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The oral–gut microbiome axis in systemic bone-related diseases

Zhiyuan Zhang^{1,2}, Lingrui Sun^{2,3}, Fangzhi Lou³ ✉, and Jingang Xiao^{1,2,3,4} ✉¹ Department of Plastic and Burn Surgery, The Affiliated Hospital, Southwest Medical University, Luzhou, 646000, China² Luzhou Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration, The Affiliated Stomatological Hospital, Southwest Medical University, Luzhou, 646000, China³ Department of Oral Implantology, The Affiliated Stomatological Hospital, Southwest Medical University, Luzhou, 646000, China⁴ Department of Oral and Maxillofacial Surgery, The Affiliated Stomatological Hospital, Southwest Medical University, Luzhou, 646000, ChinaCite This: *Oral Sci Homeost Med*, 2026, 2, 9610069

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ABSTRACT: The oral microbiome is increasingly recognized as an upstream ecological interface with systemic relevance beyond oral disease. Emerging evidence links oral dysbiosis to skeletal pathology through an oral–gut axis involving salivary microbial transfer, gut remodeling, barrier dysfunction, and microbiota-derived metabolites. In this review, we summarize current evidence supporting the oral–gut–bone axis in systemic bone-related diseases and propose an integrated framework in which oral ecological disturbance may contribute to skeletal vulnerability through gut-dependent metabolic and inflammatory relay mechanisms. We highlight three major mechanistic architectures: metabolite-centered osteoimmune regulation, barrier dysfunction with inflammatory amplification, and oral-derived microbial signaling. Across rheumatoid arthritis, osteoarthritis, and osteoporosis, these pathways are associated with distinct downstream phenotypes, including inflammatory bone erosion, degenerative joint remodeling, and systemic bone loss. Short-chain fatty acids, valeric acid, bile acid derivatives, and tryptophan-derived indoles emerge as key intermediates linking microbial ecology to osteoclastogenesis, osteoblast activity, immune polarization, and joint homeostasis. We also discuss translational opportunities involving metabolite restoration, microbiota-targeted intervention, host-pathway modulation, and mechanism-guided biomarker development. Despite recent progress, most current evidence remains associative, and major gaps persist in causal inference and functional validation.

KEYWORDS: oral microbiome, oral–gut–bone axis, osteoimmunity, microbiota-derived metabolites, bone-related diseases

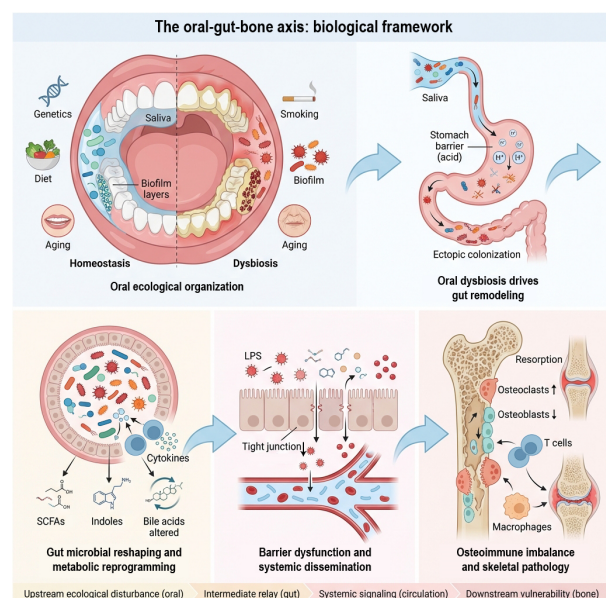
1 Introduction

The oral microbiome is increasingly recognized as a structured, host-shaped ecosystem rather than a simple reservoir of local commensals and pathogens^[1]. Distinct microbial communities occupy saliva, the tongue, dental plaque, and oral mucosal surfaces, and are shaped by host genetics, diet, age, oral hygiene, smoking habits, and other environmental factors^[2]. Accordingly, oral dysbiosis should not be viewed only as a local event, but as a potential upstream disturbance with systemic consequences.

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✉ Address correspondence to Fangzhi Lou, loufangzhi@swmu.edu.cn; Jingang Xiao, xiaojingang@swmu.edu.cn



Before considering its potential routes of systemic communication, existing evidence supports a link between oral dysbiosis and bone-related diseases. Human studies have reported alterations in oral microbial community structure in patients with rheumatoid arthritis and among postmenopausal women with different bone-mass states^[3,4]. In preclinical studies, salivary microbiota derived from periodontitis donors aggravated systemic bone loss and osteoclastogenesis in ovariectomized mice^[5]. In addition, oral microbial products can directly modulate bone remodeling; for example, *Porphyromonas gingivalis* LPS promotes osteoclastogenesis and impairs osteoblast differentiation^[6]. Together, these findings support a biologically plausible link between oral ecological disturbance and distant skeletal homeostasis, although causal evidence in humans remains limited.

One major route by which oral dysbiosis may influence distant organs is the oral–gut microbiome axis. Oral microorganisms are



continuously swallowed with saliva and shed biofilm, thereby interacting with the gastrointestinal ecosystem^[7]. Under conditions of ecological imbalance, this process may contribute to gut microbial reshaping, impaired barrier integrity, and altered mucosal immunity^[8]. Increasing evidence supports this concept in systemic disease, most notably in rheumatoid arthritis, where coordinated perturbations in oral and gut microbiomes have been observed and are partly normalized after treatment^[9,10].

This framework is highly relevant to bone-related diseases, which are increasingly understood as disorders of immune-metabolic dysregulation rather than purely local structural damage^[11]. Rheumatoid arthritis, osteoarthritis, and osteoporosis all involve disrupted osteoimmune homeostasis, including aberrant osteoclastogenesis, impaired osteoblast function, inflammatory amplification, and maladaptive tissue remodeling^[12-14]. In parallel, studies in both humans and animal models have linked microbiota composition and function to bone mineral density, skeletal microarchitecture, joint degeneration, and inflammatory bone destruction^[15,16].

A major recent advance in this field is the shift from taxonomic description to functional mechanism. In particular, microbiota-derived metabolites have emerged as critical mediators linking microbial ecosystems to skeletal pathology^[17,18]. Short-chain fatty acids, bile acid derivatives, and tryptophan-derived indoles have all been implicated in the regulation of T-cell polarization, inflammatory tone, osteoclast differentiation, osteoblast maturation, and joint homeostasis^[19,20]. Moreover, fecal microbiota transplantation, salivary microbiota transfer, single-strain intervention, and metabolite rescue studies now provide growing causal support for microbiome-driven skeletal phenotypes^[21-23]. Collectively, these findings suggest that the oral-gut-bone axis may be driven not only by the expansion of pathogenic taxa, but also by the loss of protective microbial functions and metabolite-producing networks.

Despite this progress, the field remains fragmented. Oral microbiota, gut microbiota, circulating metabolites, immune phenotypes, and bone outcomes are still often studied in isolation, and most human evidence remains associative. A more integrated framework is therefore needed, in which oral dysbiosis is considered the upstream ecological disturbance, the gut serves as a critical intermediate relay, and osteoimmunity represents the downstream vulnerability state linking microbial disruption to skeletal pathology.

In this review, we summarize current evidence supporting the oral-gut microbiome axis in systemic bone-related diseases. We first discuss the biological basis of this axis, including oral ecological organization, oral-to-gut communication, barrier dysfunction, and osteoimmune susceptibility. We then examine the principal mechanistic pathways linking microbial dysbiosis to skeletal pathology, with particular emphasis on metabolite-centered signaling, inflammatory amplification, and oral-derived microbial effects on systemic bone remodeling. Finally, we synthesize disease-specific evidence in rheumatoid arthritis, osteoarthritis, and osteoporosis, and discuss emerging therapeutic opportunities centered on microbial ecosystem restoration, metabolite supplementation, and host-pathway targeting.

2 The biological basis of the oral-gut-bone axis

Traditional gut-bone axis models primarily conceptualize the

intestinal microbiota as the proximal microbial compartment influencing skeletal homeostasis through microbiota-derived metabolites, mucosal barrier function, and immune signaling^[16]. The oral-gut-bone axis proposed here does not replace this framework, but extends it upstream. The oral cavity continuously delivers microorganisms and microbial products to the gastrointestinal tract through swallowed saliva and shed biofilm material, while disruption of periodontal or oral mucosal barriers may provide additional microbial and inflammatory inputs^[24-33]. Under permissive conditions, oral ecological disturbances may therefore precede and contribute to downstream gut microbial remodeling. Thus, the distinctive contribution of the oral compartment is its potential role as an upstream ecological source rather than an obligatory component of all gut-bone interactions. Within this framework, the oral-gut-bone axis can be conceptualized as a multistep process linking oral ecological disturbance, gut remodeling, systemic signaling, and ultimately skeletal vulnerability (Fig. 1).

2.1 Oral ecological organization and host determinants

The oral microbiome is better understood as a spatially compartmentalized ecosystem than as a uniform microbial assemblage, with distinct niches spanning saliva, the tongue, supragingival and subgingival plaque, and oral mucosal surfaces^[34,35]. These sites differ in oxygen tension, nutrient availability, epithelial turnover, host-derived substrates, and biofilm architecture, thereby supporting distinct microbial communities with different functional capacities^[1,36]. Oral dysbiosis should therefore be understood as a site-dependent ecological shift rather than a single-state event.

This ecological organization is strongly shaped by host factors. Recent work indicates that host genetic variation can influence oral microbial composition, while age, smoking, diet, oral hygiene, and systemic health status also contribute to variation in oral community structure and resilience^[34,37-39]. These determinants are especially relevant to bone-related disease because they influence not only whether oral dysbiosis develops, but also whether it remains localized or progresses into a broader systemic perturbation.

Under homeostatic conditions, the oral ecosystem contributes to local stability through structured biofilm organization and microbe-microbe interactions that restrain excessive expansion of pathobionts. By contrast, once ecological balance is disrupted, the oral microbiome may shift toward a dysbiotic state characterized by inflammatory amplification and increased systemic pathogenic potential^[40-42]. This distinction between homeostatic and dysbiotic oral ecosystems provides the conceptual starting point for understanding the oral-gut-bone axis.

2.2 From oral dysbiosis to gut remodeling

A central premise of the oral-gut axis is that oral microorganisms are continuously delivered to the gastrointestinal tract through swallowed saliva and shed biofilm-associated material^[24]. In healthy individuals, long-term intestinal colonization by oral microbes may be limited by gastric acidity, bile exposure, anaerobic conditions, and colonization resistance from resident gut communities. However, under conditions of ecological imbalance, oral-derived microorganisms can reshape gut community structure and alter mucosal immune tone^[25,36]. Experimental work has shown that oral bacteria can ectopically colonize the intestine and drive inflammatory T-cell responses, supporting a causal basis for oral-to-

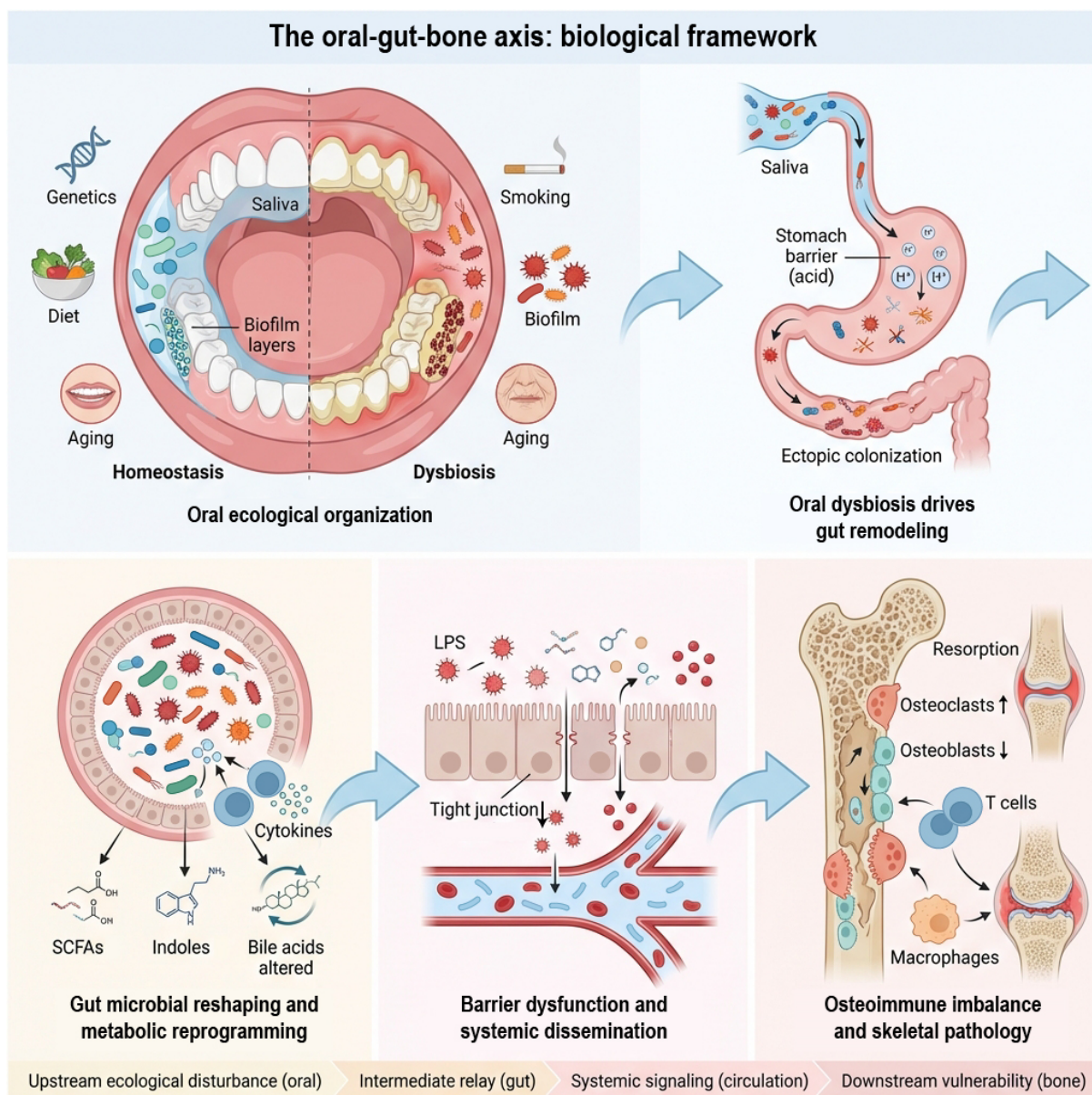


Figure 1 The oral–gut–bone axis is conceptualized as a multistep framework linking oral ecological disturbance with potential downstream skeletal effects. Host factors shape oral ecological organization and influence the transition from homeostasis to dysbiosis. Dysbiotic oral communities may influence gut ecology through salivary microbial transfer, possible ectopic intestinal persistence, and altered mucosal immune tone. Gut remodeling may be accompanied by metabolic reprogramming and barrier dysfunction, which may facilitate systemic exposure to microbial products, inflammatory mediators, and microbiota-derived metabolites. These signals may then influence osteoimmune homeostasis, potentially shifting the balance between bone resorption and bone formation and contributing to skeletal vulnerability.

