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Osteoporosis and periodontal diseases – An update on their association and mechanistic links

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1. INTRODUCTION

Periodontitis and osteoporosis are prevalent inflammation-associated skeletal disorders that pose significant public health challenges to our aging population. Periodontal diseases consist of a spectrum of disorders in the dento-gingival tissues with a predominant dysbiotic and inflammatory nature.[1,2] Gingivitis, the most common form of periodontal disease is a reversible inflammatory response to the accumulation of bacterial plaque and is self-limiting upon removal of the plaque. On the other hand, periodontitis represents a chronic inflammation of the deeper periodontal tissue and alveolar bone, leading to progressive deepening of the gingival sulcus and further accumulation of plaque and calculus. In the advanced stage, periodontitis is associated with irreversible destruction of alveolar bone and loss of tooth support, causing tooth mobility and drifting. Current disease model suggests periodontitis results from multifactorial interactions between dysbiotic subgingival biofilm, host immune response and environmental/risk factors, such as genetic contribution, aging, nutritional deficiencies, hormonal balance, and tobacco use.[3] According to the latest National Health and Nutrition Examination Survey ending in 2014, 42% of American adults 30 or older have periodontitis.[4] The prevalence and susceptibility of periodontal diseases increase with age.[3,4] While approximately 4.1% of US adults aged 30–44 have severe periodontitis, the prevalence rate doubles to 10.4% in the 45–65, and 9.05% in the 65 and older group, respectively.[4]

Osteoporosis is an age-related bone disease characterized by deterioration of bone density and architecture, along with increased fracture risk. Afflicting over 200 million worldwide,[5] it is the most common metabolic bone disease, which places 1 in 3 women and 1 in 5 men over 50 at risk for fracture.[6] Aging of the population likely accelerates the economic

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burden of the associated mortality and morbidity. In 2025, the cost of osteoporotic fractures is projected to rise over 50% from 17 billion dollars in 2005.[7]

Both periodontitis and osteoporosis are bone disorders closely associated with inflammation and aging. With multiple shared risk factors and links in pathogenic mechanisms, there has been consistent intrigue on whether a systemic skeletal disease like osteoporosis will amplify the alveolar bone loss in periodontitis. While the initial clinical findings up to the early 2000s were controversial at best, recent studies have provided more compelling evidence to suggest an association between these two disorders. In this review, we have evaluated the literature published in the past 25 years to provide an update on the association between osteoporosis and periodontitis, followed by a robust discussion of their mechanistic links, shared risk factors, and therapeutic implications.

2. CLINICAL CORRELATION BETWEEN PERIODONTITIS AND OSTEOPOROSIS

The link between periodontitis and osteoporosis was first drawn in 1960, where periodontitis was initially considered a local manifestation of systemic “pre-senile osteoporosis.”[8] Although it was soon revealed that bacterial plaque is a primary etiological factor separating these two disorders, the intrigue has driven extensive studies and meta-analysis centered around two questions: (1) whether systemic weakening of bone mass in osteoporosis enhances the propensity for localized alveolar bone loss; and (2) whether osteoporosis exacerbates loss of attachment and other clinical manifestations of periodontitis. However, depending on the different clinical and radiological parameters used as determinants for periodontitis and osteoporosis, studies to date have yielded varied strength in the association between these two diseases. Before delving into the literature further, the evolving classification and diagnostic criteria for periodontitis and osteoporosis need to be clarified.

Over the past 4 decades, the classification of periodontal diseases has been through several major updates, given emerging evidence on pathogenic factors, host response, and association with systemic diseases.[2,9,10] In the most recent 2017 world workshop, periodontitis has been reclassified into three main forms: necrotizing periodontitis, periodontitis as a manifestation of systemic disease, and periodontitis, which combines two previously separate “chronic” and “aggressive” categories.[11] Several systemic and genetic disorders significantly compromise the intrinsic immune system, leading to early presentation of severe periodontitis. As a consequence of Down syndrome, patients experience altered T lymphocyte migration to the periodontium. The compromised immune response predisposes them to infections, and periodontal attachment loss begins as early as adolescence.[12] Individuals with Papillon-Lefèvre syndrome may lose primary and permanent teeth at a young age because of defects in neutrophil function.[13] These conditions should be grouped as “periodontitis as a manifestation of systemic disease,” and be classified based on the primary conditions.[14] In contrast, several common systemic diseases, including osteoporosis, exert relatively moderate influence on the pathogenesis of periodontitis. While contributing to loss of periodontal apparatus, these systemic diseases

do not lead to periodontal manifestations with unique onset or severity, thus should be considered as risk factors. Of note, the task force from the 2017 workshop concluded that osteoporosis is significantly associated with higher prevalence and severity of radiographic alveolar bone loss. However, there is no clear association with other clinical parameters of periodontitis.[14]

