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Review

Oral microbiota dysbiosis; mechanisms driving systemic bone loss and osteoporosis risk

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Abstract

Oral microbiota dysbiosis, particularly in periodontitis, represents a significant yet under-recognized contributor to systemic bone loss and heightened osteoporosis risk. Disruption of the symbiotic oral microbial community permits pathobiont expansion, notably Porphyromonas gingivalis triggering chronic gingival inflammation. This local inflammatory milieu drives alveolar bone resorption through receptor activator of nuclear factor kappa-B ligand (RANKL)-mediated osteoclastogenesis and matrix metalloproteinase activation. Notably, these pathological processes extend beyond the oral cavity by three interconnected mechanisms of hematogenous dissemination of periodontal pathogens and their virulence factors, which directly stimulate osteoclast differentiation in distant skeletal sites and by systemic spillover of pro-inflammatory cytokines, amplifying bone-resorptive signaling throughout the skeleton, across with dysregulation of the gut-bone axis, as oral pathobionts translocate to the gastrointestinal tract, altering gut permeability and microbiome composition to further exacerbate inflammatory bone loss. Epidemiological studies consistently associate periodontitis with reduced bone mineral density and increased fracture incidence, independent of traditional osteoporosis risk factors. Animal models confirm that oral pathogen challenge accelerates trabecular bone loss in long bones and vertebrae. These findings position oral dysbiosis as a modifiable risk factor for osteoporosis, suggesting that periodontal therapy and microbiome-targeted interventions may offer adjunctive strategies for skeletal health preservation. Future research should prioritize longitudinal human studies to establish causality and evaluate whether periodontal treatment attenuates systemic bone loss trajectories in at-risk populations.

Keywords: Bone mineral density, Oral microbiota dysbiosis, Osteoporosis, Vitamin D receptors, Parathyroid hormone, Vitamin D

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Introduction

The oral cavity hosts over 700 bacterial species, alongside fungi, viruses, and archaea, forming biofilms on teeth, gums, and mucosa (1). Oral microbiota dysbiosis is increasingly recognized as a driver of localized periodontal destruction and a potent instigator of systemic inflammation capable of accelerating bone resorption throughout the body. This phenomenon positions oral health as a critical, yet often overlooked, determinant of osteoporosis risk, a condition afflicting over 200 million people globally and contributing to nearly nine million fractures annually (2, 3). Understanding the mechanisms by which a diseased oral microbiome propagates bone loss transcends dental medicine; it represents a paradigm shift in how we conceptualize skeletal homeostasis, revealing the mouth as a portal through which chronic inflammation penetrates to the entire skeletal system (4). In health, *Streptococcus* and *Actinomyces* dominate, maintaining equilibrium by microbial competition and host immune tolerance. Dysbiosis elevates pathogens like *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Filifactor alocis*, reducing diversity and favoring anaerobes. This shift correlates with periodontal pocket formation, gingival bleeding, and alveolar bone resorption locally (5); however, swallowed saliva seeds the gut, inducing entero-oral dysbiosis axis that amplify systemic effects (6). This study sought to review the oral microbiota dysbiosis and the mechanisms driving systemic bone loss and osteoporosis risk.

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords such as 'bone mineral density', 'oral microbiota dysbiosis', 'osteoporosis', 'vitamin D receptors', 'vitamin D' and 'parathyroid hormone'.

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Implication for health policy/practice/research/medical education

Oral microbiota dysbiosis refers to an imbalance in the complex microbial communities inhabiting the oral cavity, shifting from a symbiotic state dominated by commensal species to one enriched with pathobionts that provoke chronic inflammation and tissue destruction. This dysbiosis, often triggered by poor oral hygiene, smoking, diabetes, or hormonal changes, disrupts local homeostasis in the periodontium and extends its influence systemically, contributing to bone pathologies beyond the jaws, including osteoporosis as a condition characterized by reduced bone mineral density and increased fracture risk. Recent studies from metagenomic studies and animal models links oral dysbiosis, particularly in periodontitis, to systemic bone loss through microbial translocation, inflammatory cascades, and modulation of bone remodeling pathways.

