




Review

Overview on Osteoporosis, Periodontitis and Oral Dysbiosis: The Emerging Role of Oral Microbiota

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Abstract: Osteoporosis (OP) is a bone disease consisting of a progressive loss of bone mineral density (BMD) and therefore resulting in greater susceptibility to fractures. OP shares a number of risk factors and demographic characteristics with periodontitis (PD), a bacteria-induced chronic inflammation of periodontal structures that leads to loss of alveolar bone and teeth. In the last decade, with the advent of gut and oral microbiome studies and profiling, a growing diagnostic and prognostic significance has been attributed to dysbiosis associated with various systemic and organ-specific pathologies. This evidence has inspired research on modulating the microbiota to restore health by the use of prebiotics and probiotics. The aim of this work is to overview the bidirectional interrelationships between OP and PD, reporting the most recent evidence on triggering factors and, mainly, the role of gut and oral dysbiosis in the onset and progression of both OP and PD, with the perspective in their therapy.

Keywords: osteoporosis; periodontitis; oral health; bone and bones/metabolism; microbiome; microbiota; prebiotics; probiotics; mouth diseases; osteology

1. Introduction

Numerous systemic conditions and diseases can be associated with or influenced by oral health. From syndromic disorders with oral manifestations [1–4] to systemic diseases with oral involvement [5–7] or oral diseases with extra-oral effects and correlations [8–12], oral health is a condition often related to general well-being.

The present work aimed to overview the bidirectional interrelationships between osteoporosis and oral health, focusing on the new findings from the study of the oral microbiome and on the emerging involvement of oral dysbiosis in the onset of this systemic bone disease.

2. Osteoporosis

Osteoporosis (OP) is a common systemic bone disease, in which a generalized and progressive loss of bone mineral density (BMD) increases bone fragility and susceptibility to fracture, which can occur during daily activities or minor trauma [13,14].

OP is more prevalent among older women (postmenopausal OP), in whom decreased estrogen [15,16] associated with oxidative stress [16,17] is responsible for the loss of BMD [18]; however, it is also reported in men [19] over the age of 65, in association with the use of oral glucocorticoids, androgen deprivation therapy for prostate cancer and various systemic diseases (chronic liver diseases, history of stroke, smoking and alcohol consumption, hyperparathyroidism and/or hyperthyroidism) [20].

OP may be preceded by osteopenia, which is a less severe condition of BMD loss than OP and is associated with a lower risk of bone fractures than in subjects with OP [21].

According to Sozen et al. [22], worldwide, one in three women and one in five men over the age of 50 will suffer an osteoporotic fracture in their lifetime [23], and the most recent reports from the U.S. National Osteoporosis Foundation [24] have confirmed a prevalence 10.2 million Americans over the age of 50 with osteoporosis, and 43.4 million elderly people with low BMD; in Europe, the International Osteoporosis Foundation [25] estimated 22 million women and 5.5 million men with osteoporosis and 3.5 million people with new fragility fractures, while the prevalence of OP in Asian countries ranges from 35.2% to 25.1% of elderly women and is considered superior to that of Caucasian women (10.8%) [26].

3. Periodontitis

OP can affect any bone in the body, and, therefore, also the jaws, resulting in cortical thinning increasing with age [27].

Bone thinning and decreased BMD of the jaws are not the only associations between OP and oral health, but several interrelationships between OP and oral diseases have been reported, mainly with regard to OP and periodontal disease and OP and oral dysbiosis.

Among the periodontal diseases, periodontitis (PD) is a bacterially triggered chronic inflammatory condition responsible for the progressive and irreversible destruction and loss of the connective periodontal attachment and alveolar bone resorption, resulting in tooth loss in adults over the age of 50 [28,29]. The etiology of PD is supported by genetic and environmental factors [30,31] and the bacteria responsible for starting the host's inflammatory overreaction have historically been identified as Gram-negative/facultative anaerobic bacteria (mainly *Treponema denticola* and *Porphyromonas gingivalis*) that colonize the gingival pocket of predisposed subjects [32]. At this site, the release of a series of proinflammatory cytokines enhances local inflammation which is perpetuated and leads to the progressive destruction of periodontal structures, as the periodontal connective ligaments and the alveolar bones [15,33].