gut microbial transmission^[27]. More direct human evidence comes from a high-resolution observational study showing oral-to-gut bacterial transmission, in which shared sequence variants were identified between salivary and fecal microbiota, providing evidence consistent with oral bacteria reaching and persisting within the gut microbial ecosystem^[28]. This concept is further strengthened by recent evidence from Crohn's disease showing that *Veillonella*, an oral commensal, can colonize the intestine under inflammatory conditions, providing direct support for the idea that oral-derived bacteria can achieve stable intestinal persistence^[29]. More recent studies further support the ectopic occurrence and adaptation of oral-associated bacteria within gastrointestinal niches. *Streptococcus anginosus*, a common oral-associated species, has been reported to be enriched in human gastric mucosa and gastric cancer tissue and

to persist in the gastric environment in experimental models^[43]. Similarly, the oral-associated anaerobe *Peptostreptococcus stomatis* is enriched in fecal samples across colorectal cancer cohorts and can be detected in colonic and tumor-associated tissues^[44]. More direct human evidence has recently been provided by paired, strain-resolved analysis demonstrating distal gut colonization by oral bacteria within the same individuals in a defined clinical context^[45]. However, ectopic detection or enrichment of oral-associated species should not by itself be interpreted as direct evidence of oral-to-gut transmission. Stronger inference requires paired within-individual sampling, strain-resolved genomic analysis, and preferably longitudinal tracking.

Human and experimental evidence increasingly supports this model in systemic inflammatory disease. In rheumatoid arthritis,

both oral and gut microbiomes are perturbed, and these abnormalities are partly normalized after treatment, consistent with coordinated dysbiosis across the two compartments, although it does not establish a causal relationship between them^[46]. Additional metagenomic work in rheumatoid arthritis further supports a disease-associated restructuring of gut microbial ecology, reinforcing the idea that oral–gut communication may involve shared inflammatory and metabolic reprogramming^[47].

More direct evidence relevant to bone biology has emerged from salivary microbiota transfer models. In ovariectomized mice, transfer of periodontitis-associated salivary microbiota reshaped gut microbial composition and altered intestinal metabolic activity, supporting the view that oral dysbiosis can act upstream of gut remodeling in a skeletal disease context^[5]. These findings place oral dysbiosis upstream of gut remodeling in a skeletal disease context and support the view that the gut may function as an intermediate relay between oral ecological disturbance and distal bone pathology.

2.3 Barrier dysfunction and systemic dissemination of microbial signals

The biological impact of oral–gut communication is unlikely to depend on microbial transfer alone. Barrier dysfunction represents a second critical dimension of axis biology^[30,31]. Once epithelial and mucosal barriers are compromised, microbial-associated molecular patterns, inflammatory mediators, and, in some contexts, live bacteria may gain access to the circulation or distant tissues, thereby amplifying systemic inflammatory signaling^[32,33]. In parallel, microbiota-derived metabolites may also enter the bloodstream and act as endocrine-like signals without requiring overt microbial translocation^[48–50].

Although direct evidence for each of these routes remains uneven across bone-related diseases, strong causality templates have been established in other gut–organ axes^[51,52]. In a recent gut–liver study, dysbiotic microbiota disrupted gut barrier integrity, promoted translocation of live bacteria to the liver, and accelerated distal pathology through receptor-mediated signaling in the target organ^[53]. While not a skeletal model, this work provides an important mechanistic framework for the oral–gut–bone field by showing how ecological disruption, barrier injury, and distal tissue damage can be linked within a single causal sequence.

In this context, circulating microbial signals should be regarded as plausible intermediates between oral–gut disruption and bone pathology. Rather than framing the axis solely in terms of bacterial movement, it may be more useful to view it as a broader process in which gut remodeling alters barrier function and systemic signal output, thereby creating conditions that favor immune dysregulation and skeletal vulnerability.

2.4 Osteoimmunity as the downstream vulnerability framework

The reason oral–gut dysbiosis can influence bone-related diseases lies in the immune sensitivity of skeletal tissues. Bone is continuously remodeled through tightly coordinated interactions among osteoclasts, osteoblasts, stromal cells, and immune cells^[54,55]. Disturbances in this network can shift skeletal homeostasis toward excessive resorption, impaired formation, inflammatory erosion, or maladaptive remodeling. Osteoimmunity therefore provides the downstream vulnerability framework through which microbial perturbations may be translated into skeletal pathology^[56].

Within this framework, oral–gut dysbiosis may influence bone by altering inflammatory thresholds, immune-cell polarization, osteoclastogenic programming, and the balance between bone resorption and bone formation. The specific phenotype that emerges is likely to depend on disease context and the pathways engaged. In inflammatory arthritis, autoimmune amplification and bone erosion may predominate; in osteoarthritis, low-grade inflammation and maladaptive joint remodeling may become more prominent; and in osteoporosis-related settings, altered osteoclast–osteoblast balance may represent the dominant consequence. Taken together, these observations suggest that the oral–gut–bone axis should not be viewed simply as a question of microbial presence or absence. Rather, it reflects a broader biological process in which oral ecological disruption, gut remodeling, barrier dysfunction, and osteoimmune susceptibility interact to determine whether microbial perturbation is translated into bone-related pathology.

3 Core mechanistic pathways linking the oral–gut axis to bone-related diseases

3.1 Metabolite-centered osteoimmune regulation

One of the clearest mechanistic advances in this field is the recognition that the oral–gut–bone axis is mediated not only by shifts in microbial composition, but also by changes in microbiota-derived metabolites. These metabolites function as biologically active intermediates between ecological disruption and skeletal pathology by modulating immune tone, osteoclast differentiation, osteoblast maturation, and tissue remodeling^[16]. Accordingly, dysbiosis may promote bone-related disease not only through pathobiont expansion, but also through the depletion or rewiring of protective metabolite-producing networks.

3.1.1 Short-chain fatty acids and related metabolites

Short-chain fatty acids are important mediators linking gut microbial metabolism, immune regulation, and bone homeostasis. Butyrate can regulate intestinal barrier function and multiple immune-cell populations through G-protein-coupled receptor signaling and histone deacetylase inhibition^[57]. A classic animal study further showed that butyrate promotes regulatory T-cell expansion and enhances expression of the osteogenic factor WNT10B in bone-marrow CD8⁺ T cells, thereby promoting bone formation^[58].

In rheumatoid arthritis, untreated patients exhibit depletion of butyrate-producing bacteria together with expansion of butyrate-consuming species, alterations associated with ACPA positivity, disease activity, joint deformity, and bone erosion. Cell and animal studies further indicate that butyrate promotes Treg differentiation, suppresses inflammatory T-cell and antibody responses, and inhibits osteoclast formation, thereby attenuating experimental arthritis and bone destruction^[59]. However, the corresponding patient evidence remains predominantly observational.

Recent osteoporosis-related studies further extend this mechanism. *Lactobacillus acidophilus* or butyrate intervention can improve intestinal barrier function, reduce B-cell RANKL and osteoclast RANK expression, and suppress osteoclastogenesis and bone resorption^[60]. Colon-targeted butyrate postbiotic delivery has also been shown to reduce proinflammatory macrophage activation and systemic inflammation and to restore osteoblast–osteoclast balance^[61]. Together, these findings suggest that butyrate may

influence bone remodeling through both gut barrier-immune-osteoclast and Treg-CD8⁺ T-cell-WNT10B pathways, although direct intervention evidence remains largely preclinical. A related metabolite-centered mechanism has been reported for valeric acid. In osteoporosis-related studies, *Bacteroides vulgatus* has been inversely associated with bone mineral density, whereas valeric acid has been associated with better skeletal health. Experimental evidence further indicates that valeric acid suppresses osteoclast differentiation and promotes osteoblast maturation, suggesting that microbial organic acids may regulate both bone resorption and formation^[21].

3.1.2 Tryptophan-derived indoles

Tryptophan metabolism has emerged as another major signaling hub linking microbial dysbiosis to skeletal pathology. In ovariectomized mice, periodontitis-associated salivary microbiota suppressed intestinal tryptophan metabolism, and indole-3-lactic acid (ILA) was identified as a key protective metabolite in this setting. Importantly, ILA supplementation attenuated osteoclastogenesis and mitigated bone loss, indicating that altered indole metabolism is functionally involved in microbiota-driven skeletal pathology. Recent work has broadened this framework by showing that indole-3-acetic acid (IAA), another indole metabolite generated by the gut microbiota, exerts protective effects on bone in osteoporosis. In an ovariectomy-induced bone loss model, gut microbial alteration was accompanied by reduced serum IAA levels, and IAA abundance was positively associated with both bone mass and *Lactobacillus* enrichment. Mechanistically, IAA suppressed RANKL-induced PI3K-AKT signaling and reactive oxygen species (ROS) generation, reduced NFATc1 nuclear translocation, and ultimately inhibited osteoclast differentiation and bone resorption^[63]. Consistently, *in vivo* IAA supplementation alleviated ovariectomy-induced bone loss, supporting a direct functional role for tryptophan-derived indoles in restraining osteoclastogenic remodeling.

The relevance of indole signaling is further strengthened by recent work on indole-3-propionic acid (IPA). Although this evidence was generated outside bone-specific models, IPA has been shown to enhance mitochondrial respiration in CD4⁺ T cells, promote fatty acid and amino acid oxidation, and inhibit the differentiation of pathogenic Th1 and Th17 cells via a PPAR β / δ -dependent mechanism^[63]. These findings provide a plausible mechanistic framework through which tryptophan-derived indoles could reshape osteoimmunity by altering immune-cell metabolism rather than by acting directly on bone cells alone.

Taken together, current evidence suggests that depletion or rewiring of indole-producing pathways may represent a convergent mechanism by which oral-gut dysbiosis is translated into systemic inflammatory and osteoclastogenic vulnerability.

3.1.3 Bile acid derivatives and endocrine relay signaling

Bile acids are increasingly recognized as host-microbiota co-metabolites whose signaling properties are jointly shaped by microbial transformation and host counter-regulation, making them well suited to relay gut ecological changes into systemic metabolic and endocrine responses^[64]. Microbiota-derived skeletal signals do not always act directly on immune or bone cells. In osteoarthritis, an important alternative mechanism involves endocrine relay signaling. Recent work identified reduced glycoconjugate deoxycholic acid (GUDCA) as a feature of osteoarthritis

and showed that modulation of the gut microbiota-GUDCA-intestinal FXR axis alters GLP-1 release from intestinal L cells, with downstream protection in joint tissues. This is mechanistically important because it demonstrates that gut-derived metabolites can influence distal skeletal pathology through an intermediate gut-endocrine pathway rather than through direct microbial dissemination or classical inflammatory spread alone^[65].

A conceptually related mechanism has also been reported outside bone-specific models. In obesity-prone individuals, gut microbiota-driven remodeling of the bile acid pool was associated with depletion of glycodeoxycholic acid (GDCA), and gut microbial transfer was sufficient to recreate bile acid imbalance together with systemic physiologic disturbance. Mechanistically, GDCA activated TGR5 signaling, enhanced brown adipose thermogenesis, and stimulated ileal GLP-1 secretion, providing independent support for the idea that dysbiosis-associated bile acid remodeling can be transduced through an intestinal receptor-endocrine relay rather than by direct microbial spread alone^[66]. Further support comes from an environmentally triggered metabolic model in which 4-hydroxyphenanthrene reduced *Bacteroides uniformis* and HDCA, activated intestinal FXR-neurotensin signaling, and exacerbated obesity^[67]. More broadly, this pathway expands the mechanistic repertoire of the oral-gut-bone axis by showing that dysbiosis-associated metabolic changes may be relayed through intestinal receptors and circulating hormones to influence remote skeletal tissues.

