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Osteoporosis and Periodontitis

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Abstract

Osteoporosis and periodontitis are both diseases characterized by bone resorption. Osteoporosis features systemic degenerative bone loss that leads to loss of skeletal cancellous microstructure and subsequent fracture, whereas periodontitis involves local inflammatory bone loss, following an infectious breach of the alveolar cortical bone, and it may result in tooth loss. Most cross-sectional studies have confirmed the association of osteoporosis and periodontitis primarily on radiographic measurements and to a lesser degree on clinical parameters. Multiple shared risk factors include age, genetics, hormonal change, smoking, as well as calcium and vitamin D deficiency. Both diseases could also be risk factors for each other and have a mutual impact that requires concomitant management. Suggested mechanisms underlying the linkage are disruption of the homeostasis concerning bone remodeling, hormonal balance, and inflammation resolution. A mutual interventional approach is emerging with complex treatment interactions. Prevention and management of both diseases require interdisciplinary approaches and warrants future well-controlled longitudinal and interventional studies for evidence-based clinical guidelines.

Keywords

Periodontitis; Osteoporosis; Risk factor; Mechanism; Bone; Inflammation; Estrogen

Introduction

Osteoporosis and periodontitis are prevalent conditions. Osteoporosis impacts half of the elderly over 65 [1], and periodontal disease affects half of the adult population [2]. The number of patients who suffer from these diseases is expected to increase as the population advances in age. Both health problems require expensive, long-term medical and dental care. Osteoporosis is a systemic skeletal disorder with compromised bone density and strength that leads to increased risk of bone fracture [3]; whereas periodontitis is considered a local infection with a host inflammatory response within the supporting tissues of the teeth that results in alveolar bone loss [4]. Both diseases are defined by a preponderance of bone resorption, and their progression or severity is assessed systemically and/or locally. It is reasonable to argue that systematic skeletal change inevitably impacts the jaws and alveolar

Compliance with Ethical Standards

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bone. As early as 1960, there were discussions about periodontal disease also being a degenerative disease termed “presenile osteoporosis” [5], but the primary etiology of periodontitis was later demonstrated as bacterial plaque [6, 7]. The multifactorial nature of the host response to the periodontal disease, as well as its association and mutual skeletal impact are still an interesting debate in the field [8–10]. This report updates the current understanding and scientific advancement that is pertinent to these two bone-resorbing diseases. Their updated association, shared risk factors, potential mechanisms, mutual impact, and interactive treatment will be discussed.

Association Between Osteoporosis and Periodontitis

The association of osteoporosis and periodontitis in clinical studies is defined by the subjects and measuring methods. In general, osteoporosis affects more women [1] and periodontitis affects more men [2]. Most of the cross-sectional association studies were conducted within elderly post-menopausal women, where a general positive correlation was found [8, 10], indicating such association may exist in this subset of the population. In addition, depending on the clinical and radiographic parameters used for both diseases, the strength of the association may vary significantly.

The techniques currently used to assess osteoporosis include dual-photon absorptiometry (DPA), dual-energy absorptiometry (DXA), and quantitative computerized tomography (QCT). The definition of osteoporosis proposed by the World Health Organization (WHO) [11] is a bone mineral density (BMD) score of 2.5 standard deviations or more below (T-score) of the average peak in young adults. Preferred locations for diagnosing osteoporosis with BMD are the spine and hip and femur. Some studies use a dichotomous diagnosis system while others use continuous BMD for statistical assessment, which can also result in variability. On the other hand, methods for assessing periodontal conditions and oral bone loss include clinical probing depth (PD), attachment levels (CAL), tooth loss, radiographic measures of alveolar crest height (ACH), absolute bone density (DXA, DPA, QCT), and computer-assisted densitometry image analysis (CADIA). In summary, the parameters used for periodontal disease can be divided into clinical periodontal examinations (PD, CAL, tooth loss) and radiographic examinations (ACH, DXA, DPA, QCT). A recent systematic review has shown that the association between osteoporosis and the clinical parameters of periodontitis are still inconclusive (six positive vs. five negative studies) but there is a significant association with tooth loss [10]. However, if we measure radiographic findings (osteoporotic change of the jaw or alveolar bone), there is a very strong correlation (18 positive vs. 3 negative studies) [10]. These results suggest a specific mechanistic relationship between the two bone-resorbing disorders.