Bone effects of periodontitis

Periodontitis, is a chronic inflammatory disease driven by dysbiotic biofilms, which affects many people around the world. Its hallmark is the destruction of the periodontal ligament and alveolar bone. This localized bone loss is mediated by a complex interplay where pathogenic bacteria like *P. gingivalis*, *T. forsythia*, and *T. denticola* evade host defenses, subvert immune responses, and stimulate the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) from gingival tissues (7). Importantly, these inflammatory mediators do not remain confined to the oral cavity. They enter the systemic circulation, creating a state of low-grade, chronic inflammation that permeates distant sites, including skeletal tissue. Numerous studies demonstrated that serum levels of IL-6 and TNF-α elevated in periodontitis patients that directly stimulate osteoclastogenesis, across with suppressing of osteoblast activity (7). In addition, the RANKL (receptor activator of nuclear factor kappa-B ligand)/RANK/OPG pathway, as the master regulator of bone remodeling becomes dysregulated under this inflammatory assault. Meanwhile, RANKL, expressed by osteoblasts and immune cells, binds to RANK on osteoclast precursors, triggering their differentiation and activation (8). It should remember that, osteoprotegerin (OPG), a decoy receptor produced by osteoblasts, normally inhibits this process. In periodontitis, the inflammatory milieu upregulates RANKL expression while down-regulating OPG, tipping the balance decisively toward bone resorption (9). Accordingly, circulating inflammatory cytokines originating from the dysbiotic oral environment can induce RANKL expression on bone marrow stromal cells and osteoblasts throughout the skeleton, effectively turning the entire body into a site of heightened bone turnover favoring loss (10). Beyond the systemic inflammatory cascade, oral pathogens themselves possess insidious capabilities to directly influence bone metabolism at distant sites. *Porphyromonas gingivalis*, a keystone pathogen in periodontal dysbiosis, exemplifies this threat. It produces potent virulence factors, notably gingipains and lipopolysaccharide (LPS), which exhibit remarkable systemic reach (11). Animal models provide compelling evidence that, intravenous injection of *P. gingivalis* in mice triggers significant trabecular bone loss in the femur and tibia, independent of direct infection at those sites. This condition occurs through multiple direct mechanisms (12). First, *P. gingivalis* LPS binds to Toll-like receptors (TLR2 and TLR4) on osteoblasts and osteoclast precursors. Additionally, TLR4 activation on osteoclast precursors directly enhances their responsiveness to RANKL, accelerating differentiation (13). Simultaneously, LPS signaling in osteoblasts suppresses their bone-forming activity and increases their production of RANKL and inflammatory cytokines, creating a vicious cycle (10). Second, gingipains can cleave and inactivate OPG in the circulation, removing a crucial brake on osteoclast activity systemically (14). Third, *P. gingivalis* can invade endothelial cells and even survive within macrophages, using these cells as Trojan horses to disseminate throughout the body. Once systemically disseminated, the bacteria or their persistent antigens can lodge in bone marrow, directly interacting with bone cells and resident immune populations (15). Previous studies have detected *P. gingivalis* DNA in the bone marrow of periodontitis patients with systemic inflammation, suggesting a direct microbial contribution to the bone microenvironment (4). Other periodontal pathogens, like *F. nucleatum*, exhibit similar invasive properties and can induce inflammatory bone loss in distant sites. This direct microbial invasion and persistence represent a profound mechanism by which oral dysbiosis transcends local disease to become a systemic instigator of skeletal degradation (16).

Focus on oral-bone axis

The endocrine dimension of the oral-bone axis further complicates the picture, particularly concerning sex hormones and vitamin D. Estrogen deficiency, a primary driver of postmenopausal osteoporosis, exhibits a bidirectional relationship with periodontal health (17). Estrogen possesses anti-inflammatory properties and helps maintain gingival barrier integrity. Its decline during menopause exacerbates the host response to oral pathogens, accelerating periodontal bone loss (18). Conversely, the systemic inflammation generated by periodontitis can further suppress estrogen signaling pathways and increase the metabolism of sex hormones, creating a synergistic negative feedback loop that amplifies bone loss both locally and systemically (18). Vitamin D, essential for calcium absorption and bone mineralization, also intersects critically with oral dysbiosis. Vitamin D receptors (VDRs) are expressed on immune cells and bone cells, and vitamin D modulates the immune response to infection. Vitamin D deficiency, which is highly prevalent

globally, is associated with increased susceptibility to periodontitis and more severe disease progression (19). Dysbiotic oral bacteria can exploit this: some pathogens possess enzymes that degrade vitamin D metabolites, while the chronic inflammation itself can down-regulate VDR expression in immune cells, thereby impairing the resolution of inflammation and antimicrobial defense (7). This condition creates a scenario where vitamin D deficiency promotes oral dysbiosis and inflammation, which in turn further depletes functional vitamin D activity, eventually compromising calcium homeostasis and bone mineralization throughout the skeleton (20). The dysregulation of other hormones like cortisol and parathyroid hormone adds further layers to this endocrine crosstalk, positioning the oral microbiome as a modulator of systemic hormonal balance impacting bone (21, 22).