3.2 Barrier dysfunction, innate immune activation, and inflammatory amplification

In parallel with metabolite-centered signaling, the oral-gut-bone axis may also promote skeletal pathology through barrier dysfunction and inflammatory amplification. This mechanism is particularly relevant in settings where dysbiosis is associated with increased intestinal permeability, systemic exposure to microbial products, and sustained low-grade inflammation^[68]. Rather than depending on a single organism or metabolite, this pathway reflects a broader loss of compartmentalization between host tissues and microbial signals. Conceptually, this framework is consistent with broader gut-organ axis biology, in which barrier failure facilitates translocation of microbial products and amplifies distal tissue injury.

By contrast, when mucosal barrier integrity is preserved, oral microorganisms appear to have limited capacity to establish stable colonization in the gut. Consistent with this, Etienne-Mesmin et al. showed in an *in vitro* gut simulation system that artificial inoculation with oral microbiota had minimal effects on microbial composition in both luminal and mucosal compartments, supporting the view that an intact mucosal barrier strongly restricts the persistence and ecological impact of oral microbes within the intestinal environment^[69].

The clearest skeletal evidence for this barrier-based mechanism comes from osteoarthritis. Fecal microbiota transplantation from metabolically compromised human donors into germ-free mice increased gut permeability, elevated systemic inflammatory mediators, and aggravated post-traumatic osteoarthritis, supporting a two-hit model in which dysbiosis first establishes a permissive inflammatory state and subsequent joint injury then amplifies tissue damage^[23]. In this framework, microbial disturbance does not need to directly colonize the joint to worsen disease; it is sufficient to

lower the threshold at which local injury becomes pathologic.

This inflammatory-amplification model is likely relevant beyond osteoarthritis. Increased barrier permeability may facilitate systemic exposure to microbial products that promote osteoclastogenic cytokine production, alter immune-cell polarization, and sustain a pro-resorptive inflammatory milieu^[51,70]. Barrier dysfunction should therefore be viewed as a major mechanistic architecture of the oral–gut–bone axis, operating in parallel with, and often reinforcing, metabolite-centered signaling.

3.3 Oral-derived microbial signals and systemic osteoclastogenesis

A third key pathway is the transmission of pathogenic signals from the oral cavity itself. Detailed evidence for oral-to-gut transmission is summarized in Section 2.2; this subsection focuses on oral-derived signals and downstream osteoclastogenesis. This mechanism is especially important because it positions oral dysbiosis as an upstream ecological disturbance rather than merely a secondary reflection of systemic disease. The broader conceptual basis for this pathway comes from rheumatoid arthritis, in which both oral and gut microbiomes are perturbed and may be partially normalized after treatment^[10], and from recent reviews and human investigations examining the potential roles of oral pathobionts such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in autoantigen generation and immune priming^[71–74]. This treatment responsiveness is further supported by a prospective cohort study showing that methotrexate and non-surgical periodontal treatment were associated with changes in the composition and richness of the oral–gut microbiota in rheumatoid arthritis^[75].

More direct evidence for oral-to-systemic skeletal transmission comes from salivary microbiota transfer experiments. In ovariectomized mice, salivary communities derived from periodontitis donors exacerbated bone loss and induced downstream gut ecological change, supporting the concept of an oral–gut cascade initiated by oral dysbiosis^[5]. In this setting, the key point is that the oral cavity itself can function as an upstream ecological trigger of systemic skeletal vulnerability.

Local periodontal inflammation also provides a related example of the same principle. Even when the skeletal phenotype is anatomically local, oral dysbiosis can drive inflammatory activation, reshape host–microbe equilibrium, and favor osteoclastogenic tissue remodeling. Consistent with this, recent work showed that *P. gingivalis* LPS suppresses the Sema3A/Nrp1 axis via TLR-4, thereby enhancing osteoclastogenesis while impairing osteoblast differentiation; *in vivo*, Sema3A administration attenuated P-LPS-induced inflammatory osteolysis^[6]. This supports the broader view that the oral cavity is not merely a source of biomarkers or opportunistic pathogens, but a biologically active upstream niche capable of initiating mechanistic cascades with distal skeletal consequences. Beyond whole bacteria and soluble microbial components, oral bacterial extracellular vesicles (EVs) may provide an additional route of host–microbial signaling. *In vitro*, EVs derived from *P. gingivalis*, *Tannerella forsythia*, and *Streptococcus oralis* preferentially activated TLR2 signaling in osteoclast precursors, increased osteoclastogenic cytokines including TNF- α , IL-6, and IL-1 β , and promoted osteoclast differentiation, whereas EVs from *Lactobacillus reuteri* did not show comparable effects^[76]. These findings suggest that oral bacterial EVs may contribute to

inflammatory bone resorption and could potentially serve as distal microbial signaling carriers. However, their *in vivo* distribution and effects on systemic bone remodeling remain to be established.

4 Disease-specific evidence

Although rheumatoid arthritis, osteoarthritis, and osteoporosis may share upstream disturbances such as oral dysbiosis, gut microbial remodeling, barrier dysfunction, and altered microbial metabolism, these common perturbations are translated into distinct skeletal outcomes in different disease contexts. In RA, disease specificity is primarily reflected by mucosal immune priming, modified self-antigen formation, autoantibody-related immune amplification, and inflammatory bone erosion. In OA, microbiome-associated inflammatory and metabolic susceptibility interacts with local mechanical joint injury and gut-derived endocrine signaling to promote maladaptive cartilage and subchondral bone remodeling. In OP, altered microbial metabolic signaling acts within susceptible host contexts, including estrogen deficiency and aging, to disrupt osteoclast–osteoblast coupling and promote systemic bone loss. Thus, shared upstream ecological disturbances do not necessarily imply uniform downstream skeletal pathology. Because the underlying molecular mechanisms are discussed in detail in Section 3, the following disease-specific subsections focus primarily on disease-level evidence, dominant skeletal phenotypes, and the relevance of these pathways in each disease context, with cross-references to the corresponding mechanistic sections where appropriate (Fig. 2).

4.1 Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune inflammatory disorder in which mucosal immune dysregulation, synovial inflammation, and bone erosion are central pathological features^[77]. It also represents a prototypical disease model linking the oral–gut axis to skeletal pathology. Evidence in rheumatoid arthritis spans multiple levels, including coordinated alterations in oral and gut microbial communities, functional microbial dysregulation, and associations with autoantibody generation^[78]. The established association between HLA-DRB1 and rheumatoid arthritis further suggests that aberrant T-cell selection may be a critical contributor to the development of autoreactivity^[79,80]. Notably, microbial DNA assignable to genera such as *Porphyromonas*, *Prevotella*, *Fusobacterium* has been identified in the serum and synovial compartment of patients with rheumatoid arthritis^[81]. Unlike OA and OP, the disease-specific relevance of microbiome perturbation in RA lies particularly in its coupling to the autoimmune network, including modified self-antigens, autoantibody-related immune amplification, and inflammatory osteoclastogenesis, ultimately converging on inflammatory bone erosion.

One of the most influential observations in this field is that both the oral and gut microbiomes are altered in rheumatoid arthritis and may be partially normalized after treatment^[82,83]. In particular, expansion of *Prevotella*—especially *Prevotella copri*—together with depletion of *Bacteroides* has emerged as a recurrent microbial signature, particularly in preclinical and new-onset untreated RA, although substantial geographic heterogeneity exists^[84–86]. This pattern supports the concept that RA is associated with a multisite mucosal microbial signature rather than isolated compartment-specific dysbiosis. Importantly, such microbial alterations may be particularly informative in the preclinical and early untreated stages

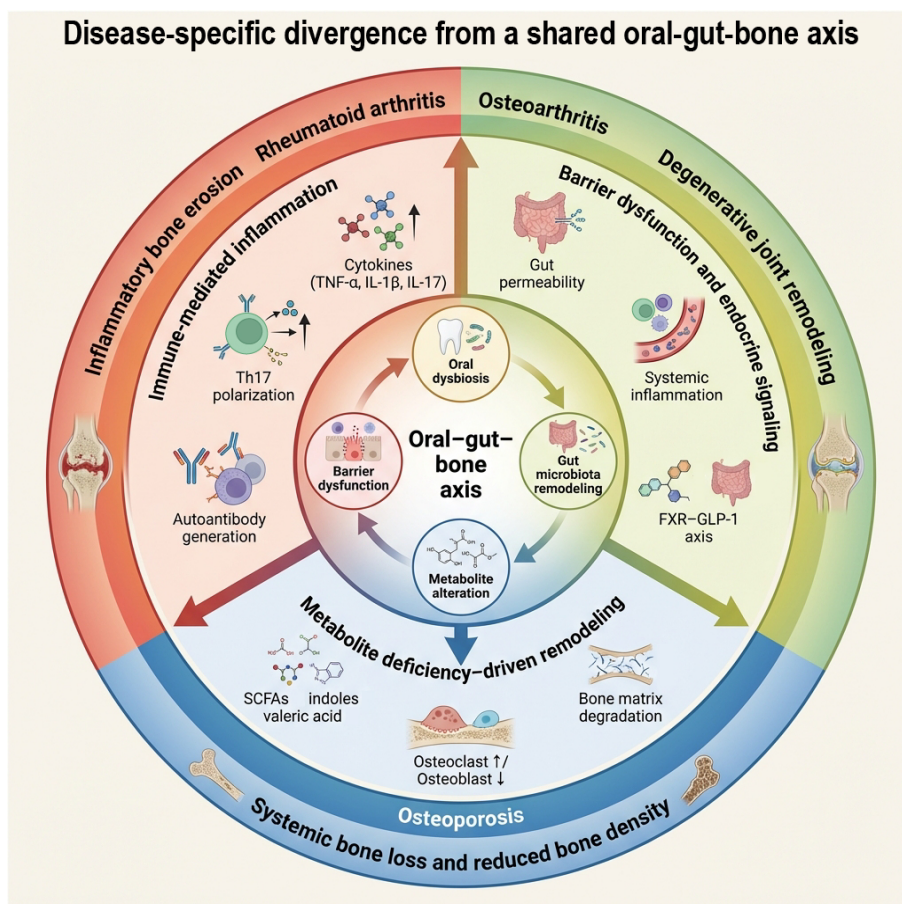


Figure 2 A shared oral-gut-bone framework may be associated with distinct skeletal phenotypes through disease-specific downstream mechanisms. Oral dysbiosis may influence gut microbial remodeling, barrier function, and metabolite profiles, but the dominant skeletal outcome varies by disease context. In rheumatoid arthritis, mucosal immune priming, autoantibody-related pathways, Th17 polarization, and inflammatory cytokines may contribute to inflammatory bone erosion. In osteoarthritis, barrier dysfunction, systemic inflammation, and gut-derived endocrine signaling may contribute to degenerative joint remodeling. In osteoporosis, depletion of protective microbial metabolites has been linked to osteoclast-osteoblast imbalance and may contribute to systemic bone loss. The figure is conceptual; the direction and strength of these relationships vary across diseases and study types, and the arrows do not imply established causality in humans.

of disease, before they are substantially modified by systemic inflammation or pharmacologic therapy^[87,88]. Moreover, these changes extend beyond taxonomic shifts to functional alterations involving redox balance and the metabolism of iron, sulfur, zinc, and arginine, suggesting that microbial function may be as important as microbial composition in RA pathogenesis^[89].

The oral microbiome has been implicated in rheumatoid arthritis through mechanisms related to modified self-antigen generation and immune priming^[71,90]. *Porphyromonas gingivalis* remains of particular interest because its peptidylarginine deiminase (PPAD) can directly catalyze protein citrullination, providing a biologically plausible route through which periodontal dysbiosis may increase the burden of citrullinated antigens associated with ACPA responses^[72,91-95]. Recent studies and reviews continue to support this mechanistic link, although the strength and specificity of the corresponding associations in human RA remain heterogeneous.

By contrast, *Aggregatibacter actinomycetemcomitans* appears to increase the modified-antigen burden indirectly rather than through a bacterial PAD. Its pore-forming leukotoxin A (LtxA) increases neutrophil membrane permeability and extracellular Ca^{2+} influx, leading to aberrant activation of host PADs, widespread hypercitrullination, cell death, and release of citrullinated proteins^[96-98]. However, recent human evidence has not been fully

consistent: associations between anti-LtxA responses and progression to arthritis have differed across independent at-risk cohorts, and recent studies have not demonstrated a stable relationship between salivary carriage of *A. actinomycetemcomitans* and RA-related clinical or serological features^[73,74]. Thus, LtxA-mediated hypercitrullination has a well-defined experimental basis but is more appropriately regarded as a potential autoantigen-generating mechanism operating in a subset of susceptible individuals rather than as a universally established pathway in RA.

Altered butyrate metabolism is also associated with the RA phenotype. Depletion of butyrate-producing taxa together with expansion of butyrate-consuming species has been associated with autoantibody production, disease activity, joint deformity, and structural bone damage^[59]. The immunoregulatory and anti-osteoclastogenic actions of butyrate are discussed in detail in Section 3.1.1 and are therefore not repeated here.

Collectively, the available evidence supports a model in which rheumatoid arthritis arises, at least in part, from coordinated mucosal dysbiosis involving both the oral cavity and the gut, followed by immune priming, autoantibody amplification, and metabolite-dependent osteoimmune imbalance. Among the skeletal disorders discussed here, rheumatoid arthritis remains the most mechanistically developed example of microbiota-associated

inflammatory bone damage.

4.2 Osteoarthritis

Osteoarthritis has traditionally been viewed as a degenerative joint disorder driven primarily by aging, biomechanics, and cartilage wear^[99]. However, recent studies indicate that osteoarthritis can also be interpreted within an oral–gut–bone framework, particularly through mechanisms involving low-grade systemic inflammation, barrier dysfunction, and metabolite-dependent endocrine signaling^[13,23].