4. Osteoporosis and Periodontitis

PD shares many risk factors with OP, such as age, smoking and/or alcohol consumption, body mass index (BMI) and menopause [34,35]. Osteoporotic women, in fact, show a greater severity of PD than women without OP, and the two pathologies together considerably affect the quality of life of the subjects [36].

Recently, Xu et al. [37] analyzed the associations between OP and risk of PD using a meta-analysis to establish whether OP is a local indicator of bone loss, or is dependent on or related to the causes of PD: it was found that OP is closely related to the increased risk of developing PD. Furthermore, women with OP present a high risk of developing PD than men and, regardless of gender, patients with OP have a two-fold higher risk of PD [38]. However, the underlying mechanisms still remain undefined [37].

Many hypotheses have arisen to explain how OP can accelerate alveolar bone resorption in PD: (1) the loss of BMD at the level of the alveolar bones could allow for deeper bacterial penetration into the enlarged periodontal space and, in a vicious circle, local inflammation could amplify and accelerate alveolar resorption [27,39]; (2) the overexpression of proinflammatory cytokines with osteoclastic activity is common to both OP and PD [40–42]; (3) some risk factors such as smoking, diabetes, and hormone levels are responsible for both OP and PD [39] (Figure 1).

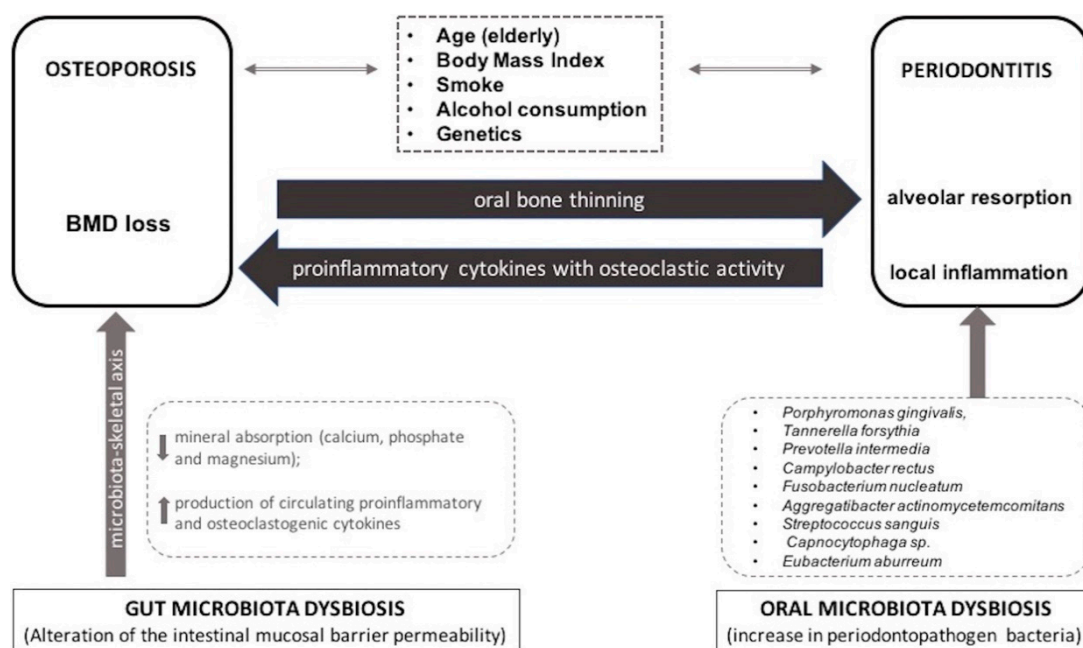


Figure 1. The bidirectional interrelationships between osteoporosis (OP) and periodontitis (PD). They share a series of common risk factors. The bone mineral density (BMD) loss associated with OP may be responsible for increasing the alveolar bone resorption in PD, and, conversely, the local inflammation peculiar of PD may activate systemic osteoclastic cytokines responsible for further BMD decrease. In this scenario, the role of gut and oral dysbiosis may enhance and/or trigger these events, leading towards a worsening of both pathologies and the healthy state of the affected subjects. BMD, Bone Mineral Density.