In general, the diagnosis and staging of periodontitis are based on a combination of examination of clinical attachment loss (CAL) and assessment of radiographic bone loss.[10] Reduction of 1–2 mm CAL and <15% of root length in bone loss is characterized as mild periodontitis (Stage I), 3–4 mm CAL and 15%−30% alveolar bone loss as moderate periodontitis (Stage II), and CAL ≥ 5 mm with >30% bone loss as severe periodontitis (Stage III and IV).[15] These measurements, when combined with parameters including probing depth (PD), bleeding on probing (BOP), tooth loss, pattern of bone loss, furcation involvement, and presence of systemic risk factors, further determine the progression rate and complexity for managing the periodontitis case.[10,15]

On the other hand, the gold standard for diagnosing osteoporosis is the evaluation of bone mineral density (BMD) of lumbar vertebrae and/or proximal femur using dual energy X-ray absorptiometry (DXA).[16] Osteoporosis is defined by a BMD score (T score) of 2.5 standard deviations or more below the average BMD of a healthy young adult. While the diagnostic criteria for osteoporosis are well established, the assessment of fracture risk for patients with low BMD takes into consideration multiple risk factors. Other validated sites and techniques for BMD measurements such as quantitative computer tomography (QCT) may also be utilized to determine fracture risk. The 10-year probability of fracture, rather than BMD alone, is suggested to determine the threshold for intervention.[16] However, in most clinical studies on the correlation with periodontitis, lumbar and/or femoral DXA was used as the indicator to represent systemic BMD associated with osteoporotic patients.

3. CORRELATION BETWEEN OSTEOPOROSIS AND ALVEOLAR BONE LOSS

As osteoporosis represents generalized thinning of trabecular and cortical bone, the long-standing hypothesis is that the alveolar bone surrounding the teeth in osteoporotic patients is more susceptible to periodontitis-related bone loss. In clinical studies examining the association between systemic and alveolar bone loss (ABL), all of the 10 studies published between 1996 and 2020 revealed an inverse correlation between systemic BMD and ABL[17–26] (Table 1). All studies employed DXA of lumbar vertebrae and/or femoral neck as a determinant of osteoporosis. However, since DXA is limited to measuring alveolar BMD in edentulous subjects, a diverse range of alternative techniques were employed to assess the ABL, including linear assessment of alveolar crest height (ACH) or ABL using intraoral[18,22,24,26,27] or panoramic radiographs,[19,25] mandibular cortical width (MCW) using panoramic radiographs,[17,19,20,25] and digital densitometry analysis of alveolar BMD.[21,23,26] Since these parameters encompass both bone volume and density, as well as cortical and trabecular bone, the conclusion that ABL is inversely correlated with systemic BMD is particularly compelling.

The ratio of compact cortical bone and spongy trabecular bone varies significantly between maxillae and mandible. With approximately 10% cortical bone in the spine and maxillae, the mandible comprises up to 80% cortical bone and 20% trabecular bone.[28] In the mandible, cortical bone is concentrated at the inferior cortex, and begins to decrease in width with time after the age of 50. Thus, the MCW is used as an index for cortical bone assessment using panoramic radiographs, where the inferior cortex is well captured. Studies showed that thinning MCW is significantly correlated with systemic BMD, and serves as a potential risk indicator for osteoporosis.[17,29,30] However, the MCW is not associated with systemic fracture risk.[17,30] In contrast to cortical bone, mandibular trabecular bone pattern is more closely related to fracture risk,[31–33] and serves as a valuable predictor for osteoporosis in women.[30,33,34] Of note, while mandibular trabecular pattern becomes more spaced and less connected with advanced age in most females, the trabecular pattern is preserved in most males.[31,35] Given the challenge of directly measuring trabecular pattern, most studies resorted to assessment of the alveolar BMD through densitometry or measurement of alveolar crest height, where most periodontal bone loss was concentrated. Consistently, both ACH and alveolar BMD are correlated with systemic BMD. Particularly in the predominantly trabecular maxillary bone, alveolar BMD is also correlated to lumbar and hip BMD.[36] Taken together, there is strong evidence supporting that osteoporosis is associated with higher susceptibility of alveolar bone loss in postmenopausal women.