Experimental evidence supports this two-hit model. Fecal microbiota transplantation from metabolically compromised human donors into germ-free mice increased intestinal permeability and systemic inflammatory mediators and aggravated post-traumatic osteoarthritis, suggesting that a microbiome-associated inflammatory state can amplify the consequences of local joint injury^[23]. Separately, recent work identified reduced glycoconjugate deoxycholic acid as a feature of osteoarthritis and showed that experimental modulation of the gut microbiota–GUDCA–intestinal FXR–GLP-1 axis protected joint tissues, providing an endocrine route through which gut microbial metabolism may influence disease progression^[65]. These studies support a gut–joint contribution to osteoarthritis but do not by themselves establish an upstream role for oral dysbiosis.

Microbiota-targeted interventions provide additional disease-specific support. In preclinical models, oral administration of live or inactivated *Clostridium butyricum* GKB7 reduced pain-related behaviors, structural damage, and inflammatory mediators, whereas fermented GKB7 inhibited the progression of anterior cruciate ligament transection-induced osteoarthritis^[100,101]. At the clinical level, a systematic review and meta-analysis of randomized intervention studies suggested that the effects of probiotics on osteoarthritis-related pain and inflammation may be strain dependent; however, the evidence remains limited by the small number of available studies and potential risk of bias^[102].

Taken together, current findings suggest that microbiome-related inflammatory, metabolic, and endocrine signals may modify osteoarthritis progression by interacting with established mechanical and age-related drivers. Nevertheless, most available evidence remains gut focused and preclinical. Direct evidence demonstrating that oral dysbiosis initiates an integrated oral–gut–bone pathway in human osteoarthritis is still limited.

4.3 Osteoporosis and systemic bone loss

In contrast to the inflammatory bone erosion of RA and the localized maladaptive joint remodeling of OA, the disease-specific skeletal phenotype of OP is generalized disruption of bone turnover and microarchitecture. Microbiome-related metabolic alterations may contribute to osteoclast–osteoblast uncoupling within susceptible host contexts, including estrogen deficiency and aging, thereby favoring systemic loss of bone mass and structural integrity^[103,104]. Within this framework, microbiome-related signals in OP are most relevant to the regulation of whole-body bone remodeling rather than autoimmune or mechanically driven joint damage.

Experimental studies provide several lines of evidence linking microbiome-related alterations to systemic bone turnover. The *Bacteroides vulgatus*–valerate axis has been associated with bone mineral density and bone remodeling^[21], while salivary microbiota transfer and periodontitis-associated microbiota/FMT models

support a potential oral–gut contribution to systemic bone loss^[5,105]. The detailed valerate, tryptophan/ILA, barrier-related, and oral-derived microbial mechanisms are discussed in Sections 3.1.1, 3.1.2, 3.2, and 3.3, respectively, and are therefore not repeated here.

Human data further strengthen this model. Population-based studies have linked the fecal microbiome to bone density, structure, and strength, supporting the clinical relevance of these experimental observations^[106]. In addition, genetically informed analyses suggest that at least part of the microbiota–bone relationship may reflect causal biology rather than purely associative variation^[107]. Although these studies do not yet establish a complete oral–gut–bone pathway in humans, they provide an important bridge between experimental mechanism and population-level skeletal phenotypes.

Taken together, these observations suggest that osteoporosis and systemic bone loss represent particularly strong examples of how metabolite deficiency and metabolic rewiring can be translated into structural skeletal outcomes within the broader oral–gut–bone framework.

4.4 Emerging skeletal contexts

Compared with rheumatoid arthritis, osteoarthritis, and osteoporosis, the role of the oral–gut axis in other skeletal settings remains less well defined. Emerging evidence is particularly relevant to osteomyelitis, bone repair and regeneration, and age-related skeletal decline, although a complete oral–gut–bone pathway has not yet been established in these contexts.

In osteomyelitis, current evidence primarily supports a relationship between oral microbial disturbances and skeletal infection. Studies of chronic osteomyelitis of the jaw have identified polymicrobial communities containing oral-associated anaerobes, including *Actinomyces*, *Fusobacterium*, *Tannerella*, and *Porphyromonas* species^[108,109]. Salivary metagenomic profiling has further identified disease-associated oral microbial signatures in chronic bacterial osteomyelitis^[110]. At distant skeletal sites, clinical reports have documented osteomyelitis caused by oral anaerobes in patients with periodontal infection or following dental procedures, suggesting that disruption of the oral barrier may occasionally permit hematogenous dissemination to bone^[111–113]. Of particular relevance to the oral–gut framework, concurrent alterations in both oral and fecal microbiota have been reported in chronic recurrent multifocal osteomyelitis^[114]. However, these observations do not establish directional oral-to-gut transmission or demonstrate that oral dysbiosis is a general causal driver of osteomyelitis.

Microbiome-related evidence is also emerging in bone repair and regeneration. Longitudinal studies of mandibular bone defects and jaw lesions have shown dynamic changes in oral microbial communities during healing, with early microbial features associated with subsequent bone-regeneration outcomes^[115,116]. Mechanistic studies further indicate that *Porphyromonas gingivalis*-derived outer membrane vesicles can impair osteogenic differentiation and bone regeneration, while experimental oral exposure to *P. gingivalis* has been shown to reduce new bone formation in femoral cortical defects^[117,118]. In parallel, fracture models support a gut–bone immune component: Dar et al. showed that fracture increases gut permeability and promotes recruitment of microbe-induced intestinal Th17 cells to the fracture callus, where they contribute to repair^[119]. Together, these findings support separate oral–bone and gut–bone contributions to skeletal healing, although studies simultaneously tracking oral microbiota, gut microbiota, and fracture outcomes remain lacking.

Age-related skeletal change represents another emerging context in which oral microbial ecology may interact with host susceptibility to bone loss. Aging is accompanied by immunosenescence, chronic low-grade inflammation, mucosal barrier dysfunction, and microbial remodeling. Recent systematic reviews indicate age-associated changes in oral microbial composition, although substantial heterogeneity related to oral hygiene, tooth loss, comorbidities, medications, diet, and lifestyle precludes definition of a universal “aging-associated oral microbiome”^[120,121]. In aged mice, altered oral microbial ecology and succinate–SUCNR1 signaling have been linked to periodontal inflammation and alveolar bone loss, while aging also increases susceptibility to *Porphyromonas gingivalis*-induced inflammatory bone resorption^[122,123]. Human studies further associate baseline subgingival microbial profiles with subsequent alveolar bone loss and report differences in salivary and plaque microbiota across postmenopausal women with different bone-mass states^[4,124]. However, evidence linking the oral microbiome specifically to systemic age-related skeletal loss remains preliminary and largely associative.

Overall, osteomyelitis, bone repair, and age-related skeletal change should currently be regarded as emerging rather than established manifestations of the oral–gut–bone axis. The available literature provides evidence for oral–bone or gut–bone relationships in these settings, but direct longitudinal or experimental demonstration of an integrated oral–gut–bone pathway remains limited. Their inclusion therefore serves to define potential extensions of the framework while highlighting important areas requiring paired oral–gut sampling and mechanistic validation. Taken together, the major mechanistic pathways linking the oral–gut–bone axis to skeletal disease, along with their disease relevance and representative evidence, are summarized in Table 1.

5 Translational implications and therapeutic prospects

5.1 Microbiota-derived metabolites as therapeutic entry points

Among the translational opportunities arising from the oral–gut–bone axis, microbiota-derived metabolites are among the most mechanistically tractable^[125]. Across multiple skeletal disease settings, metabolites repeatedly emerge as functional intermediates linking ecological disruption to osteoimmune imbalance, making them attractive therapeutic targets because they are chemically definable, biologically measurable, and potentially easier to manipulate than whole microbial communities. This principle is supported by convergent evidence from rheumatoid arthritis, osteoarthritis, and osteoporosis-related models.

Short-chain fatty acids and related organic acids illustrate this concept clearly. In rheumatoid arthritis, altered butyrate-related microbial function has been linked to autoantibody production, bone erosion, and disease severity, supporting a direct connection between microbial metabolism and inflammatory skeletal damage^[59]. In osteoporosis-related settings, valeric acid has been shown to suppress osteoclast differentiation and promote osteoblast maturation, indicating that restoration of specific metabolite pools may directly influence bone turnover^[21].

Tryptophan-derived indoles represent another promising class of

intermediates, particularly in models in which oral dysbiosis reshapes gut metabolism and downstream osteoimmune responses^[5]. Bile acid derivatives further broaden this framework by showing that gut microbial metabolism may influence distal skeletal tissues through endocrine-like signaling pathways rather than through direct microbial dissemination alone^[65]. Collectively, these findings suggest that restoring protective metabolite signaling may represent one of the most feasible and biologically grounded translational strategies in microbiome-related skeletal disease.

5.2 Microbiota-targeted intervention and ecosystem restoration

A second translational strategy is to intervene more directly at the level of the microbial ecosystem. This includes probiotics, next-generation commensals, strain-based therapeutics, and, in experimental contexts, microbiota transfer approaches^[126]. Such strategies are particularly compelling when specific organisms or microbial networks can be linked to disease-relevant metabolic or immunological functions^[127]. More broadly, these approaches align with the emerging shift in microbiome therapeutics from relatively untargeted ecological modulation toward more precise restoration of beneficial taxa and functions, although standardization, safety, and durable engraftment remain important translational challenges^[16,128].

At the same time, recent studies indicate that effective microbiota-based therapy may need to move beyond empirical probiotic supplementation toward functionally informed ecosystem restoration^[129,130]. Beneficial skeletal effects may depend not simply on the addition of individual taxa, but on re-establishing cooperative microbial networks that sustain protective metabolite production and immune homeostasis^[131]. This perspective is equally relevant at the oral level, where stabilization of oral biofilms, suppression of keystone pathobionts, and preservation of beneficial oral microbial functions may provide upstream leverage over downstream skeletal pathology. Dietary manipulation, exercise, and restoration of intestinal barrier integrity may likewise be viewed as microbiota-oriented interventions, as each can reshape gut microbial composition, host inflammatory tone, or both^[132,133].

Emerging preclinical studies show that microbiota-targeted interventions can restore intestinal barrier function, remodel gut microbial communities, and induce systemic immune regulation. In experimental rheumatoid arthritis, combining microbiome-directed therapy with local anti-inflammatory treatment can suppress inflammatory pathways and preserve bone and cartilage integrity, highlighting the translational potential of integrated systemic and local strategies^[134].

5.3 Targeting host pathways downstream of microbial signals

An additional and potentially more druggable translational route is to target host pathways that interpret microbial signals^[135]. This strategy is attractive because host receptors and downstream signaling nodes are often more pharmacologically accessible and easier to standardize than microbiome-based interventions themselves.

Secondary bile acids can enter systemic circulation and signal through host receptors such as FXR and TGR5, providing a plausible route by which gut microbial metabolism affects distal tissues through endocrine-like mechanisms^[136,137]. Specifically, the

Table 1 Representative evidence for pathways potentially linking the oral–gut–bone axis to skeletal disease.

Major pathway	Key mediators/processes	Main effects	Disease relevance	Representative evidence
Metabolite-centered osteoimmune regulation	Butyrate-producing taxa↓; altered butyrate metabolism	Impaired immune regulation; enhanced osteoclastogenic potential; increased inflammatory bone damage	Rheumatoid arthritis	Depletion of butyrate-producing organisms, together with expansion of butyrate-metabolizing species, has been linked to autoantibody production, inflammatory activity, and bone erosion[59].
Metabolite-centered osteoimmune regulation	Valeric acid	Suppresses osteoclast differentiation and promotes osteoblast maturation	Osteoporosis/systemic bone loss	Valeric acid is positively associated with skeletal health and experimentally inhibits osteoclastogenesis while promoting osteoblast maturation[21].
Metabolite-centered osteoimmune regulation	Tryptophan metabolism suppression; ILA↓	Reduced protective indole signaling; enhanced osteoclastogenesis; aggravated bone loss	Osteoporosis/systemic bone loss	Periodontitis-associated salivary microbiota suppresses intestinal tryptophan metabolism, reduces ILA availability, and worsens bone loss; ILA supplementation partially rescues this phenotype[5].
Metabolite-centered osteoimmune regulation	IPA; PPAR-dependent immunometabolic signaling	Enhances mitochondrial respiration and restrains pathogenic inflammatory differentiation	Mechanistic plausibility (non-skeletal experimental model)	In a non-skeletal experimental model, IPA enhanced mitochondrial metabolism and restrained pathogenic Th1/Th17 differentiation; its relevance to skeletal disease remains to be established[63].
Metabolite-centered osteoimmune regulation	IAA↓; PI3K-AKT/ROS/NFATc1 signaling	Inhibits osteoclast differentiation and bone resorption	Osteoporosis/systemic bone loss	Gut microbial alteration in ovariectomy-induced bone loss is accompanied by reduced serum IAA; IAA suppresses RANKL-induced PI3K-AKT signaling, ROS generation, and NFATc1 nuclear translocation, thereby alleviating osteoclastogenic remodeling and bone loss[62].
Metabolite-centered osteoimmune regulation	GUDCA↓; intestinal FXR; GLP-1 axis	Relays gut-derived metabolic signals to distal joint tissues	Osteoarthritis	Reduced GUDCA was identified as a feature of osteoarthritis, whereas experimental modulation of the gut microbiota–GUDCA–intestinal FXR–GLP-1 axis provided downstream joint protection[65].
Barrier dysfunction and inflammatory amplification	FMT from metabolically compromised donors; low-grade systemic inflammation; “two-hit” model	Systemic inflammatory priming and amplification of local joint injury	Osteoarthritis	FMT from metabolically compromised donors increases gut permeability, elevates inflammatory mediators, and aggravates post-traumatic osteoarthritis[23].
Barrier dysfunction and inflammatory amplification	Periodontitis-induced gut dysbiosis; intestinal permeability↑; FMT-supported gut causality	Gut barrier disruption and microbiota-dependent impairment of systemic bone homeostasis	Osteoporosis/systemic bone loss	Periodontitis induces gut microbial dysbiosis and increased intestinal permeability in ApoE ^{-/-} mice, while fecal microbiota transplantation supports a causal role for the gut microbiota in systemic bone homeostasis disruption[105].
Oral-derived upstream microbial triggers	<i>P. gingivalis</i> LPS; TLR-4; Sema3A/Nrp1 axis	Enhances osteoclastogenesis and impairs osteoblast differentiation	Periodontal inflammatory bone loss/oral skeletal remodeling	<i>P. gingivalis</i> LPS suppresses the Sema3A/Nrp1 axis via TLR-4, thereby enhancing osteoclastogenesis while impairing osteoblast differentiation; Sema3A attenuates inflammatory osteolysis <i>in vivo</i> [6].
Oral-derived upstream microbial triggers	<i>Porphyromonas gingivalis</i> ; <i>Aggregatibacter actinomycetemcomitans</i> ; immune priming; autoantigen-related mechanisms	Mucosal immune activation; autoantibody-related amplification; osteoclastogenic drive	Rheumatoid arthritis	<i>P. gingivalis</i> PPAD and <i>A. actinomycetemcomitans</i> LtxA-mediated host hypercitrullination provide experimentally supported autoantigen-related mechanisms, although recent human studies report heterogeneous associations[93–98].

