. Magnesium absorption is similarly enhanced by microbial action. Akkermansia muciniphila promotes magnesium absorption through upregulation of Transient Receptor Potential Melastatin6 (TRPM6) and TRPM7 channels in the colon [47,109]. Magnesium deficiency alters bone crystal structure and increases osteoclast activity, while supplementation restores bone quality by reducing IL-1β and TNF-α production [47]. In postmenopausal women, probiotic yogurt enriched with Lactobacillus strains and magnesium (250 mg/day) increased femoral neck BMD by 2.1% over 12 months [110,111].

4.4 The Hypothalamic-Pituitary-Adrenal (HPA) Axis and Glucocorticoid Overdrive

Gut dysbiosis can activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated systemic glucocorticoid levels that are detrimental to bone [112]. Pathobionts such as Enterococcus faecalis stimulate immune cells

to produce IL-1β and IL-6, which signal to the brain to enhance corticotropin-releasing hormone (CRH) production [93,112]. The resulting cortisol/corticosterone excess suppresses osteoblastogenesis, induces osteocyte apoptosis, and increases RANKL expression [35]. Probiotic interventions have been shown to dampen HPA axis hyperactivity, reduce corticosterone levels, and partially prevent stress-induced bone loss in mice, underscoring a direct link between microbial modulation, stress response, and skeletal integrity [113] (Table 4, Ref. [7,27–29,32,34,41,45,47–55,58,71,72,76,79,85–90,96,110,111,114–120]).

5. Therapeutic Strategies and Translational Applications

5.1 Probiotic and Prebiotic Interventions

Targeted manipulation of the gut microbiota through probiotic supplementation and prebiotic substrates represents a promising strategy for improving bone health [101]. Specific bacterial strains have demonstrated significant osteoprotective effects in clinical and preclinical studies [102]. Lactobacillus reuteri DSM 17938 has been shown to increase annual growth velocity by 7 cm in 1-6-year-old children, while Bifidobacterium longum enhances Insulin-like Growth Factor-1(IGF-1) activity through upregulation of Insulin-like Growth Factor-Binding Protein 3(IGFBP3) [114,115]. Similarly, Akkermansia muciniphila maintains chondrocyte morphology and improves bone microarchitecture [108]. Prebiotic approaches have also shown promise in supporting bone health. Goat milk oligosaccharides (GMO) enrich Bacteroidota populations and enhance IGF-1 receptor expression, while microbiome-directed complementary food (MDCF-2) formulations containing chickpea flour improved linear growth in malnourished children [48,116]. These findings suggest that targeted nutritional interventions can effectively modulate the gut-bone axis for therapeutic benefit [116]. However, the efficacy of probiotic interventions demonstrates considerable inter-individual variability. This heterogeneity is primarily attributed to the host's baseline gut microbiota composition, genetic makeup, dietary habits, and medication use, which collectively influence the colonization and functional expression of administered strains. Future research should therefore focus on identifying predictive biomarkers for treatment response to facilitate the development of personalized probiotic regimens, moving beyond a one-size-fits-all approach.

5.2 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) from young donor mice to aged recipients restored bone mass and microarchitecture to levels comparable to young animals [117]. These effects were mediated through restoration of IGF-1 signaling and reduction of oxidative stress in bone tissue [118]. FMT from osteoporotic patients to germ-free mice recapitulated the bone phenotype, demonstrating the causal role of microbiota in bone pathology [119,121]. Clinical applications of FMT for bone disorders are currently under investigation [120]. A pilot study of FMT in patients with corticosteroid-induced osteoporosis showed trends toward improved bone turnover markers and reduced bone loss, though larger studies are needed to confirm efficacy [122]. Safety concerns regarding long-term effects of FMT necessitate careful donor screening and monitoring [119]. The clinical application of FMT for skeletal disorders is still in its infancy, and its standardization is critical for ensuring consistent efficacy and safety. Key challenges include the establishment of rigorous donor screening protocols to exclude pathogens and undesirable metabolic phenotypes, the standardization of fecal material processing (e.g., microbial concentration, viability), and the determination of optimal delivery routes and dosages. Developing universally accepted industry standards and implementing long-term follow-up protocols are essential steps toward the rational and safe application of FMT in managing bone diseases.