A hypothesis that relates systemic osteoporosis to local osteoporotic changes in the jaws and loss of tooth-supporting alveolar bone is supported by the observations from various studies. Cross-sectional plus a longitudinal study demonstrate that total bone mass or skeletal density are closely correlated with the resorption of the alveolar crest [12–15]. However, there is a larger study that did not show a correlation between the BMD and alveolar bone height [16]. The latter method involved calibration with a standardized mineral solution equivalent to hydroxyl-apatite (HA) to conventional film. The sensitivity of the technique may have

contributed to the result [16]. These results suggest that systemic osteoporosis also has a local impact via osteoporotic changes in the jaws.

Resorption of the alveolar bone may influence clinical periodontal parameters, such as tooth loss, probing depth (PD), or clinical attachment loss (CAL) [17]. For instance, Elders et al. [16] showed a significant inverse correlation of mean alveolar bone density to tooth loss and mean probing depth in dentate subjects. However, the association of systemic osteoporosis with tooth loss, supported by positive correlations from two longitudinal studies [18, 19], may be a more sensitive indicator compared to other clinical measures, such as PD and CAL [8, 10]. The value of PD and CAL appears to depend significantly on the number of teeth retained. Since osteoporotic subjects may present with premature tooth loss, the clinical parameters are limited in sensitivity for typical cross-sectional studies. On the other hand, tooth loss may be a cumulative result of progressing periodontal pockets and attachment loss. For example, Klementti et al. [20] reported that among 227 post-menopausal women, nearly half only had teeth in the mandibular arch, a jaw with a higher BMD. This may be one of the reasons why they failed to find a positive association between osteoporosis and the Community Periodontal Index of Treatment Needs (CPITN) [21], a method that at least partially reflects PD. This also raises a suggestion for future research to clarify the number of the retained teeth, and whether clinical attachment loss is associated with gingival recession or deep periodontal pockets. In addition, bleeding upon probing (BOP), as a predictor for periodontal disease progression [22], should also be noted. Because inflammation may be a mechanism that links the two disorders, it is important to investigate that association in the future. Deep periodontal pockets with signs of inflammation that require further treatment may have an impact on the outcome and complications of the patients who share both conditions.

Although there is some inconsistency among studies, most data suggests there is an association, especially related to bone densitometric measurements on radiographs. Whether the relationship is gender, race, or age, the association of shared risk factors warrants well-controlled longitudinal study. Defining the relationship between osteoporosis and periodontitis will help identify patients with one disorder who are at a higher risk for developing the other, and thereby could benefit from coordinated interdisciplinary care.

Shared Risk Factors

Although a causal relationship is yet to be established, there are numerous shared risk factors between osteoporosis and periodontitis. These established or potential risk factors may also provide important information regarding etiologies and contributing factors that will assist clinicians in preventing or managing these two diseases simultaneously.

There are several shared risk factors for both diseases as listed in Fig. 1. Osteoporosis has been proposed as a risk factor for periodontal disease [8, 10, 23•], but prospective longitudinal studies are needed to establish a solid cause and effect relationship. Based on the data from the third National Health and Nutrition Examination Survey (NHANES III) regarding adults above the age of 50, it is estimated that 13–18 % of women (3–6 % of men) have osteoporosis in addition to 37–50 % of women and 28–47 % of men who have

osteopenia [24]. An established casual relationship would pose these subjects at a higher risk for periodontal bone loss. Although both diseases are more prevalent among elderly population [1, 25], the association is more significant in women [26], and thus, most studies focused on elderly menopausal women. The main risk factor for osteoporosis in women is menopause, which is associated with a reduced production of estrogen [27]. The latter is associated with decreased protection from bone resorption [27] as well as a suppression in calcium absorption [28]. Studies of estrogen deficiency and periodontitis are limited in humans, but animal experiments have shown that ovariectomy-induced estrogen deficiency enhances alveolar bone loss caused by experimental periodontitis [29]. Furthermore, a gonadal hormone deficiency in men can also have an impact on maintaining bone mineral density [30, 31].

Calcium and vitamin D deficiency are major risk factors for osteoporosis [32], and more recent evidence suggests a similar role for periodontitis [33–35]. Data from NHANES demonstrates that women with a low intake of dietary calcium have more severe periodontal disease [33], and a more modest relationship is suggested for men [34, 35]. The genetic component for both diseases was widely investigated and supports a future personalized medicine approach for prevention and management [36, 37, 38•, 39, 40]. Although genetic studies specifically targeting both diseases are limited, some evidence suggests the polymorphisms of the vitamin D receptor [41, 42].