clearest current example is the FXR–GLP-1 axis in osteoarthritis. Recent work has shown that gut microbial metabolism alters bile acid composition, that GUDCA-related signaling modulates intestinal FXR activity, and that this pathway influences GLP-1 release and downstream joint protection. These findings identify several plausible intervention points, including bile acid supplementation, FXR modulation, and GLP-1-based strategies[65].

Similarly, microbiota-derived metabolites may act through host immunometabolic sensors to reshape inflammatory differentiation and tissue vulnerability. More broadly, these observations indicate

that translational leverage may be achieved not only by modifying microbial communities, but also by targeting the host signaling circuits through which microbial perturbation is converted into skeletal pathology. In diseases shaped by multiple interacting mechanisms, host-pathway targeting may offer a particularly practical route when microbiome-based strategies remain difficult to standardize.

5.4 Biomarkers and mechanism-guided stratification

Beyond therapeutic intervention, the oral–gut–bone axis also

provides a framework for developing clinically relevant biomarkers for disease risk, progression, and treatment response. Oral and fecal microbiota are attractive candidate sources because they are relatively accessible, whereas circulating metabolites may provide functionally informative readouts of microbial activity^[138,139]. Integrated profiling of oral and gut microbial communities together with blood-borne metabolic signals may therefore improve patient stratification and help identify biologically distinct skeletal disease subsets^[140].

At present, however, translation into clinically useful biomarkers remains challenging. Cohort heterogeneity, compartment-specific sampling, analytical inconsistency, and the influence of diet, medication use, age, oral hygiene, and systemic comorbidity all complicate interpretation^[10]. For this reason, function-based biomarkers are likely to prove more robust than taxa-based classifiers alone^[141,142]. Metabolite profiles and pathway-level signatures may provide more stable and biologically meaningful indicators than species-level abundance measures, particularly in complex diseases in which microbial function matters more than taxonomic composition per se.

More broadly, these considerations support a shift from generic microbiome correction toward mechanism-guided stratification. The skeletal consequences of a given microbial perturbation are likely to depend on host genetics, age, menopausal status, immune tone, metabolic background, and disease-specific tissue context^[143-146]. Future translational strategies will therefore need to align interventions with dominant biological mechanisms rather than diagnosis alone. Although routine clinical implementation remains premature, the current evidence already points toward a more precise and mechanism-informed model of microbiome-based intervention in skeletal disease.

5.5 Translational bottlenecks and requirements for clinical implementation

Despite the therapeutic potential of probiotics, live biotherapeutic products, and microbiota-derived metabolites, their clinical translation remains constrained by challenges related to standardization, safety, durable engraftment, and population heterogeneity. Microbial interventions are often highly strain- and formulation-specific, requiring strain-level identification, assessment of genetic stability, potential virulence, and antimicrobial-resistance determinants, together with standardized criteria for viable-cell counts, purity, functional potency, batch-to-batch consistency, and storage stability. For multi-strain formulations, the relative abundance and potential interactions among constituent strains should also be defined. In addition, manufacturing and regulatory requirements for microbiome-based therapeutics remain incompletely harmonized across regions^[147-149].

Safety assessment is particularly important in older adults, immunocompromised individuals, and patients with impaired mucosal barrier function. Although probiotics are generally considered well tolerated, probiotic-associated microbial translocation and bloodstream infection have been reported in susceptible patients. Clinical evaluation should therefore extend beyond common adverse events to include opportunistic infection, dissemination of antimicrobial-resistance determinants, and potential long-term ecological disturbance^[150]. Durable engraftment represents an additional challenge because persistence of administered strains is influenced by the resident microbiota, diet,

medication exposure, and the local ecological environment. Short-term detection of a therapeutic strain in fecal samples should not be equated with stable colonization, and persistent colonization does not necessarily indicate sustained functional activity. Future studies should therefore evaluate strain persistence together with metabolite output and relevant host-pathway responses^[148,151].

Population heterogeneity may further contribute to variable therapeutic responses. Age, sex, menopausal status, diet, oral hygiene, baseline microbial composition, and concomitant medications may all modify the effects of microbiome-directed interventions. Clinical studies of probiotics in osteoarthritis have used heterogeneous strains, treatment durations, and outcome measures, and consistent therapeutic efficacy has not yet been demonstrated across interventions^[102]. These observations argue against a one-size-fits-all approach and support mechanism-guided patient stratification based on baseline microbial features, metabolite profiles, and relevant host characteristics.

Microbiota-derived metabolites avoid the requirement for live microbial engraftment but introduce a different set of translational challenges. Rapid intestinal absorption, first-pass metabolism, insufficient exposure of distal skeletal tissues, and dose-dependent off-target effects may limit their therapeutic utility. Clinical development will therefore require definition of pharmacokinetic-pharmacodynamic relationships, effective doses, and therapeutic windows, together with the evaluation of enteric, sustained-release, or targeted-delivery strategies^[152]. Collectively, standardized products, risk-stratified safety assessment, longitudinal validation of functional persistence, and mechanism-guided patient selection will be essential prerequisites for translating microbiome-related skeletal interventions into clinical practice.

6 Current limitations and future directions

6.1 Limited causal inference

Although interest in the oral-gut-bone axis has expanded rapidly, most available evidence remains associative, particularly in human studies^[17]. As a result, it remains difficult to determine whether microbial alterations act as causal drivers, secondary consequences, or context-dependent correlates of skeletal disease^[153]. Future studies should therefore place greater emphasis on reconstructing and validating causal chains linking oral dysbiosis, gut remodeling, systemic signaling changes, and skeletal outcomes. Future studies should prioritize longitudinal cohorts with repeated oral, gut, blood, and skeletal measurements to determine whether microbial alterations precede changes in skeletal phenotypes. Mendelian randomization, particularly bidirectional and multivariable approaches, may complement observational studies by prioritizing candidate microbial taxa, metabolites, and inflammatory mediators with potential causal relevance. However, such genetic evidence should be interpreted cautiously and subsequently validated in controlled experimental models because current microbiome GWAS remain limited by taxonomic resolution, population ancestry, and potential pleiotropy^[154,155].

6.2 Lack of multi-compartment integration

A major weakness of the current literature is the tendency to examine oral microbiota, gut microbiota, circulating metabolites, immune phenotypes, and skeletal traits in isolation. This fragmented approach limits direct evaluation of cross-compartment

biological interactions and weakens mechanistic interpretation of the axis as an integrated system^[156,157]. More importantly, the limitation is not merely one of sampling breadth, but also of true host–microbiome multi-omics integration, as the parallel collection of microbial and host data alone is insufficient without systems-level analytical frameworks. Current evidence suggests that microbial alterations may propagate through metabolite-mediated and host regulatory layers, including epigenomic responses, yet these intermediate compartments are rarely assessed together in the same subjects^[158,159]. Study designs that simultaneously assess these compartments in the same subjects will be essential for defining the biological continuity of the oral–gut–bone axis.

Accordingly, future studies should adopt matched multi-compartment sampling, ideally collecting saliva or dental plaque, feces, serum/plasma, and peripheral immune cells from the same individuals at matched time points. Where clinically feasible, synovial fluid, bone marrow, or surgical bone specimens may provide additional tissue-level information. These samples could be integrated using strain-resolved metagenomics, metabolomics, immune phenotyping, and host transcriptomic profiling to construct oral–gut–immune–metabolic signatures associated with skeletal phenotypes. Paired longitudinal oral and fecal sampling combined with shotgun metagenomics would also provide stronger evidence for oral-to-gut microbial transmission than cross-sectional taxonomic comparisons alone^[45,160].

6.3 Overreliance on taxonomic profiling

The field still relies heavily on compositional profiling, even though many microbiome studies have historically focused on individual taxa while underexamining the broader metabolic potential of microbial communities^[161,162]. Functional inference is particularly important because unrelated individuals may share far more microbial metabolic pathways than species, consistent with substantial redundancy across taxonomically distinct microbes. In turn, pathway-level features may be more informative than species abundance alone, as microbial metabolic pathways have been shown to exhibit a broader metabolic footprint and substantially more metabolite associations than individual species^[142,163]. Future work should therefore prioritize metagenomic, metabolomic, and systems-level analyses, ideally complemented by transcript-level functional readouts, to identify the microbial functions and host pathways most relevant to osteoimmune regulation^[164].

6.4 Inadequate consideration of host context and model complexity

The skeletal consequences of microbial perturbation are unlikely to be uniform across individuals, as they are shaped by host genetics, age, sex, menopausal status, immune state, and metabolic background^[165–167]. At the same time, many current animal models fail to adequately capture the chronic, spatially structured, and multisite nature of human oral–gut communication^[168]. More physiologically relevant models and more refined host stratification will be necessary to improve both mechanistic precision and translational relevance.

Human-relevant experimental systems may help address this limitation. Patient-derived gingival or intestinal organoids can be cocultured with candidate microorganisms, microbial metabolites, or immune cells to evaluate donor- and strain-specific responses^[169,170]. Gut-on-chip platforms can further reproduce

epithelial barriers, oxygen gradients, vascular interfaces, and mechanical forces under more physiologically relevant conditions^[171]. In future oral–gut–bone studies, outputs from these models could be coupled with osteoclast precursors, osteoblasts, or bone organoids to test whether microbiome-derived signals influence bone-cell phenotypes.

6.5 Need for a unified yet testable framework

Although evidence is strongest in rheumatoid arthritis, osteoarthritis, and osteoporosis, the broader scope of the oral–gut–bone axis remains incompletely defined^[172]. It is therefore important to distinguish disease settings supported by direct evidence from those that remain largely speculative. Going forward, the field will benefit from a unified yet testable framework in which metabolite-centered regulation, barrier dysfunction, and oral-derived upstream perturbation are evaluated as interacting components of a shared biological system.

7 Conclusion

The oral microbiome should be viewed not only as a local determinant of oral health, but also as an upstream ecological interface that can influence systemic skeletal pathology through oral–gut communication, barrier dysfunction, and osteoimmune remodeling. Importantly, the biological significance of the oral–gut–bone axis lies less in individual pathobionts than in the disruption of protective microbial functions and metabolite-producing networks. In this context, short-chain fatty acids, valeric acid, bile acid derivatives, and tryptophan-derived indoles emerge as key intermediates linking microbial ecology to inflammatory amplification, osteoclastogenesis, osteoblast support, and joint homeostasis. At present, research on the role of the oral microbiome in bone-related diseases remains relatively limited, and further in-depth investigation will be needed to clarify its disease-specific functions, mechanisms, and translational relevance. Future progress will depend on defining the microbial–metabolite–host circuits that may contribute to systemic bone-related diseases and may serve as the basis for mechanism-guided intervention.

Abbreviations

FMT	fecal microbiota transplantation
FXR	farnesoid X receptor
GLP-1	glucagon-like peptide-1
IAA	indole-3-acetic acid
ILA	indole-3-lactic acid
IPA	indole-3-propionic acid
RA	rheumatoid arthritis
ROS	reactive oxygen species
GDCA	glycodeoxycholic acid
GUDCA	glycoursodeoxycholic acid
HDCA	hyodeoxycholic acid
HLA-DRB1	human leukocyte antigen-DRB1

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Data availability statement

N/A

Author contribution

F.L. and J.X. guided and revised the manuscript. Z.Z. wrote the manuscript. L.S. revised the manuscript. All the authors participated in editing the content of this paper and approved the final version.

Ethics approval and consent

There is no need for ethics approval and consent to participate because this is a review paper without human or animal experiments.

Consent for publication

All authors agree to publish.

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article.