5.3 Hormone-Targeted Therapies

The growing understanding of gut hormones in bone metabolism has spurred interest in hormone-based therapeutics for skeletal disorders [49]. GIP receptor agonists and GLP-2 analogs show particular promise for conditions characterized by increased bone resorption [49,50]. The finding that GIP retains its bone-protective effects in pancreatic-insufficient cystic fibrosis (PI-CF) patients even when its insulinotropic actions are impaired suggests that GIP-based therapies could benefit patients with various forms of bone loss [50]. Dual- and multi-receptor agonists represent an advanced approach in this domain [51]. Tirzepatide (GIP/GLP-1 receptor agonist) and CagriSema (GLP-1/amylin analogue) may offer synergistic benefits for bone health through combined activation of complementary signaling pathways [51,52]. However, concerns remain about potential over-suppression of bone turnover, which could lead to increased bone fragility despite improved density metrics [52]. Prolonged and profound suppression of bone remodeling presents several potential long-term consequences for bone quality and fracture risk. While increased bone mineral density (BMD) is typically associated with reduced fracture risk, excessively suppressed turnover impairs the repair of microdamage that accumulates during normal mechanical loading. This can lead to increased tissue age, advanced glycation end-product accumulation, and altered collagen cross-linking patterns, ultimately compromising bone toughness and increasing susceptibility to atypical fractures [45,54]. Clinical evidence from long-term antiresorptive therapies demonstrates that excessive suppression of bone turnover (evidenced by very low levels of bone turnover markers such as CTX) is associated with increased risk of atypical femoral fractures, though the specific risk profile for gut hormone-based therapies requires

Table 5. Potential biomarkers for diagnosing and monitoring gut-bone axis dysregulation.

Biomarker category	Specific biomarker	Biological significance	Assay/measurement	Association with bone health
Microbial metabolites	Fecal/Serum SCFAs (Butyrate, Propionate)	Direct mediators of microbial influence on bone (HDAC inhibition, GPCR activation)	GC-MS LC-MS/MS	Low levels associated with increased bone resorption and inflammation.
	Serum Ursodeoxycholic Acid (UDCA)/GUDCA	FXR modulators with osteoprotective and chondroprotective potential	LC-MS/MS	UDCA supplementation increased BMD. Low GUDCA correlates with OA severity.
	Urinary/Serum Indole Derivatives (I3A, IPA)	Indicators of bacterial tryptophan metabolism and AhR ligand availability		Levels may predict responsiveness to pre/probiotics targeting tryptophan metabolism.
Gut barrier function	Serum Zonulin	Regulator of intestinal tight junctions; marker of "leaky gut"	ELISA	Elevated levels correlate with increased bone resorption markers (CTX) in celiac disease.
	Circulating LPS (Endotoxemia)	Marker of bacterial translocation and systemic inflammation	LAL assay ELISA	Inverse correlation with BMD; high levels confer 3.2× greater fracture risk.
	Lipopolysaccharide-Binding Protein (LBP)	Acute-phase reactant that binds LPS, amplifying immune response	ELISA	Elevated LBP indicates chronic, low-grade endotoxemia and inflammation.
Bone turnover & systemic inflammation	Citrullinated Proteins (ACPA)	Autoantibodies generated due to loss of gut barrier function and dysbiosis	ELISA	Link gut dysbiosis, RA, and associated inflammatory bone loss.
	Ratio of ucOC to cOC	Indicator of vitamin K status and osteocalcin activation	ELISA	High ratio indicates vitamin K deficiency and impaired bone mineralization.
Reference	[21–34,37,38,81,88,89,91]	[9–12,29,39,40,71,72,81]	N/A	[21–34,37,38,64,88,89,91,92]

GPCR, G-Protein-Coupled Receptor; GC-MS, Gas Chromatography-Mass Spectrometry; LC-MS/MS, Liquid Chromatography-Tandem Mass Spectrometry; LAL, Limulus Amebocyte Lysate assay; cOC, circulating Osteocalcin; RA, Rheumatoid Arthritis.

further investigation [53,108]. Therefore, careful monitoring of bone turnover markers and periodic assessment of treatment duration may be necessary to balance the benefits of reduced bone resorption against the potential risks of oversuppression when using dual- and multi-receptor agonists for bone disorders [54].

5.4 FXR Targeting and Bile Acid Modulation

Recent research has revealed a novel "gut-bile acid-joint axis" with implications for bone health [54]. The study demonstrated that glycoursodeoxycholic acid (GUDCA) levels inversely correlate with osteoarthritis severity through selective inhibition of the FXR in the intestine [55]. This discovery suggests that existing bile acid-based medications, such as UDCA, might be repurposed for bone disorders through FXR modulation [56]. The reduction of C. bolteae in osteoarthritis patients' guts and its association with disease severity further supports the therapeutic potential of microbiome modulation targeting specific bacterial taxa [57]. This approach may be particularly relevant for age-related bone loss, given the significant shifts in gut microbiota composition that occur with aging [54,55].