As a caveat, only one study dating back to 1992 found no statistically significant correlation between alveolar bone height and systemic BMD in women between 46 and 55 years of age.[37] It is possible that the results were confounded by the number of retained teeth in the subjects, as the study included a high percentage of edentulous subjects. And the relative young age of these perimenopausal women in the study could explain a lack of contribution from postmenopausal osteoporosis. While most of the studies were cross-sectional, a 5-year longitudinal study examining the effect of estrogen replacement therapy also demonstrated significant improvement in mandibular bone mass in association with BMD of the spine and wrist.[38] As 70% of all fractures happen in osteoporotic females[5] and with the traditional view that osteoporosis is predominantly associated with postmenopausal estrogen deficiency, it is not surprising that most studies focused on postmenopausal women. Despite limited findings supporting the trend,[17] given the distinct gender-specific pattern of alveolar bone loss, further analysis is required to confirm if osteoporosis is associated with alveolar bone loss in men.

4. CORRELATION BETWEEN OSTEOPOROSIS AND PERIODONTAL ATTACHMENT LOSS

While radiographic assessment of alveolar bone loss is an important criterion, CAL reflects the lifetime experience of periodontitis and is a critical outcome measurement for diagnosing and staging of periodontitis.[10] Of 23 studies published between 1995 and 2020, 17 revealed a significant correlation between CAL and osteoporosis[18,24,25,39–60] (Table 2). These included 18 cross-sectional and 5 longitudinal studies, ranging from a sample size of 30[54] to 2990.[44] Most studies focused on postmenopausal women aged between 41 and 80 years old. Lumbar and/or femoral DXA was used to represent systemic BMD, but the clinical outcome

measurements for CAL as determinants of periodontitis were more variable, especially considering the inclusion of other parameters, such as PD and BOP. The lack of a consistent CAL criteria could contribute to variability in the conclusions of these studies. However, the more recent studies since 2010 used CAL > 5 mm as a determinant for severe periodontitis, in accordance with the clinical classification criteria. In these 11 studies, all demonstrated positive association between CAL and systemic BMD, except for one study that utilized a much more stringent criteria of CAL > 7 mm.[48] Consistently, two systematic reviews from 2010 and 2017 reached similar conclusions.[61,62] Taking into consideration the bias and qualities of the evidence, Penoni et al suggested that 10 out of 11 studies with high quality evidence demonstrated positive correlation between CAL and systemic BMD.[61] Particularly, compiling the data from all 11 studies, the low BMD group had 3.04% more sites with CAL > 4 mm and 5.07% sites with CAL > 6 mm, compared to normal BMD group. With 30% of sites as the threshold, this difference could create a significant clinical implication in a shift from localized to generalized periodontitis.[4,61]

Loss of clinical attachment in severe periodontitis culminates in the destruction of alveolar bone support and tooth loss. Of the 16 studies that evaluated correlation between tooth loss and systemic BMD, 11 showed a positive association,[25,44,45,47,50,53,54,63–66] while 5 studies reported conflicting results.[43,49,58,59,67] The lack of correlation could be due to a relatively small sample size and inclusion of confounding factors such as age in the earlier studies.[43,49,58] When corrected for confounding factors including age and smoking, a large group multicenter study showed compelling association between tooth loss with systemic BMD.[63] Of note, tooth loss is also a clinical endpoint associated with multiple factors beyond periodontitis. The contribution of osteoporosis may be of minor importance in comparison to other clinical and socioeconomic factors, such as access to dental care and oral hygiene habits.