Role of inflammaging

The concept of inflammaging, known as the chronic, sterile, low-grade inflammation characteristic of aging is profoundly relevant to understanding the oral-bone connection in osteoporosis. Aging is associated with a natural decline in immune function and an increase in baseline pro-inflammatory cytokines. In fact, oral dysbiosis acts as a powerful accelerator of this process (23); whereas, the persistent antigenic load from a dysbiotic oral biofilm chronically stimulates the innate immune system, particularly macrophages and neutrophils. Over time, this situation leads to immune cell exhaustion and a shift toward a pro-inflammatory phenotype (24). Senescent cells, which accumulate with age and secrete inflammatory factors like the senescence-associated secretory phenotype (SASP) are also increased in periodontal tissues of individuals with dysbiosis (25). Likewise, the systemic inflammatory mediators originating from the oral cavity, such as IL-6, TNF-α and C-reactive protein contribute directly to the inflammaging milieu (26). Given that, this chronic inflammation has detrimental effects on bone; it also promotes osteoclast survival and activity by RANKL-independent pathways, which induces oxidative stress along with damage to the osteoblasts and osteocytes, which impairs the bone's ability to repair micro-damage (27). Then, osteocytes, as key regulators of bone remodeling, become dysregulated under chronic inflammation, increasing their expression of RANKL and sclerostin (28). Therefore, the synergy between age-related inflammaging and inflammation driven by oral dysbiosis creates a perfect storm for accelerated skeletal deterioration, particularly in the elderly, where both osteoporosis and severe periodontitis are highly prevalent. This state explains epidemiological observations linking poor oral health to increased fracture risk in older adults, independent of traditional osteoporosis risk factors (29). Preliminary studies have consistently shown that individuals with severe periodontitis have significantly lower bone mineral density at the hip and spine compared to periodontally healthy individuals, even after adjusting for age, smoking, diabetes, and body mass index (30). Previous studies on the impact of non-surgical periodontal therapy on systemic markers showed significant reductions in circulating IL-6, TNF-α, and CRP levels following successful treatment (31-33). A recent meta-analysis concluded that periodontal treatment resulted in a statistically significant increase in bone mineral density compared to control groups, with the strongest effects observed in the hip region (34). In addition, animal models provide definitive causal evidence; whereas germ-free mice colonized with dysbiotic human periodontal microbiota develop significantly greater systemic inflammation and trabecular bone loss in long bones compared to mice colonized with a healthy microbiota (4). Animal models also demonstrate that antibiotics targeting periodontal pathogens or immunomodulatory therapies can mitigate this bone loss (35).

Relationship of gut microbiome with oral cavity

The gut microbiome, often considered the central player in the microbiome-bone axis, is not isolated from the oral cavity. Oral dysbiosis can directly seed and alter the gut microbiota, a process known as oralization of the gut. Swallowing introduces billions of oral bacteria daily into the gastrointestinal tract (36). In health, stomach acid and gut defenses limit this; nevertheless, in conditions like acid suppression therapy, inflammatory bowel disease, or simply with aging and dysbiosis in the gut itself, oral pathobionts can colonize the gut (37). At this condition, *P. gingivalis*, *F. nucleatum*, and *Klebsiella* species from the oral cavity have been found to translocate and persist in the gut microbiome of individuals with periodontitis (38). Though, the oral-gut axis has profound implications for bone health, gut dysbiosis independently drives systemic inflammation and affects bone by metabolite production like short-chain fatty acids like butyrate, which generally promote bone formation but can be depleted in dysbiosis, modulation of the gut barrier, and immune cell education (39). The translocation of oral pathogens exacerbates gut dysbiosis and barrier dysfunction, amplifying systemic LPS levels and inflammatory cytokine production (40). Butyrate-producing bacteria, crucial for maintaining gut barrier integrity and regulating T-regulatory cells are often depleted in both oral and gut dysbiosis (40-42). Reduced butyrate levels diminish its anti-inflammatory effects and its direct positive effects on osteoblast differentiation and inhibition of osteoclast formation (40-43). Accordingly, oral dysbiosis does not act in isolation; whilst it perturbs the gut ecosystem, creating a synergistic inflammatory burden that further undermines skeletal homeostasis through multiple interconnected pathways. The clinical implications of this oral-systemic bone axis are profound and necessitate a paradigm