5. Periodontitis and Osteoporosis

Conversely, other studies have considered that PD and its periodontopathogen bacteria can directly and indirectly promote the onset of OP, which is the chronic inflammatory state responsible for activation of osteoclast not only at the level of oral sites [39], but also elsewhere, as demonstrated in various systemic diseases and conditions triggered and/or aggravated by the presence of PD, such as rheumatoid arthritis [43], cardiovascular diseases [11,44,45], and neurodegenerative diseases such as Parkinson's [46] and Alzheimer's disease [47,48].

6. Microbiome, Dysbiosis and Osteoporosis

In recent years, a few more pieces to the puzzle of the association between OP and oral health have been added from studies on the microbiome and its relationship to bone metabolism: after the completion of the mapping of the human genome to sequence and identification of all human genes [49], research has begun to focus on mapping the human microbiome and the related microbiota [50]. By definition, the human microbiota is the collection of all the microorganisms, including eukaryotes, archaea, bacteria and viruses, living in association with the human body in specific ecological niches, while the term "microbiome" refers to all of their genetic material [51–53].

The richest and most studied human niche is the gut environment, which accounts for 95% of all microorganisms present on and in the human body, but other environments have also been identified, such as nose, eyes, stomach, genitalia, skin and mouth [54].

The findings of differences in oral bacterial composition in unhealthy states, also known as oral dysbiosis, have increasingly opened up new scenarios in the study of the mechanisms underlying OP.

The first research on the human oral microbiome was published in 2010 [55], and, among the over 600 species identified with cultural and non-cultural techniques, 169 seem to be indigenous of the oral cavity (the so-called "core oral microbiome"), arranged, in physiological conditions, in quantity and

quality in three different ecological niches/intraoral habitats, classified as: Group 1, buccal mucosa, keratinized gingiva, and hard palate; Group 2, saliva, tongue, tonsils, and throat (back wall of oropharynx); and Group 3, sub- and supra-gingival plaque [56,57].

6.1. Gut Microbiome/Microbiota and OP

Recently, Xu et al. [13] identified and characterized a specific change in gut microbiota of OP patients, consisting of an increase of the total amount of intestinal bacteria, with a prevalence of Bacteroidetes over Firmicutes in the OP group, thus reporting a characteristic fingerprint of gut bacteria composition associated with OP (*Bacteroidetes*, *Prevotellaceae* family, *Ruminococcaceae* family, *Faecalibacterium* genus, and *Dialister* genus). Additionally, Das et al. found a greater abundance of *Actinomyces*, *Eggerthella* and *Clostridium Cluster XIVa* in OP subjects compared to a control group [23].

The evidence of pathways through the gut microbiota can influence bone metabolism and its homeostasis lead to the hypothesis of a “microbiota-skeletal” axis [58,59] (Figure 1). According to a series of studies, the gut microbiota is capable of:

1. influencing the absorption of mineral (calcium, phosphate and magnesium) [60];
2. interfering with the immune system (through the production of proinflammatory and osteoclastogenic circulating cytokines that can guide bone resorption in inflammatory conditions [23,60];
3. regulating the synthesis of serotonin and other neurotransmitters involved in bone metabolism [58,59].

Furthermore, in a state of dysbiosis, the intestinal mucosal barrier is more permeable and the abundance of the bacterial endotoxin lipopolysaccharide (LPS) easily increases in serum as well, favoring endotoxemia and osteoclastic activity, thus negatively affecting BMD [58,59].

6.2. Oral Microbiome/Microbiota and OP

One of the first investigations about the correlation between oral bacteria and OP was provided by Liang et al., who, in 2013, reported statistically significant reductions in the oral bacterial lining of the tongue of OP women compared to non-OP women [61].