Since the task force report from the 2017 world workshop, which perceived insufficient evidence to support a connection,[14] there have been a remarkable number of studies and systematic reviews supporting the association between osteoporosis and CAL or other clinical parameters of periodontitis. Considering the numerous risk factors associated with both diseases, further confirmation of the association calls for correction for confounding factors in the data analysis and for well-controlled longitudinal studies in the future.

5. INFLAMMATION AND BONE HOMEOSTASIS

Although the pathogenesis and progression of periodontitis depend on the host interaction with the dysbiotic biofilm,[68] the ensuing inflammation and its influence on bone homeostasis play critical roles in both osteoporosis and periodontitis, and could serve as the central mechanistic link between these disorders.

The healthy skeleton undergoes continuous remodeling process, which allows new bone to replace the old as part of physiological development and in response to factors, such as mechanical loading. Normal bone turnover relies on an orchestrated balance between bone resorption by osteoclasts and bone formation by osteoblasts, essential for the maintenance of a stable bone mass and mineral homeostasis.[69]

Inflammation is characterized by the activation of various immune cells in the innate and adaptive immunity, resulting in an elevation of immune cytokine production in the cellular environment. The cytokines activated during the course of inflammatory responses have profound effects on the differentiation and activity of osteoblasts and osteoclasts and, therefore, are considered to be mediators of inflammation-associated osteoporosis and periodontitis.

In periodontitis, persistent microbial biofilm on the tooth surface elicits the recruitment of polymorphonuclear neutrophils from the vasculature to the site of infection. As the first line of defense against the pathogens, neutrophil recruitment is influenced by a multitude of factors, including bacterial products, immune cytokines, chemokines, and lipid mediators.[70,71] Detection of bacteria by toll-like receptors (TLRs) via binding of bacterial products to TLRs activates the innate immune system.[72] Subsequent crosstalk between innate and adaptive host response stimulate lymphocyte activation and amplification of local inflammatory signaling cascade, including nuclear factor-kappa B (NF-κB), activator protein 1 (AP-1), and p38 pathways.[70] The local alveolar bone loss appears to be at least partly mediated by bacteria-activated T lymphocytes stimulating receptor activator of nuclear factor kappa-B ligand (RANKL) signaling to promote osteoclastogenesis.[73,74] In addition to osteoclasts, enhanced inflammation could also inhibit osteoblast lineage cells to further uncouple the balance in bone remodeling, culminating in a net bone loss.[75]

The uncoupling of bone remodeling also drives systemic inflammatory bone disorders, including osteoporosis. With enhanced cytokine secretions, inflammation, particularly activation of NF-κB signaling, promotes osteoclasts and simultaneously suppresses osteoblasts.[76] The genetic or chemical inhibition of NF-κB signaling has been shown to attenuate bone loss in osteoporosis and arthritis.[77] For instance, TNF blockers have been an effective approach to dramatically slow down the progression of local and systemic bone loss in rheumatoid arthritis.[78,79] Growing evidence suggests that modulating the inflammatory responses have profound influence on the balance in bone remodeling and could represent an important therapeutic approach.

NF-κB signaling is a major signaling pathway activated during most inflammatory responses.[80–82] NF-κB represents a family of five proteins (c-Rel, RelA/p65, RelB, NF-κB1/p50, and NF-κB2/p52), all of which play critical roles in osteoimmunology and aging.[80] NF-κB proteins exist as homo- or heterodimers and form a complex with inhibitors of κB (IκBs) in the cytoplasm. Upon stimulation by various inflammatory cytokines, activation of IκB kinases (IKKs) phosphorylates, and degrade IκBs to release NF-κB, which translocate into the nucleus to activate transcription of various target genes. Genetic manipulation of various NF-κB pathway components in animal models have shown that NF-κB signaling has profound effects on bone formation and resorption. Double knockout mice of *Nfkb1* and *Nfkb2* did not form osteoclasts *in vivo* or *in vitro*.[83] Conditional *Ikkb* knockout mice using a Mx1 promoter showed osteopetrotic phenotype and decreased osteoblast numbers.[84] In the context of osteoporosis, mice overexpressing an *IkkΥ* dominant-negative gene in mature osteoblasts showed enhanced osteoblast formation and suppressed osteoclast activation following ovariectomy (OVX), a mouse model of estrogen-deficiency induced osteoporosis.[76] In the periodontal tissue, inhibition of NF-κB signaling

in the osteoblast lineage cells directly impaired osteoclastic bone resorption and promoted bone formation,[75] further affirming their regulatory roles in bone remodeling.