shift in healthcare (4). Osteoporosis management has traditionally focused on calcium/vitamin D supplementation, anti-resorptive drugs, and anabolics, alongside lifestyle modifications. The recognition of oral dysbiosis as a significant contributor demands the integration of comprehensive oral health assessment and periodontal management into osteoporosis prevention and treatment protocols (44). Hence, routine screening for periodontitis in individuals identified as high-risk for osteoporosis like postmenopausal women and those with low bone mineral density. Treatment consists of effective periodontal therapy, rigorous plaque control, professional debridement, and potentially adjunctive antimicrobials or host modulation therapy, which are not only a dental care but also regarded as a systemic anti-inflammatory and bone-protective intervention (45). Forthcoming therapeutic strategies hold exciting promise, since targeted probiotics or prebiotics designed to restore a healthy oral microbiome and suppress pathobionts (46); vaccines against key periodontal pathogens like *P. gingivalis*; or small-molecule inhibitors blocking specific virulence factors or disruptive inflammatory pathways (47). Other approaches based on an individual's oral microbiome profile, inflammatory status, and genetic susceptibility could optimize prevention and treatment strategies for both periodontitis and osteoporosis (48).

Role of systemic inflammation

Oral pathobionts induce Th17 cells releasing IL-17, which boosts IL-6, TNF-α, and RANKL from osteoblasts and T cells. IL-6 activates JAK/STAT3, sustaining inflammation and suppressing osteoblastogenesis by inhibiting Runx2 and Osterix (49). In postmenopausal models, estrogen deficiency exacerbates this condition; while oral dysbiosis correlates with lower BMD, as Aggregatibacter enrichment links to glycan metabolism and cGMP-PKG pathways disrupting calcium homeostasis (50). NLRP3 inflammasome activation by P. gingivalis or T. denticola Td92 protein generates IL-1β, pyroptosis, and further osteoclast priming (51). At this condition, microbial metabolites contribute profoundly, since short-chain fatty acids (SCFAs) from oral-gut translocation, like butyrate from *Fusobacterium*, modulate immunity but in excess promote Th17 differentiation (52). Besides, *P. gingivalis* gingipains cleave OPG, unmasking RANKL and directly fostering osteoclasts (53). In mouse models, P. gingivalis gavage induces gut dysbiosis, elevates serum LPS, and accelerates trabecular bone loss in femurs and vertebrae, mimicking osteoporosis (54). In addition, periodontitis strengthens osteoporosis risk (55). In fact, osteoimmunology bridges oral dysbiosis to bone (56). Indeed, B cells amplify by APRIL/BAFF, sustaining plasma cells producing osteoclastogenic IgG (53). In germ-free mice, periodontitis fails to induce bone loss, but SPF recolonization restores it, underscoring microbiota necessity (39). Furthermore, Wnt and Notch pathways integrate microbial signals (57). In peri-implantitis models, similar dysbiosis drives remote bone loss via microbial seeding (58,59).

Conclusion

Oral microbiota dysbiosis represents a significant, modifiable risk factor for systemic bone loss and osteoporosis through interconnected inflammatory and microbial pathways. Periodontal pathogens, particularly Porphyromonas gingivalis drive alveolar destruction locally while simultaneously promoting systemic bone resorption by hematogenous dissemination and chronic low-grade inflammation. These microbes stimulate gingival fibroblasts and immune cells to upregulate RANKL expression, disrupting the RANKL/RANK/OPG balance and triggering excessive osteoclastogenesis. Concurrently, pathogens like *P. gingivalis* invade osteoblasts, inhibiting their differentiation and mineralization capacity, thereby uncoupling bone remodeling in favor of net resorption. Systemic inflammation amplifies this process. Elevated TNF-α, IL-1β and IL-6, not only enhance osteoclast activity but also suppress osteoblast function, thereby creating a pro-resorptive milieu throughout the skeleton. Emerging evidence further implicates the oral-gut-bone axis, where oral dysbiosis alters gut microbiota composition, compromises intestinal barrier integrity, and facilitates bacterial translocation exacerbating systemic inflammation and trained immunity that perpetuates bone loss. Critically, severe periodontitis increases osteoporosis risk by up to 6-fold, underscoring the clinical relevance of this relationship. Conversely, osteoporosis may predispose individuals to accelerated alveolar bone loss, suggesting bidirectional crosstalk between systemic and oral skeletal compartments. Future therapeutic strategies should therefore target oral microbial homeostasis through periodontal intervention, probiotics, or anti-inflammatory approaches to mitigate systemic bone deterioration. Integrating oral health assessments into osteoporosis screening protocols could enable earlier identification of at-risk individuals and facilitate holistic management of skeletal integrity across the lifespan.

Authors' contribution

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Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

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Ethical issues (including plagiarism, data fabrication, double

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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