Five years later, in 2018, Banack et al. [62] published the results of a 15-year prospective cohort study, called “OsteoPerio Study”, to explore the risk factors for the development and progression of OP and PD in postmenopausal women and highlight the relationship between oral microbiota and oral and systemic health in postmenopausal women. The OsteoPerio Study results confirmed that: (1) OP women had almost double the risk of oral BMD loss compared to non-OP women; (2) systemic and oral BMD loss was greater in older women; (3) severity of PD was inversely associated with BMD. Furthermore, the same authors found, in PD subjects, a strong positive association between specific oral periodontopathogen bacteria (*Porphyromonas gingivalis*, *Tannerella forsythia*, *Prevotella intermedia* and *Campylobacter rectus*) and severe oral bone loss. Similarly, Brennan et al. [63] tested the association between the presence of oral bacterial infection and oral bone loss in 1256 postmenopausal women, thus reporting eight subgingival bacterial species were mainly associated with severe oral bone loss: *Streptococcus sanguis*, *Prevotella intermedia*, *Tannerella forsythensis*, *Capnocytophaga* sp., *Eubacterium saburreum*, *Campylobacter rectus*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. On the contrary, Hernández-Vigueras et al. [27], who also conducted an observational cross-sectional study to profile the oral microbiota of postmenopausal women with and without OP, found that nearly 79% of the women with PD also suffered OP, but no statistically significant differences were found in the quantity and quality of periodontopathogen bacteria investigated (*Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Campylobacter rectus*, and *Tannerella forsythia*) (Figure 1).

7. Discussion

In recent years, the importance of oral health for general well-being has been increasingly confirmed by scientific evidence, elucidating how oral infections and dysbiosis contribute to the triggering or worsening of various types of systemic diseases.

In light of these findings, it has been shown that periodontal pathogenic bacteria as well as intestinal dysbiosis are also involved in the determinism of BMD loss, actively contributing to the onset and worsening of OP (Figure 1).

This evidence has inspired research on the modulation of the microbiota to restore health by the use of prebiotics and probiotics. In particular, it has been shown that a number of host-indigestible food compounds (prebiotics such as galactooligosaccharide, inulin, and resistant starch) are involved in digestive processes by providing nourishment for healthy gut bacteria and thus promoting mineral absorption by enterocytes [59,64]. Moreover, among the living microorganisms that have a positive effect on bone health by acting at the digestive level and known as “probiotics”, *Lactobacillus* sp. (mainly *L. reuteri*, *L. casei*, *L. rhamnosus* and *L. salivarius*) and *Bifidobacteria*, seem to significantly decrease osteoclastogenesis and stop bone resorption [59,65].

Promising results on the use of prebiotics and probiotics have also recently emerged for the restoration of oral dysbiosis [66,67] and as adjunctive therapeutic agents to periodontal treatments [68]. Prebiotics promote the nourishment of beneficial bacteria, thus promoting the restoration of a balanced and healthy oral microbiota [69,70]. For example, Rosier et al. [71] reported the effect of nitrate as prebiotic in modulating the composition of the oral microbiome by significantly reducing periodontopathogen bacteria such as *Porphyromonas*, *Fusobacterium*, *Leptotrichia* and *Prevotella*. Other studies have also reported the benefits of using probiotics: from the use of *Lactobacillus* sp. in addition to non-surgical periodontal therapy [72], to its adoption to improve the periodontal conditions [73], it results in a reduction of the need for antibiotics [74] and in safe and effective support to conventional mechanical therapies in the management of PD, with positive effects on both oral health and its systemic consequences [75,76]. Another probiotic commensal widely investigated is *Streptococcus* sp. and the mechanisms by which it is able to mitigate the periodontopathogen activity of *Porphyromonas gingivalis*. Hanel et al. [77] addressed the competitive adhesiveness of *Streptococci* sp. to oral epithelial cells as responsible for reducing the invasiveness of *Porphyromonas gingivalis*, while Ohshima et al. [78], defined the ability of *Streptococcus gordonii* to mitigate and modulate the inflammatory signaling triggered by *Porphyromonas gingivalis* and Ho et al. [79] identified the ability of *Streptococcus cristatus* to alter the expression of virulent genes of *Porphyromonas gingivalis*.

On these bases, we can guide dentists to not underestimate the OP problem when facing a postmenopausal woman with or without signs and diagnosis of PD and encourage deeper study on oral dysbiosis and its rebalancing through the use of food products with appropriate and beneficial bacteria.

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