Smoking is a dose-dependent, major risk factor for periodontal disease [25], and has also been implicated in osteoporosis, especially as a predictor for facture risk [43]. Since osteoporosis may also involve inflammatory bone loss [44] (See Section “Potential Mechanisms Between Osteoporosis and Periodontitis”), it is of interest that a focal infection such as periodontitis could be a risk factor for osteoporosis. Could “presenile osteoporosis of the jaw” be an early sign of osteoporosis? Currently, it is still unclear whether there is an inverse interaction of periodontal disease to systemic bone remodeling [9]. A large prospective cohort study by Persson et al. [45] reported that osteoporotic patients with periodontitis have a higher risk for hip/hand fracture. More recently, experimental periodontitis aggravated systemic ovariectomy -induced bone loss [46••]. Although indirect evidence continues to accumulate, prospective and interventional clinical studies are needed to clearly establish the relationship to serve as an evidence base for future clinical management.

Potential Mechanisms Between Osteoporosis and Periodontitis

Systemic to Local Bone Resorptive Disease

Osteoporosis is a systemic bone-resorbing disease affecting mostly cancellous bone, whereas periodontal disease involves a local infection of the periodontium that first attacks the cortical bone and results in a dimensional change of the alveolar ridge. Since there is a strong association between systematic and local osteoporotic changes in the jaw [12], osteoporosis of the alveolar bone may constitute a “weakened resistance” of the periodontium to infectious challenge. This mechanism is well described in the literature and is consistent with the earlier proposal that osteopenia in the jaw (a non-inflammatory form of dental disease), is a sign of presenile osteoporosis [5]. However, given that the link

between alveolar bone resorption and tooth loss is stronger than other clinical measurements of periodontal disease [8], it is possible that the osteoporotic change of the alveolar (tooth-supporting) bone directly contributes to premature loss of teeth through non-infectious mechanisms. It has been proposed that the mechanical challenge from occlusal forces causes an increased prevalence of micro-fractures in the osteoporotic alveolar bone that may lead to fatigue failure [47, 48]. The concept of noninflammatory degenerative disease of the periodontium was once considered obsolete; however, the latter potential mechanism encourages further investigation of this potential systemic factor from the host perspective.

Hormonal Impact on Bone Homeostasis and Inflammation

Several hormones may play important roles in regulating bone homeostasis, including estrogen, testosterone, cortisol, as well as parathyroid and thyroid hormones. The imbalance of these hormones may impact the metabolism of calcium/phosphate and bone homeostasis. Recently studies have also demonstrated that some of these hormones can also regulate inflammation [49–51].

Estrogen deficiency following menopause in women is a major risk factor for osteoporosis [27]. Hormonal changes impact systemic bone homeostasis and inflammatory responses. Estrogen deficiency also compromises calcium absorption and increases calcium excretion that leads to additional calcium requirements [28]. Reduced levels of estrogen also induce osteocyte apoptosis, which disrupts the homeostasis of bone [52]. The role of estrogen in inflammation is gaining attention, and the action of estrogen may be both pro-inflammatory and anti-inflammatory depending on the physiologic context [49]. In lipopolysaccharide (LPS)-stimulated human monocytes, lower levels of estrogen stimulate IL-1 mRNA expression [53], yet higher levels of estrogen attenuate IL-6 secretion and oxidative stress [54]. Therefore, estrogen may have an impact on both bone homeostasis and inflammation.

In animal models, estrogen deficiency aggravates the severity of experimental periodontitis [29]. Ovariectomized rats have higher expression of IL-6, RANKL, osteoprotegerin (OPG), to a lesser extent, and downregulation of IL-10 in the periodontal tissue, suggesting the impact of estrogen hormone on inflammatory bone resorption [55•]. Hormone replacement therapy (HRT) in humans improves mandibular bone density and reduces gingival bleeding and the number of teeth lost due to periodontitis [56, 57]. These results suggest a potential role of estrogen deficiency in periodontal disease.

Another essential hormone for bone homeostasis is parathyroid hormone (PTH), which increases bone resorption to ensure sufficient calcium in the blood. Intermittent PTH application improves periodontal healing and promotes bone regeneration in extraction sites [58, 59]. Most recently, PTH was found to regulate pro-resolving lipid mediators, which promoted macrophage efferocytosis for bone homeostasis [51]. These findings suggest that PTH can regulate bone homeostasis through inflammation-related pathways and highlights an important role of PTH in promoting bone healing and regeneration.

Together, these results suggest that the interaction of hormones related to bone remodeling and inflammation may be a mechanism that links osteoporosis and periodontitis.