5.5 Engineered Microbial Therapeutics

Synthetic biology approaches offer innovative strategies for targeting the gut-bone axis [58]. The development of engineered Trp CB has demonstrated impressive results in animal models of osteoporosis and intestinal dysfunction [59]. This intervention not only repaired intestinal barrier function but also increased P1NP by 1.7-fold while reducing osteoclast numbers by 41.8% [60]. Notably, this approach demonstrated efficacy across age groups, increasing trabecular bone number by 35% and cortical bone density by 18.4% in 22-month-old aged mice [8]. The cross-age applicability suggests that microbial therapeutics might address both inflammatory and age-related bone loss through shared mechanisms involving barrier protection and inflammation reduction [61]. Despite the promising therapeutic potential of engineered bacteria, their long-term safety remains a paramount concern for clinical translation. Potential risks include the horizontal gene transfer of engineered constructs to host cells or other members of the indigenous microbiota, unpredictable behavior and evolution of engineered strains within the complex gut ecosystem, and unintended immunogenic reactions. Consequently, the implementation of robust biocontainment strategies and comprehensive long-term toxicological studies are imperative prerequisites before these innovative therapies can be widely applied in clinical settings.

5.6 Precision Nutrition and Microbiome Modulation

Advancements in precision nutrition have enabled targeted dietary interventions based on individual microbiome compositions [62]. High-throughput sequencing identifies microbial signatures associated with bone health, allowing for personalized prebiotic and probiotic recommendations [63]. For instance, individuals with low Prevotella abundance benefit more from arabinoxylan oligosaccharides, which increase SCFA production and improve calcium absorption [64]. Machine learning algorithms integrating microbiome data, genetic polymorphisms, and clinical parameters predict responsiveness to specific interventions [65]. A recent clinical trial demonstrated that personalized nutrition plans based on gut microbiota composition increased lumbar spine BMD in osteopenic patients [66]. This approach represents a paradigm shift toward precision medicine in bone health management [66] (Table 5, Ref. [9–12,21–34,37–40,64,71,72,81,88,89,91,92]).

5.7 Phage-Based Therapies

Bacteriophages offer targeted manipulation of gut microbiota to promote bone health [67]. Phages specifically targeting osteoclast-promoting bacteria (e.g., Clostridium histolyticum) reduce bacterial load and subsequent bone resorption [67,68]. In a proof-of-concept study, oral administration of C. histolyticum-specific phages (10^9 PFU/day) reduced serum CTX levels and increased trabecular bone volume in osteoporotic mice [69]. Phage therapy also minimizes disruption to beneficial microbiota, avoiding off-target effects common with broad-spectrum antibiotics. Phage engineering further enhances specificity and efficacy: modular phage platforms equipped with CRISPR-Cas systems can selectively deplete pathobionts while delivering osteogenic genes to gut epithelial cells. Safety studies indicate minimal off-target effects or immune activation, supporting phage therapy as a precision tool for gut-bone axis modulation [68,123].

6. Future Perspectives

6.1 Deepening Mechanistic Insights

Future research should employ single-cell multi-omics to decipher cell-type-specific responses to microbial signals in bone marrow niches. Spatial transcriptomics of gut-bone organoids will elucidate how microbial metabolites directly influence osteocyte-osteoblast crosstalk [124]. Advanced organoid and microphysiological systems (e.g., gut-bone organ-on-a-chip) could model bidirectional crosstalk in a human-relevant context. Advanced imaging techniques can track metabolite distribution in bone tissue, while gnotobiotic models with humanized microbiota will provide physiologic relevance. Key unanswered questions include: How do microbial signals integrate with mechanical loading? Do osteocytes directly sense gut-derived metabolites? Resolving these mechanisms will unlock new therapeutic targets [94].

6.2 Targeting Microbial Metabolite Pathways

Precision interventions using metabolite analogs or receptor-specific modulators hold promise. AhR agonists (e.g., FICZ) and FXR antagonists (e.g., guggulsterone)

show efficacy in preclinical models [125]. Synthetic biology approaches may engineer Lactobacillus strains to secrete PTH (1–34) or OPG in response to inflammation, creating "smart probiotics" for dynamic bone protection. Nanoparticle-based delivery of SCFAs to bone marrow via intestinal targeting could overcome bioavailability challenges [70].

6.3 Stratified Medicine and Microbiome-Based Diagnostics

Integration of multi-omics data with clinical parameters using machine learning algorithms will facilitate patient stratification and predictive biomarker identification [126]. Validation of microbial signatures or metabolite profiles (e.g., serum zonulin, fecal butyrate) could guide personalized nutritional or probiotic interventions [127].

6.4 Advancing Therapeutic Modalities

Bacteriophage Therapy: Targeted depletion of pro-osteoclastic bacteria (e.g., C. bolteae, C. histolyticum) may reduce bone resorption with minimal microbiota disruption [128]. FMT: Standardized protocols and long-term outcomes in osteoporotic patients need evaluation in randomized controlled trials [120]. Gene and Cell Therapy: CRISPR-based editing of microbial or host genes (e.g., FTO SUMOylation sites) may correct aberrant bone remodeling in inflammatory settings [129].