References

- [1] Mark Welch, J. L.; Ramirez-Puebla, S. T.; Borisy, G. G. Oral microbiome geography: Micron-scale habitat and niche. *Cell Host Microbe* **2020**, *28*, 160–168.
- [2] Gomez, A.; Espinoza, J. L.; Harkins, D. M.; et al. Host genetic control of the oral microbiome in health and disease. *Cell Host Microbe* **2017**, *22*, 269–278.e3.
- [3] Qian, B. F.; Fang, Z. W. The association between oral microbiome diversity and rheumatoid arthritis: A nationwide cross-sectional study. *Clin. Rheumatol.* **2026**, *45*, 697–706.
- [4] Liu, M.; Wu, M.; Tang, Y. J.; et al. Correlation between oral microbial characteristics and overall bone density of Postmenopausal women based on macrogenomic analysis. *Front. Cell. Infect. Microbiol.* **2025**, *15*, 1663645.
- [5] Wang, N. N.; Qian, J.; Wang, M.; et al. Periodontitis-associated salivary microbiota exacerbates systemic osteoclastogenesis via gut modulation and tryptophan metabolism suppression in ovariectomized mice. *Int. J. Oral Sci.* **2026**, *18*, 14.
- [6] Feng, J. Y.; Fu, D. J.; Phan, S.; et al. P. gingivalis LPS drives osteoclastogenesis and impairs osteoblast differentiation by suppressing Sema3A/Nrp1 via TLR-4. *Int. Dent. J.* **2025**, *75*, 103941.
- [7] Sedghi, L.; DiMassa, V.; Harrington, A.; et al. The oral microbiome: Role of key organisms and complex networks in oral health and disease. *Periodontology 2000* **2021**, *87*, 107–131.
- [8] Atarashi, K.; Suda, W.; Luo, C. W.; et al. Ectopic colonization of oral bacteria in the intestine drives T_H1 cell induction and inflammation. *Science* **2017**, *358*, 359–365.
- [9] Maeda, Y.; Takeda, K. Host-microbiota interactions in rheumatoid arthritis. *Exp. Mol. Med.* **2019**, *51*, 1–6.
- [10] Zhang, X.; Zhang, D. Y.; Jia, H. J.; et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat. Med.* **2015**, *21*, 895–905.
- [11] Hajishengallis, G.; Chavakis, T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat. Rev. Immunol.* **2021**, *21*, 426–440.
- [12] Rauner, M.; Bozec, A. Mechanisms of osteoclast activation in inflammatory bone loss in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **2026**, *22*, 42–61.
- [13] Tang, S. A.; Zhang, C. Q.; Oo, W. M.; et al. Osteoarthritis. *Nat. Rev. Dis. Primers* **2025**, *11*, 10.
- [14] Mi, B. B.; Xiong, Y.; Knoedler, S.; et al. Ageing-related bone and immunity changes: Insights into the complex interplay between the skeleton and the immune system. *Bone Res.* **2024**, *12*, 42.
- [15] Lucas, S.; Omata, Y.; Hofmann, J.; et al. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. *Nat. Commun.* **2018**, *9*, 55.
- [16] Lyu, Z. T.; Hu, Y. F.; Guo, Y. M.; et al. Modulation of bone remodeling by the gut microbiota: A new therapy for osteoporosis. *Bone Res.* **2023**, *11*, 31.
- [17] Ma, Z. Q.; Zuo, T.; Frey, N.; et al. A systematic framework for understanding the microbiome in human health and disease: From basic principles to clinical translation. *Signal Transduct. Target. Ther.* **2024**, *9*, 237.
- [18] Arifuzzaman, M.; Collins, N.; Guo, C. J.; et al. Nutritional regulation of microbiota-derived metabolites: Implications for immunity and inflammation. *Immunity* **2024**, *57*, 14–27.
- [19] Li, Z. H.; Deng, W. D.; Yang, L. X.; et al. Lipid metabolism in homeostasis and disease. *Signal Transduct. Target. Ther.* **2026**, *11*, 55.
- [20] Song, X. Y.; Sun, X. M.; Oh, S. F.; et al. Microbial bile acid metabolites modulate gut ROR γ regulatory T cell homeostasis. *Nature* **2020**, *577*, 410–415.
- [21] Lin, X.; Xiao, H. M.; Liu, H. M.; et al. Gut microbiota impacts bone via *Bacteroides vulgatus*-valeric acid-related pathways. *Nat. Commun.* **2023**, *14*, 6853.
- [22] Peng, X.; Cheng, L.; You, Y.; et al. Oral microbiota in human systematic diseases. *Int. J. Oral Sci.* **2022**, *14*, 14.
- [23] Huang, Z. Y.; Chen, J.; Li, B. L.; et al. Faecal microbiota transplantation from metabolically compromised human donors accelerates osteoarthritis in mice. *Ann. Rheumatic Dis.* **2020**, *79*, 646–656.
- [24] Wu, S. W.; Ye, X. Y.; Wang, J. S.; et al. Microbial crosstalk along the oral–gut axis: Organ-specific oncogenic adaptations of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. *Neoplasia* **2026**, *74*, 101290.
- [25] Lou, F. Z.; Yan, L.; Luo, S. H.; et al. Dysbiotic oral microbiota-derived kynurenine, induced by chronic restraint stress, promotes head and neck squamous cell carcinoma by enhancing CD8⁺ T cell exhaustion. *Gut* **2025**, *74*, 935–947.
- [26] Xu, Y. W.; Xiong, Z.; Zhang, P. K.; et al. Microbiota metabolite taurodeoxycholic acid maintains intestinal tissue residency of innate lymphoid cells via engagement with P2Y10 receptor. *Sci. Adv.* **2025**, *11*, eadt9645.
- [27] Kitamoto, S.; Nagao-Kitamoto, H.; Jiao, Y. Z.; et al. The intermucosal connection between the mouth and gut in commensal pathobiont-driven colitis. *Cell* **2020**, *182*, 447–462.e14.
- [28] Kageyama, S.; Sakata, S.; Ma, J.; et al. High-resolution detection of translocation of oral bacteria to the gut. *J. Dent. Res.* **2023**, *102*, 752–758.
- [29] Yang, Z. Y.; Wang, J. L.; Chen, Y. F.; et al. *Veillonella* intestinal colonization promotes *C. difficile* infection in Crohn's disease. *Cell Host Microbe* **2025**, *33*, 1518–1534.e10.
- [30] Schwabe, R. F.; Greten, T. F. Gut microbiome in HCC—Mechanisms, diagnosis and therapy. *J. Hepatol.* **2020**, *72*, 230–238.
- [31] Neurath, M. F.; Artis, D.; Becker, C. The intestinal barrier: A pivotal

- role in health, inflammation, and cancer. *Lancet Gastroenterol. Hepatol.* **2025**, *10*, 573–592.
- [32] Byndloss, M.; Devkota, S.; Duca, F.; et al. The gut microbiota and diabetes: Research, translation, and clinical applications-2023 diabetes, diabetes care, and diabetologia expert forum. *Diabetes Care* **2024**, *47*, 1491–1508.
- [33] Xie, M. X.; Yuan, K.; Zhang, Y. X.; et al. Tumor-resident probiotic *Clostridium butyricum* improves aPD-1 efficacy in colorectal cancer models by inhibiting IL-6-mediated immunosuppression. *Cancer Cell* **2025**, *43*, 1885–1901.e10.
- [34] Baker, J. L.; Mark Welch, J. L.; Kauffman, K. M.; et al. The oral microbiome: Diversity, biogeography and human health. *Nat. Rev. Microbiol.* **2024**, *22*, 89–104.
- [35] Lin, Y. W.; Liang, X. Y.; Li, Z. Y.; et al. Omics for deciphering oral microecology. *Int. J. Oral Sci.* **2024**, *16*, 2.
- [36] Proctor, D. M.; Fukuyama, J. A.; Loomer, P. M.; et al. A spatial gradient of bacterial diversity in the human oral cavity shaped by salivary flow. *Nat. Commun.* **2018**, *9*, 681.
- [37] Wu, J.; Peters, B. A.; Dominianni, C.; et al. Cigarette smoking and the oral microbiome in a large study of American adults. *ISME J.* **2016**, *10*, 2435–2446.
- [38] Bertelsen, R. J.; Barrionuevo, A. M. P.; Shigdel, R.; et al. Association of oral bacteria with oral hygiene habits and self-reported gingival bleeding. *J. Clin. Periodontology* **2022**, *49*, 768–781.
- [39] Santonocito, S.; Giudice, A.; Polizzi, A.; et al. A cross-talk between diet and the oral microbiome: Balance of nutrition on inflammation and immune system's response during periodontitis. *Nutrients* **2022**, *14*, 2426.
- [40] Lamont, R. J.; Koo, H.; Hajishengallis, G. The oral microbiota: Dynamic communities and host interactions. *Nat. Rev. Microbiol.* **2018**, *16*, 745–759.
- [41] Hajishengallis, G.; Lamont, R. J.; Koo, H. Oral polymicrobial communities: Assembly, function, and impact on diseases. *Cell Host Microbe* **2023**, *31*, 528–538.
- [42] Sepich-Poore, G. D.; Zitvogel, L.; Straussman, R.; et al. The microbiome and human cancer. *Science* **2021**, *371*, eabc4552.
- [43] Fu, K. L.; Cheung, A. H. K.; Wong, C. C.; et al. *Streptococcus anginosus* promotes gastric inflammation, atrophy, and tumorigenesis in mice. *Cell* **2024**, *187*, 882–896.e17.
- [44] Huang, P. M.; Ji, F. F.; Cheung, A. H.; et al. *Peptostreptococcus stomatis* promotes colonic tumorigenesis and receptor tyrosine kinase inhibitor resistance by activating ERBB2-MAPK. *Cell Host Microbe* **2024**, *32*, 1365–1379.e10.
- [45] Raychaudhuri, S.; Gem, H.; Chung, K.; et al. Distal gut colonization by oral bacteria during intensive chemotherapy: Direct evidence from strain-level analysis of paired samples. *NPJ Biofilms Microbiomes* **2025**, *11*, 88.
- [46] Reytor-González, C.; Román-Galeano, N. M.; Aules-Curicama, L. S.; et al. The oral-gut-immune-nutrition axis in rheumatoid arthritis: Molecular mechanisms and therapeutic implications. *Int. J. Mol. Sci.* **2026**, *27*, 2385.
- [47] Kishikawa, T.; Maeda, Y.; Nii, T.; et al. Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population. *Ann. Rheumatic Dis.* **2020**, *79*, 103–111.
- [48] Ma, Y. F.; Zhong, Y. F.; Tang, W. J.; et al. *Lactobacillus reuteri* ZJ617 attenuates metabolic syndrome via microbiota-derived spermidine. *Nat. Commun.* **2025**, *16*, 877.
- [49] Luo, S. H.; Lou, F. Z.; Yang, P. R.; et al. Dysregulation of oral microbial eicosapentaenoic acid induced by chronic restraint stress exacerbates periodontitis via M1 macrophage polarization. *Adv. Sci. Weinheim Baden Wurttemberg Ger.* **2026**, *13*, e21346.
- [50] Min, B. H.; Devi, S.; Kwon, G. H.; et al. Gut microbiota-derived indole compounds attenuate metabolic dysfunction-associated steatotic liver disease by improving fat metabolism and inflammation. *Gut Microbes* **2024**, *16*, 2307568.
- [51] Zhou, J. F.; Zeng, X. X.; Sun, J.; et al. Gut microbiota-derived indole-3-lactic acid suppresses anti-PD-1 efficacy in esophageal squamous cell carcinoma. *Cell Host Microbe* **2026**, *34*, 639–656.e10.
- [52] Zhang, W.; Chen, S. N.; Huang, X. Q.; et al. Kynurenic acid mitigates poststroke brain damage through the gut-brain neural circuit. *Gut* **2026**, gutjnl–2025–337690.
- [53] Wang, X. L.; Fang, Y.; Liang, W.; et al. Gut-liver translocation of pathogen *Klebsiella pneumoniae* promotes hepatocellular carcinoma in mice. *Nat. Microbiol.* **2025**, *10*, 169–184.
- [54] Veis, D. J.; O'Brien, C. A. Osteoclasts, master sculptors of bone. *Annu. Rev. Pathol.* **2023**, *18*, 257–281.
- [55] Wu, Z. B.; Li, W. M.; Jiang, K. L.; et al. Regulation of bone homeostasis: Signaling pathways and therapeutic targets. *MedComm* **2024**, *5*, e657.
- [56] de Molon, R. S.; Vernal, R.; Oliveira, G. E.; et al. Inflammatory bone loss and signaling pathways in periodontitis: Mechanistic insights and emerging therapeutic strategies. *Bone Res.* **2026**, *14*, 1.
- [57] Mann, E. R.; Lam, Y. K.; Uhlig, H. H. Short-chain fatty acids: Linking diet, the microbiome and immunity. *Nat. Rev. Immunol.* **2024**, *24*, 577–595.
- [58] Tyagi, A. M.; Yu, M. C.; Darby, T. M.; et al. The microbial metabolite butyrate stimulates bone formation via T regulatory cell-mediated regulation of WNT10B expression. *Immunity* **2018**, *49*, 1116–1131.e7.
- [59] He, J.; Chu, Y. N.; Li, J.; et al. Intestinal butyrate-metabolizing species contribute to autoantibody production and bone erosion in rheumatoid arthritis. *Sci. Adv.* **2022**, *8*, eabm1511.
- [60] Dong, J. J.; Shu, G. Z.; Yang, J.; et al. Mechanistic study on the alleviation of postmenopausal osteoporosis by *Lactobacillus acidophilus* through butyrate-mediated inhibition of osteoclast activity. *Sci. Rep.* **2024**, *14*, 7042.
- [61] Yu, T. T.; Bai, R. S.; Wang, Z. M.; et al. Colon-targeted engineered postbiotics nanoparticles alleviate osteoporosis through the gut-bone axis. *Nat. Commun.* **2024**, *15*, 10893.
- [62] Bai, J. W.; Han, G. Y.; Fan, J. X.; et al. Gut microbial metabolite alleviates osteoporosis by attenuating AKT-NFATc1 signaling pathway and ROS production. *Free Radic. Biol. Med.* **2026**, *243*, 351–366.
- [63] Li, Q.; de Oliveira Formiga, R.; Puchois, V.; et al. Microbial metabolite indole-3-propionic acid drives mitochondrial respiration in CD4⁺ T cells to confer protection against intestinal inflammation. *Nat. Metab.* **2025**, *7*, 2510–2530.
- [64] Won, T. H.; Arifuzzaman, M.; Parkhurst, C. N.; et al. Host metabolism balances microbial regulation of bile acid signalling. *Nature* **2025**, *638*, 216–224.
- [65] Yang, Y. H.; Hao, C.; Jiao, T. Y.; et al. Osteoarthritis treatment via the GLP-1-mediated gut-joint axis targets intestinal FXR signaling. *Science* **2025**, *388*, eadt0548.
- [66] Ma, H.; Wu, Y. Q.; Li, D. L.; et al. Gut microbiota drives the metabolic dysregulation in obesity-prone individuals by impairing GDCa-mediated activation of brown adipose thermogenesis and ileal GLP-1 secretion. *Acta Pharm. Sin. B* **2026**, *16*, 836–853.
- [67] Qin, G. Q.; Xu, Z.; Yuan, C.; et al. 4-Hydroxyphenanthrene exacerbates obesity by altering gut microbiota and bile acid metabolism. *Nat. Commun.* **2026**, *17*, 5894.
- [68] Li, C. H.; Fan, Y.; Chen, X. M. Oral microbiota-driven immune modulation along the oral-gut axis: From local signals to systemic inflammation. *NPJ Biofilms Microbiomes* **2026**, *12*, 46.
- [69] Etienne-Mesmin, L.; Meslier, V.; Uriot, O.; et al. *In vitro* modelling of oral microbial invasion in the human colon. *Microbiol. Spectr.* **2023**, *11*, e0434422.
- [70] Zhang, Y. N.; Tu, S. Y.; Shao, X.; et al. Microbiota-derived IPA protects against colitis by regulating intestinal HMGS₂-mediated