Inflammation and Bone Homeostasis

Although osteoporosis was not considered an immunological disorder in the past, recent studies are indicative of the overlapping relationship between osteoporosis and inflammation [44, 60–62]. Patients with osteoporosis have elevated systemic levels of pro-inflammatory cytokines: IL-1, IL-6, and TNF-α [63, 64], which are all considered osteoclastogenic bone resorption-inducing cytokines [65]. Among these cytokines, the levels of IL-6 predict bone mineral density change [66] as well as fracture rate [67].

These inflammatory cytokines and other factors in the circulation not only impact systemic bone remodeling but also act locally to compromise the tissue response to periodontal disease (e.g., TNF-α also induces collagenase activity) [68]. Focal infection of the periodontium in turn may also release these inflammatory cytokines into the system and broadly impact inflammatory diseases [69]. It is very likely that one of the mechanisms underlying both diseases is through inflammatory pathways.

With the advances in understanding inflammation, it is now known that the resolution phase of inflammation is an active process orchestrated by pro-resolving lipid mediators (SPMs) [70]. Homeostatic bone remodeling involves “physiologic inflammation” to recruit non-phlogistic macrophages for clearance of apoptotic bone cells [51, 71]. Understanding the role of SPMs in bone homeostasis is a new field in osteoimmunology and can lead to further elucidation of the links between osteoporosis, inflammation, and periodontitis.

It is possible that the potential mechanisms are all linked to each other in various pathways. Patients with both osteoporosis and periodontitis may serve as a disease model in the future to study the etiologies and the mechanisms between bone disorders and inflammatory diseases.

Interdisciplinary Management of Osteoporosis and Periodontitis

Given the shared risks and mutual impact of both diseases, it is of interest to know whether the strategies for prevention and treatment of osteoporosis and periodontitis are shared. Osteoporosis is considered a “modifiable risk factor” for periodontitis with regard to host modulation therapy [23•, 72••, 73]. Osteoporotic elderly women who were not treated for the condition have a higher risk for severe periodontal disease [74•].

Early diagnosis of osteoporosis is also essential for managing the disease and for suppressing facture incidence. In elderly women, a significant association was found between mandibular basal bone and hip bone density [73]. In a study of 525 women, assessing the trabecular pattern features from dental panoramic radiographs can predict the measurement of DXA bone mineral density with high internal consistency [75]. It is possible that regular dental images could serve as a low-cost screening tool for osteoporosis.

Regarding the shared risk factor from calcium and vitamin D deficiency, oral supplementation of these two elements shows a positive impact on both diseases. Clinical studies, including RCT, have reported oral supplementation of calcium (1000 mg or more daily) and vitamin D (400 IU) improves periodontal conditions and helps to retain the teeth

[18, 76–78]. However, a recent longitudinal study indicated that patients with lower (<30 nmol/L) 25-hydroxyvitamin D [25 (OH) D] levels could still be maintained periodontally stable for 5 years [79, 80•]. Therefore, future studies may need to include both the blood test readings, and all the sources for vitamin D for better elucidation of the metabolic dynamics. On the other hand, vitamin D deficiency (<20 nmol/L) at the time of periodontal surgery negatively affected treatment outcomes for up to 1 year [59]. In terms of managing osteoporosis, a meta-analysis concluded that oral supplementation of 700–800 instead of 400 IU vitamin D per day can reduce the risk of fracture [32]. In general, oral supplementation with calcium and vitamin D appear to have a positive impact on both osteoporosis and periodontal disease.

Smoking has been established as a major risk factor for periodontitis and osteoporotic fractures [25, 43]. Reduced smoking is associated with a suppressed incidence of fractures [43], especially in the vertebral column [43, 81] and reduced prevalence of periodontal disease [82]. Smoking is the most detrimental modifiable risk factor that should be pro-actively managed [83]. Although hormone replacement therapy (HRT) is not frequently recommended for the management of osteoporosis, it has demonstrated its beneficial effect on tooth retention [84]. PTH, teriparatide, and administration may also improve the treatment outcome for osteoporosis [85] and promote periodontal regeneration [86].

The benefits of oral bisphosphonates on periodontal alveolar bone loss was demonstrated in randomized controlled, double-blinded clinical trials for type II diabetic patients as an adjunctive measure to conventional anti-infective therapy through debridement [87]. In addition in this study, a decrease in hemoglobin A1c levels was noted for both control and experimental groups after the combination treatment. Although anti-resorptive medications such as bisphosphonates and RANK ligand inhibitor have shown beneficial impact on both diseases [73], the emerging risk for medication-related osteonecrosis of the jaw (MRONJ) is a concern. Patients receiving these antiresorptive medications, especially when taken for more than 4 years orally or through intravenous injection, have a higher risk of developing exposed bony lesions in the oral cavity [88]. Because the benefit of anti-resorptive medication for preventing osteoporotic fractures far outweighs the risk of MRONJ, taking these medications is still recommended. Since the population of patients with a history of bisphosphonate therapy continues to increase, dentists should be familiar with the most recent clinical guidelines for managing these patients [88, 89].