6.5 Clinical Translation and Standardization

Well-designed human trials are essential to validate efficacy and safety of microbiome-targeting interventions. Neurobiome-modulating approaches may synergize with existing therapies to address neurogenic components of bone loss. Harmonization of microbial analysis methods, intervention formulations, and outcome measures will facilitate cross-study comparisons and meta-analyses.

6.6 Exploring Novel Avenues

The gut-brain-bone axis, particularly autonomic nervous system mediation, represents an underexplored area. Vagal nerve stimulation or neurobiome-modulating approaches may offer novel therapeutic opportunities for metabolic bone diseases.

6.7 Long-Term Safety and Efficacy of Microbiome Modulation

While promising, long-term consequences of profound microbiome alteration (e.g., via FMT or engineered bacteria) remain unknown. Potential risks include off-target immune effects, horizontal gene transfer, and metabolic disturbances [130]. Rigorous post-marketing surveillance and long-term animal studies are imperative to monitor for adverse effects such as abnormal bone remodeling patterns or hepatic steatosis.

6.8 Integration With Osteoimmunology and Systems Biology

The gut-bone axis must be understood within the broader framework of systemic immunometabolism [131]. Future studies should employ systems biology approaches to construct predictive models that integrate microbiome data with immune cell profiles, serum metabolomes, and bone turnover markers [132]. This will help identify master regulators of the axis and develop multi-target therapies that simultaneously address gut permeability, immune dysregulation, and metabolic dysfunction to achieve superior osteoprotection [132].

7. Conclusion

The gut-bone axis represents a sophisticated multidimensional system that integrates microbial, endocrine, immune, and neural signals to maintain skeletal homeostasis [103]. Rather than being a simple linear relationship, this axis comprises numerous feedback loops and cross-regulatory mechanisms that respond to nutritional status, inflammatory signals, and metabolic demands. The evidence summarized in this review supports a paradigm shift in which bone health is understood as a systemic outcome influenced significantly by gastrointestinal processes. Recent discoveries have illuminated several promising therapeutic directions. The identification of FTO SUMOylation as a key epigenetic mechanism in IBD-induced bone loss provides a novel target for intervention [85]. Similarly, the development of engineered tryptophan-producing bacteria offers an innovative approach to simultaneously address intestinal barrier dysfunction and bone loss [61]. The differential effects of gut hormones on bone metabolism—with GIP but not GLP-1 reducing bone resorption in PI-CF patients—suggests that precision approaches targeting specific hormonal pathways may yield better outcomes than broad-spectrum interventions [99]. Despite significant progress, important challenges remain in translating these findings into clinical practice. The strain-specific effects of probiotics, individual variability in microbiome composition, and complex dose-response relationships present obstacles to developing universally effective therapies [133]. Future research should focus on identifying specific microbial strains and consortia with optimal osteoprotective properties, developing targeted delivery systems for microbial metabolites, and conducting large-scale human trials to validate preclinical findings. While traditional calcium and vitamin D supplementation remains relevant, the evidence suggests that addressing microbial dysbiosis, intestinal inflammation, and gut barrier integrity may be equally important for preventing and treating bone disorders. As research in this field advances, targeting the gut-bone axis offers promise for developing more effective and comprehensive strategies to maintain skeletal health throughout the lifespan.

Abbreviations

ANOVA, analysis of variance; SEM, structural equation modeling; GDP, gross domestic product; HLM, hierarchical linear modeling; HDAC, histone deacetylases; GPR, G protein-coupled receptor; RUNX2, Runt-related transcription factor 2; OVX, Ovariectomy; BV/TV, Bone volume per tissue volume; BMD, Bone Mineral Density; FXR, farnesoid X receptor; PKA, protein kinase A; IBD, inflammatory bowel disease; HR, hazard ratio; CYP1A1, Cytochrome P450 family 1 subfamily A member 1; TGR5, Takeda G protein-coupled Receptor 5; NFATc1, Nuclear Factor of Activated T-cells, Cytoplasmic 1; VDR, Vitamin D Receptor; cAMP, Cyclic Adenosine Monophosphate; FGF, Fibroblast Growth Factor; MK, Midkine; ucOC, Under-carboxylated Osteocalcin; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, Heme Oxygenase-1; NQO1, NAD(P)H: quinone oxidoreductase 1; PI-CF, Pancreatic Insufficient Cystic Fibrosis.

Author Contributions

ZBS, ZJY: Conceptualization, Writing – Original Draft Preparation, Supervision. DJY: Data Curation, Formal Analysis, Investigation, Visualization. JJC, YLX: Validation, Resources, Writing – Review & Editing. GYW, Project Administration, Funding Acquisition, Supervision, Figures Production, References Collection. 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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Conflict of Interest

The authors declare no conflict of interest.

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

During the preparation of this work the authors used ChatGPT-3.5 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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