- ketogenesis to facilitate mucosal healing. *Nat. Commun.* **2026**, *17*, 2437.
- [71] Alghamdi, M. A.; Redwan, E. M. Interplay of microbiota and citrullination in the immunopathogenesis of rheumatoid arthritis. *Probiotics Antimicrob. Proteins* **2022**, *14*, 99–113.
- [72] Sherina, N.; de Vries, C.; Kharlamova, N.; et al. Antibodies to a citrullinated *Porphyromonas gingivalis* epitope are increased in early rheumatoid arthritis, and can be produced by gingival tissue B cells: Implications for a bacterial origin in RA etiology. *Front. Immunol.* **2022**, *13*, 804822.
- [73] Martinsson, K.; Di Matteo, A.; Öhman, C.; et al. Antibodies to leukotoxin A from the periodontal pathogen *Aggregatibacter actinomycetemcomitans* in patients at an increased risk of rheumatoid arthritis. *Front. Med.* **2023**, *10*, 1176165.
- [74] Svård, A.; LoMartire, R.; Martinsson, K.; et al. Presence and immunoreactivity of *Aggregatibacter actinomycetemcomitans* in rheumatoid arthritis. *Pathog. Basel Switz.* **2024**, *13*, 368.
- [75] Oliveira, S. R.; de Arruda, J. A. A.; Corrêa, J. D.; et al. Methotrexate and non-surgical periodontal treatment change the oral-gut microbiota in rheumatoid arthritis: A prospective cohort study. *Microorganisms* **2023**, *12*, 68.
- [76] Kim, H. Y.; Song, M. K.; Lim, Y.; et al. Effects of extracellular vesicles derived from oral bacteria on osteoclast differentiation and activation. *Sci. Rep.* **2022**, *12*, 14239.
- [77] Smolen, J. S.; Aletaha, D.; Barton, A.; et al. Rheumatoid arthritis. *Nat. Rev. Dis. Primers* **2018**, *4*, 18001.
- [78] Chen, S. L.; Hoang, M. H.; Hu, D. S.; et al. Gut microbiota in early and established stages of rheumatoid arthritis: From pathogenesis to promising prevention and treatment. *Ann. Med.* **2026**, *58*, 2613484.
- [79] Padyukov, L. Genetics of rheumatoid arthritis. *Semin. Immunopathol.* **2022**, *44*, 47–62.
- [80] Srivastava, S.; Rasool, M. Genetics, epigenetics and autoimmunity constitute a Bermuda triangle for the pathogenesis of rheumatoid arthritis. *Life Sci.* **2024**, *357*, 123075.
- [81] Cheng, M. Y.; Zhao, Y.; Cui, Y. Z.; et al. Stage-specific roles of microbial dysbiosis and metabolic disorders in rheumatoid arthritis. *Ann. Rheumatic Dis.* **2022**, *81*, 1669–1677.
- [82] Zheng, Z. S.; Liu, X. Y.; Zhang, Y. A.; et al. Research trends and hotspots on gut microbiota in rheumatoid arthritis: A bibliometric analysis from 2004 to 2024. *Clin. Exp. Rheumatol.* **2026**, *44*, 11–21.
- [83] Coradduzza, D.; Bo, M.; Congiargiu, A.; et al. Decoding the microbiome's influence on rheumatoid arthritis. *Microorganisms* **2023**, *11*, 2170.
- [84] Maeda, Y.; Rabenow, M.; Xiang, W.; et al. Mucosal innate immune activation as the trigger to *Prevotella* species-induced arthritis in genetically resistant mice. *Cell Rep.* **2026**, *45*, 116755.
- [85] Qi, X. Y.; Liu, M. X.; Jiang, X. J.; et al. Gut microbiota in rheumatoid arthritis: Mechanistic insights, clinical biomarkers, and translational perspectives. *Autoimmun. Rev.* **2025**, *24*, 103912.
- [86] Nii, T.; Maeda, Y.; Motooka, D.; et al. Genomic repertoires linked with pathogenic potency of arthritogenic *Prevotella copri* isolated from the gut of patients with rheumatoid arthritis. *Ann. Rheumatic Dis.* **2023**, *82*, 621–629.
- [87] Alpizar-Rodriguez, D.; Lesker, T. R.; Gronow, A.; et al. *Prevotella copri* in individuals at risk for rheumatoid arthritis. *Ann. Rheumatic Dis.* **2019**, *78*, 590–593.
- [88] Scher, J. U.; Sczesnak, A.; Longman, R. S.; et al. Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *eLife* **2013**, *2*, e01202.
- [89] Jiang, L. J.; Shang, M. M.; Yu, S. N.; et al. A high-fiber diet synergizes with *Prevotella copri* and exacerbates rheumatoid arthritis. *Cell. Mol. Immunol.* **2022**, *19*, 1414–1424.
- [90] Maeda, Y.; Kurakawa, T.; Umemoto, E.; et al. Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. *Arthritis Rheumatol. Hoboken N J* **2016**, *68*, 2646–2661.
- [91] Zaragoza-García, O.; Castro-Alarcón, N.; Pérez-Rubio, G.; et al. Serum levels of IFABP2 and differences in *Lactobacillus* and *Porphyromonas gingivalis* abundance on gut microbiota are associated with poor therapeutic response in rheumatoid arthritis: A pilot study. *Int. J. Mol. Sci.* **2023**, *24*, 1958.
- [92] Flak, M. B.; Colas, R. A.; Muñoz-Atienza, E.; et al. Inflammatory arthritis disrupts gut resolution mechanisms, promoting barrier breakdown by *Porphyromonas gingivalis*. *JCI Insight* **2022**, *7*, e165600.
- [93] Maresz, K. J.; Hellvard, A.; Sroka, A.; et al. *Porphyromonas gingivalis* facilitates the development and progression of destructive arthritis through its unique bacterial peptidylarginine deiminase (PAD). *PLoS Pathog.* **2013**, *9*, e1003627.
- [94] Malcolm, J.; Nyirenda, M. H.; Brown, J. L.; et al. C-terminal citrullinated peptide alters antigen-specific APC: T cell interactions leading to breach of immune tolerance. *J. Autoimmun.* **2023**, *135*, 102994.
- [95] Bereta, G. P.; Strzelec, K.; Łazarz-Bartyzel, K.; et al. Identification of a new genetic variant (G231N, E232T, N235D) of peptidylarginine deiminase from *P. Gingivalis* in advanced periodontitis. *Front. Immunol.* **2024**, *15*, 1355357.
- [96] König, M. F.; Abusleme, L.; Reinholdt, J.; et al. *Aggregatibacter actinomycetemcomitans*-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. *Sci. Transl. Med.* **2016**, *8*, 369ra176.
- [97] Gómez-Bañuelos, E.; König, M. F.; Andrade, F. Microbial pathways to subvert host immunity generate citrullinated neoantigens targeted in rheumatoid arthritis. *Curr. Opin. Struct. Biol.* **2022**, *75*, 102423.
- [98] Looh, S. C.; Soo, Z. M. P.; Wong, J. J.; et al. *Aggregatibacter actinomycetemcomitans* as the aetiological cause of rheumatoid arthritis: What are the unsolved puzzles? *Toxins* **2022**, *14*, 50.
- [99] Glyn-Jones, S.; Palmer, A. J. R.; Agricola, R.; et al. Osteoarthritis. *Lancet* **2015**, *386*, 376–387.
- [100] Chen, L. C.; Lin, Y. Y.; Tsai, Y. S.; et al. Live and dead *Clostridium butyricum* GKB7 diminish osteoarthritis pain and progression in preclinical animal model. *Environ. Toxicol.* **2024**, *39*, 4927–4935.
- [101] Chen, W. C.; Chen, L. C.; Tsai, Y. S.; et al. Fermented *Clostridium butyricum* GKB7 inhibits osteoarthritis induced by anterior cruciate ligament transection in a preclinical model. *Int. J. Med. Sci.* **2026**, *23*, 1190–1197.
- [102] Moyseos, M.; Michael, J.; Ferreira, N.; et al. The effect of probiotics on the management of pain and inflammation in osteoarthritis: A systematic review and meta-analysis of clinical studies. *Nutrients* **2024**, *16*, 2243.
- [103] Hu, H. Y.; Dai, X.; Yang, J. Z.; et al. Targeting gut-microbiota-dependent choline metabolite trimethylamine N-oxide ameliorates bone health in ovariectomized mice. *Life Sci.* **2026**, *392*, 124310.
- [104] Shi, H. J.; Huang, L.; Zhang, J. H.; et al. Gut microbiota regulates brain-bone axis to influence osteoporosis pathogenesis and treatment. *Res. Wash. D C* **2026**, *9*, 1178.
- [105] Li, L. L.; Wang, M.; Bao, J.; et al. Periodontitis may impair the homeostasis of systemic bone through regulation of gut microbiota in ApoE^{−/−} mice. *J. Clin. Periodontology* **2022**, *49*, 1304–1319.
- [106] Orwoll, E. S.; Parimi, N.; Wiedrick, J.; et al. Analysis of the associations between the human fecal microbiome and bone density, structure, and strength: The osteoporotic fractures in men (MrOS) cohort. *J. Bone Miner. Res.* **2022**, *37*, 597–607.
- [107] Chen, S.; Zhou, G. W.; Han, H. W.; et al. Causal effects of specific gut microbiota on bone mineral density: A two-sample Mendelian randomization study. *Front. Endocrinol.* **2023**, *14*, 1178831.
- [108] Gaetti-Jardim Júnior, E.; Fardin, A. C.; Gaetti-Jardim, E. C.; et al. Microbiota associated with chronic osteomyelitis of the jaws. *Publ. Braz. Soc. Microbiol.* **2010**, *41*, 1056–1064.
- [109] Goda, A.; Maruyama, F.; Michi, Y.; et al. Analysis of the factors affecting the formation of the microbiome associated with chronic