Osteoporotic patients with periodontitis require treatment for both conditions. Current trends in the treatment of osteoporosis are focused more on fracture prevention than on BMD levels. Recent association studies have chosen to investigate pathological fractures relative to the status of periodontal disease, and the presence of periodontitis is associated with an increased risk of fractures [90, 91]. Another more convincing prospective study showed that elderly patients with generalized severe periodontitis have an odds ratio (OR) of hip/hand fracture of 1.8:1 and after adjustment for age, the OR increased to 12 [45]. Experimental periodontitis was found to aggravate systemic ovariectomy-induced bone loss [46••]. Moreover, data from a large national longitudinal health insurance database showed that the incidence positively correlated with the severity of periodontitis. In addition, the risk of osteoporosis in patients with periodontitis increased dramatically (OR = 6.37) when these

patients do not have professional periodontal maintenance [92••]. Therefore, it is important that patients with osteoporosis and periodontitis be treated concomitantly as well as have regular recall visits for monitoring and maintenance care.

Osteoporosis patients may also present with premature loss of teeth and a partially edentulous dentition that requires dental implant restoration. Osteoporosis was once considered a relative contraindication for dental implant therapy. However, recent data indicate that patients with osteoporosis have similar high success rates [93]. In addition, studies have shown that dental implants placed in fully edentulous patients may stimulate bone growth [94]. Therefore, osteoporotic patients may still be good candidates for dental implant therapy.

There are several considerations in managing patients with both osteoporosis and periodontitis. Treating both diseases simultaneously may have a positive synergistic effect for improved outcomes for interdisciplinary care. More longitudinal and interventional clinical studies are needed to recommend clinical guidelines for co-managing both diseases. Clinicians should be aware and knowledgeable of both conditions to make the proper referrals for co-management of the diseases.

Conclusion

Osteoporosis and periodontitis are both diseases with excessive bone resorption. There may be a disruption of the homeostasis involving bone remodeling, hormonal balance, as well as inflammation progression and resolution. Several shared risk factors exist, and their interactive impact is emerging. Well-controlled clinical studies are needed to establish an evidence base for efficient interdisciplinary management of both diseases.

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•• Of major importance

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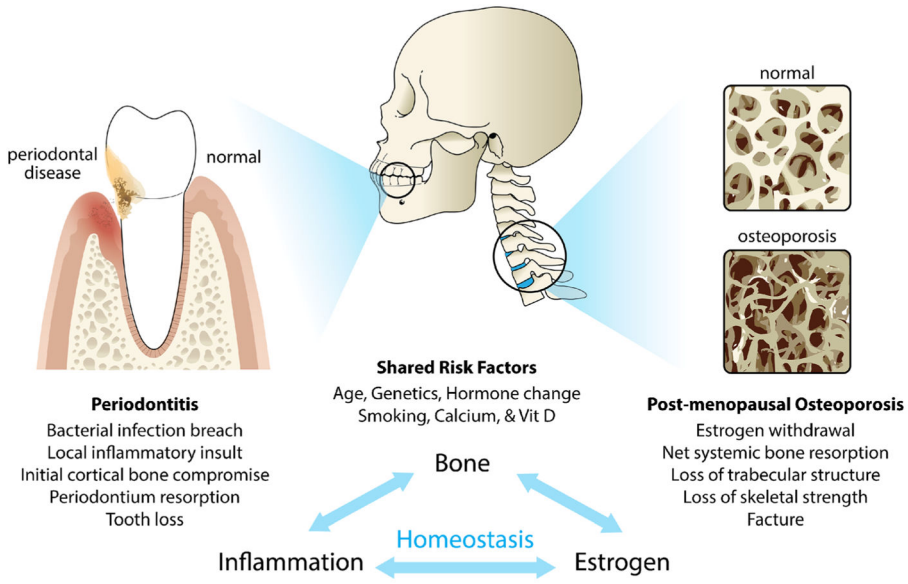

Fig. 1.

Schematic illustration of the association between periodontitis and osteoporosis. The diagram highlights the osseous target for periodontal disease (alveolar cortical bone) and osteoporosis (trabecular bone). Shared risk factors and potential mechanisms underlying both diseases are also listed