- osteomyelitis of the jaw. *Clin. Microbiol. Infect.* **2014**, *20*, O309–O317.
- [110] Yahara, H.; Yanamoto, S.; Takahashi, M.; et al. Shotgun metagenomic analysis of saliva microbiome suggests *Mogibacterium* as a factor associated with chronic bacterial osteomyelitis. *PLoS One* **2024**, *19*, e0302569.
- [111] Itoh, N.; Akazawa, N.; Ishibana, Y.; et al. Femoral osteomyelitis caused by oral anaerobic bacteria with mixed bacteremia of *Campylobacter rectus* and *Parvimonas micra* in a chronic periodontitis patient: A case report. *BMC Infect. Dis.* **2022**, *22*, 613.
- [112] Oka, K.; Nakano, Y.; Sazumi, Y.; et al. Clival osteomyelitis with cavernous sinus thrombosis due to *Fusobacterium nucleatum* and *Campylobacter rectus* induced by tooth extraction. *Intern. Med. Tokyo Jpn.* **2018**, *57*, 3325–3328.
- [113] Khan, M. W. Z.; Moez, A.; Farooq, S.; et al. Severe actinomycotic discitis osteomyelitis and bacteremia in an immunocompetent adult following dental cleaning: A case report. *Clin. Case Rep.* **2025**, *13*, e70189.
- [114] Rausch, P.; Hartmann, M.; Baines, J. F.; et al. Analysis of the fecal and oral microbiota in chronic recurrent multifocal osteomyelitis. *Arthritis Res. Ther.* **2022**, *24*, 54.
- [115] Sanjar, F.; Silliman, D. T.; Johnson, I. J.; et al. Identification of temporal shifts of oral bacteria in bone regeneration following mandibular bone defect injury and therapeutic surgery in a porcine model. *Mol. Oral Microbiol.* **2024**, *39*, 381–392.
- [116] Zeng, B.; Maitikuerban, M.; Chen, L. L.; et al. Microbiome dynamics and early microbial signatures predict bone regeneration in marsupialized jaw lesions: A longitudinal 16S sequencing cohort study. *J. Oral Microbiol.* **2026**, *18*, 2684137.
- [117] Luo, X. H.; Wang, Y. Z.; Ning, T. T.; et al. Outer membrane vesicles of *Porphyromonas gingivalis* impede bone regeneration by inducing ferroptosis via the Hippo-YAP signaling pathway. *J. Nanobiotechnol.* **2025**, *23*, 358.
- [118] Okumura, G.; Kondo, N.; Sato, K.; et al. Experimental arthritis and *Porphyromonas gingivalis* administration synergistically decrease bone regeneration in femoral cortical defects. *Sci. Rep.* **2019**, *9*, 20031.
- [119] Dar, H. Y.; Perrien, D. S.; Pal, S.; et al. Callus $\gamma\delta$ T cells and microbe-induced intestinal Th17 cells improve fracture healing in mice. *J. Clin. Investig.* **2023**, *133*, e166577.
- [120] Carbone, E.; Fabrizi, E.; Rivabene, R.; et al. Human oral microbiome in aging: A systematic review. *Mech. Ageing Dev.* **2025**, *226*, 112080.
- [121] Rozas, N. S.; Stephens, N.; Lu, K. Y.; et al. Differences in oral microbiota between elderly and adults: A systematic review. *Arch. Oral Biol.* **2025**, *175*, 106278.
- [122] Xu, F. X.; Guo, Y. Q.; Thomas, S. C.; et al. Succinate modulates oral dysbiosis and inflammation through a succinate receptor 1 dependent mechanism in aged mice. *Int. J. Oral Sci.* **2025**, *17*, 47.
- [123] Song, Y. R.; Chung, J. Aging aggravates periodontal inflammatory responses and alveolar bone resorption by *Porphyromonas gingivalis* infection. *Curr. Issues Mol. Biol.* **2023**, *45*, 6593–6604.
- [124] LaMonte, M. J.; Andrews, C. A.; Hovey, K. M.; et al. Subgingival microbiome is associated with alveolar bone loss measured 5 years later in postmenopausal women. *J. Periodontology* **2021**, *92*, 648–661.
- [125] Yang, J. M.; Xiao, Y. W.; Cui, J. F.; et al. A 4-guanidinobutanoic acid-SLC36A1 axis drives a microbiota–host feedback loop to regulate intestinal homeostasis. *Gut Microbes* **2026**, *18*, 2639216.
- [126] Al-Fakhry, O. M.; Elekhawwy, E. Next-generation probiotics: The upcoming biotherapeutics. *Mol. Biol. Rep.* **2024**, *51*, 505.
- [127] Harini, J. N.; Gayathri, G.; Mahadevan, S.; et al. Effects of probiotic supplements on bone mineral density and bone turnover markers in postmenopausal women: A systematic review. *Clin. Nutr. ESPEN* **2025**, *69*, 503–515.
- [128] Lynch, L. E.; Lahowetz, R.; Maresso, C.; et al. Present and future of microbiome-targeting therapeutics. *J. Clin. Investig.* **2025**, *135*, e184323.
- [129] Lv, J. L.; Hao, P. D.; Zhou, Y.; et al. Role of the intestinal flora-immunity axis in the pathogenesis of rheumatoid arthritis-mechanisms regulating short-chain fatty acids and Th17/Treg homeostasis. *Mol. Biol. Rep.* **2025**, *52*, 617.
- [130] Jiang, Y. S.; Jiang, S. M.; Wang, Z. T.; et al. Precise probiotic therapy: Advances, bottlenecks, and the road to microbiome-informed nutrition. *Gut Microbes* **2026**, *18*, 2623359.
- [131] Guo, D. D.; Mu, W.; Shen, F. L.; et al. *Achyranthes bidentata* polysaccharides alleviates rheumatoid arthritis via the gut microbiota-barrier-metabolite axis *in vitro* and *in vivo*. *Int. J. Biol. Macromol.* **2026**, *340*, 149469.
- [132] Nova, E.; Gómez-Martínez, S.; González-Soltero, R. The influence of dietary factors on the gut microbiota. *Microorganisms* **2022**, *10*, 1368.
- [133] Gleason, B.; Chisari, E.; Parvizi, J. Osteoarthritis can also start in the gut: The gut-joint axis. *Indian J. Orthop.* **2022**, *56*, 1150–1155.
- [134] Wang, R. X.; Tong, A. Y.; Jin, K. Y.; et al. Harnessing the gut-immune-joint axis: Oral microalgae-based thermoresponsive microspheres enhance intra-articular therapy for rheumatoid arthritis. *Bioact. Mater.* **2026**, *61*, 72–91.
- [135] Kim, S.; Seo, S. U.; Kweon, M. N. Gut microbiota-derived metabolites tune host homeostasis fate. *Semin. Immunopathol.* **2024**, *46*, 2.
- [136] Kim, T. Y.; Kim, S.; Kim, Y.; et al. A high-fat diet activates the BAs-FXR axis and triggers cancer-associated fibroblast properties in the colon. *Cell. Mol. Gastroenterol. Hepatol.* **2022**, *13*, 1141–1159.
- [137] Sorrentino, G.; Perino, A.; Yildiz, E.; et al. Bile acids signal via TGR5 to activate intestinal stem cells and epithelial regeneration. *Gastroenterology* **2020**, *159*, 956–968.e8.
- [138] Ling, C. W.; Miao, Z. L.; Xiao, M. L.; et al. The association of gut microbiota with osteoporosis is mediated by amino acid metabolism: Multiomics in a large cohort. *J. Clin. Endocrinol. Metab.* **2021**, *106*, e3852–e3864.
- [139] Palacios-González, B.; Ramírez-Salazar, E. G.; Rivera-Paredes, B.; et al. A multi-omic analysis for low bone mineral density in postmenopausal women suggests a RELATIONSHIP between diet, metabolites, and microbiota. *Microorganisms* **2020**, *8*, 1630.
- [140] Guan, Z. M.; Liu, Y. P.; Zhao, J. Y.; et al. Altered gut microbiota and serum metabolite profiles characterize postmenopausal bone loss: Insights into the gut-bone axis. *Front. Microbiol.* **2026**, *17*, 1750495.
- [141] Rettedal, E. A.; Ilesanmi-Oyelere, B. L.; Roy, N. C.; et al. The gut microbiome is altered in postmenopausal women with osteoporosis and osteopenia. *JBM Plus* **2021**, *5*, e10452.
- [142] Visconti, A.; Le Roy, C. I.; Rosa, F.; et al. Interplay between the human gut microbiome and host metabolism. *Nat. Commun.* **2019**, *10*, 4505.
- [143] Wu, K. C.; McCauley, K. E.; Lynch, S. V.; et al. Alteration in the gut microbiome is associated with changes in bone metabolism after laparoscopic sleeve gastrectomy. *J. Bone Miner. Res.* **2024**, *39*, 95–105.
- [144] Zhou, T.; Heianza, Y.; Chen, Y. H.; et al. Circulating gut microbiota metabolite trimethylamine N-oxide (TMAO) and changes in bone density in response to weight loss diets: The POUNDS lost trial. *Diabetes Care* **2019**, *42*, 1365–1371.
- [145] Li, C.; Huang, Q.; Yang, R.; et al. Gut microbiota composition and bone mineral loss-epidemiologic evidence from individuals in Wuhan, China. *Osteoporos. Int.* **2019**, *30*, 1003–1013.
- [146] Das, M.; Cronin, O.; Keohane, D. M.; et al. Gut microbiota alterations associated with reduced bone mineral density in older adults. *Rheumatol. Oxf. Engl.* **2019**, *58*, 2295–2304.
- [147] Microbiome Therapeutics Innovation Group, Barberio, D. Navigating regulatory and analytical challenges in live

- biotherapeutic product development and manufacturing. *Front. Microbiomes* **2024**, *3*, 1441290.
- [148] Tseng, C. H.; Wong, S.; Yu, J.; et al. Development of live biotherapeutic products: A position statement of Asia-Pacific Microbiota Consortium. *Gut* **2025**, *74*, 706–713.
- [149] Wang, W. H.; Bu, N.; Cao, H. L.; et al. Shaping the future of probiotics, live biotherapeutic products, and fecal microbiota transplantation: 30 scientific recommendations from the CHINAGUT Conference. *iMeta* **2025**, *4*, e70083.
- [150] Sada, R. M.; Matsuo, H.; Motooka, D.; et al. *Clostridium butyricum* bacteremia associated with probiotic use, Japan. *Emerg. Infect. Dis.* **2024**, *30*, 665–671.
- [151] Yadegar, A.; Bar-Yoseph, H.; Monaghan, T. M.; et al. Fecal microbiota transplantation: Current challenges and future landscapes. *Clin. Microbiol. Rev.* **2024**, *37*, e0006022.
- [152] Williams, L. M.; Cao, S. J. Harnessing and delivering microbial metabolites as therapeutics via advanced pharmaceutical approaches. *Pharmacol. Ther.* **2024**, *256*, 108605.
- [153] Li, Z. R.; Wang, Q.; Huang, X. F.; et al. Microbiome's role in musculoskeletal health through the gut-bone axis insights. *Gut Microbes* **2024**, *16*, 2410478.
- [154] Hong, Y. C.; Yang, M. H.; Xu, X.; et al. Gut microbiota, inflammatory proteins and bone mineral density in different age groups: A Mendelian randomization study. *Medicine* **2025**, *104*, e41875.
- [155] Zhu, W. D.; Ma, S. W.; Zheng, X. W.; et al. The role of gut microbiota and plasma metabolites in osteoporosis: Insights from Mendelian randomization analysis. *Medicine* **2025**, *104*, e44409.
- [156] Chetty, A.; Blekhman, R. Multi-omic approaches for host-microbiome data integration. *Gut Microbes* **2024**, *16*, 2297860.
- [157] Wang, Q.; Wang, K. C.; Wu, W. R.; et al. Host and microbiome multi-omics integration: Applications and methodologies. *Biophys. Rev.* **2019**, *11*, 55–65.
- [158] Kellermayer, R. Challenges for epigenetic research in inflammatory bowel diseases. *Epigenomics* **2017**, *9*, 527–538.
- [159] Integrative HMP iHMP Research Network Consortium. The Integrative Human Microbiome Project: Dynamic analysis of microbiome-host omics profiles during periods of human health and disease. *Cell Host Microbe* **2014**, *16*, 276–289.
- [160] Zhao, X.; Wu, B.; Han, P. L.; et al. Gut microbiota-metabolome remodeling associated with low bone mass: An integrated multi-omics study in fracture patients. *Front. Mol. Biosci.* **2025**, *12*, 1646361.
- [161] Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature* **2012**, *486*, 207–214.
- [162] Meawad, M.; Singh, D.; Deng, A.; et al. Functional archetypes in the human gut microbiome reveal metabolic diversity, stability, and influence disease-associated signatures. *Microbiome* **2025**, *13*, 241.
- [163] Lozupone, C. A.; Stombaugh, J. I.; Gordon, J. I.; et al. Diversity, stability and resilience of the human gut microbiota. *Nature* **2012**, *489*, 220–230.
- [164] Tigchelaar, E. F.; Bonder, M. J.; Jankipersadsing, S. A.; et al. Gut microbiota composition associated with stool consistency. *Gut* **2016**, *65*, 540–542.
- [165] Qin, Y. W.; Havulinna, A. S.; Liu, Y.; et al. Combined effects of host genetics and diet on human gut microbiota and incident disease in a single population cohort. *Nat. Genet.* **2022**, *54*, 134–142.
- [166] Qi, Q. J.; Gao, C. N.; Meng, X.; et al. Oral microbiota dynamics across the lifespan: Age, sex, race and socioeconomic influences in the US population. *J. Clin. Periodontology* **2025**, *52*, 1560–1572.
- [167] Kverka, M.; Stepan, J. J. Associations among estrogens, the gut microbiome and osteoporosis. *Curr. Osteoporos. Rep.* **2024**, *23*, 2.
- [168] Kriaa, A.; Mariaule, V.; De Rudder, C.; et al. From animal models to gut-on-chip: The challenging journey to capture inter-individual variability in chronic digestive disorders. *Gut Microbes* **2024**, *16*, 2333434.
- [169] Al-Qadami, G.; Raposo, A.; Chien, C. C.; et al. Intestinal organoid coculture systems: Current approaches, challenges, and future directions. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2025**, *328*, G252–G276.
- [170] Fofanova, T. Y.; Karandikar, U. C.; Auchtung, J. M.; et al. A novel system to culture human intestinal organoids under physiological oxygen content to study microbial-host interaction. *PLoS One* **2024**, *19*, e0300666.
- [171] Ballerini, M.; Galiè, S.; Tyagi, P.; et al. A gut-on-a-chip incorporating human faecal samples and peristalsis predicts responses to immune checkpoint inhibitors for melanoma. *Nat. Biomed. Eng.* **2025**, *9*, 967–984.
- [172] Longo, U. G.; Lalli, A.; Bandini, B.; et al. Role of the gut microbiota in osteoarthritis, rheumatoid arthritis, and spondylarthritis: An update on the gut-joint axis. *Int. J. Mol. Sci.* **2024**, *25*, 3242.



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