In addition to components of NF-κB signaling pathways, manipulation of proinflammatory cytokines, such as TNFα, interleukin-1 (IL-1), and IL-6, also profoundly impact systemic and periodontal bone loss. In humans, IL-1β level is elevated significantly in gingival crevicular fluid at sites of periodontal attachment loss.[85] Chemical or genetic inhibition of IL-1 in mice resulted in significantly suppressed pathogenic bacterial load.[86,87] Conversely, transgenic mice over-expressing IL-1α developed attachment loss and alveolar bone destruction paralleling periodontitis.[88] Injection of recombinant human TNF-α ameliorated periodontal inflammation and bone loss in a rat ligature model.[89] Interestingly, genetic ablation of TNF receptor p55 in mice increased bacterial load of *A actinomycetemcomitans* via reduced amount of neutrophilic antimicrobial myeloperoxidase.[90] Despite the reduced host response to bacterial pathogens, the periodontal inflammation and alveolar bone loss were both reduced in the p55 knockout mice, suggesting that the critical role of cytokine amplification and NF-κB signaling, rather than pathogen load alone, in the progression of periodontitis. As TNF-α and IL-1 activate NF-κB signaling pathway, increased cytokine production effectively induces RANKL signaling, essential for osteoclastogenesis and subsequent periodontal bone resorption.[91] As for osteoporosis, serum IL-1 level was higher in osteoporotic women for as long as 15 years after menopause, and the IL-1 level was inversely correlated to systemic BMD.[92] Three recent large-cohort nested epidemiological studies confirmed this immunological link whereby a 1.5- to 3-fold increase in osteoporotic fracture risk was associated with higher level of inflammatory markers (TNF and IL-6 receptors).[93] Mice lacking TNF-α are resistant to OVX-induced bone loss. In rodent OVX models, simultaneous administration of IL-1 and TNF-α was required to completely abrogate the osteoporotic bone loss in rats,[94] implicating synergistic coordination between immune cytokines. These evidence from human and animal models suggest NF-κB–related cytokines play a central role in periodontitis and osteoporosis.

Apart from the inflammatory cytokines, the complement system represents a critical component of the innate immunity responsible for first-line host defense and further elicitation of adaptive immune response. This network of more than 50 proteins mediates response to microbial infections or tissue damage,[95] thereby amplifying and modulating the host immune response via activation of NF-κB and AP-1 pathways to elevate the plasma levels of IL-6, TNF-α, and IL-1β.[96] Three distinct pathways that activate the complement system (classical, lectin and alternative) converge at the C3 protein, a central component of the complement system.[97] Multiple lines of evidence from clinical and animal studies have strongly supported the role of C3 and complement system in the progression of periodontitis. The amount of activated complement fragments in the gingival crevicular fluid (GCF) is elevated in periodontitis patients compared to healthy samples,[98,99] and C3 activation decreases after periodontal therapy.[100] C3-deficient mice showed significantly less bone loss and inflammation in three distinct models of periodontal bone loss induced by bacterial inoculation, ligature, and aging.[101] Consistently, C3 inhibition in non-human primates also protects against the development of periodontitis, and the amount of NF-κB–related inflammatory cytokines dramatically decreased in the GCF of primates treated with C3 inhibitor.[101] On the other hand, C3-deficient mice, compared to wild-type controls,

show significantly lower trabecular loss and less cortical erosion after OVX, suggesting that C3 activation is required in osteoporotic bone loss as well.[102] These studies collectively demonstrate that the complement system associated with NF-κB signaling activation play a key role in the regulation of systemic and periodontal bone loss.

Mechanistically, NF-κB signaling mediates the uncoupling of bone remodeling via simultaneous but opposite effects on osteoclasts and osteoblasts. Osteoclast differentiation and activation are regulated by both systemic hormones and cytokines secreted locally into the bone microenvironment. As the bone formation and resorption are coupled, osteoclasts can be regulated by osteoblasts, marrow stromal cells, osteocytes, as well as lymphocytes in the bone marrow. Two key transcription factors required for osteoclasts are c-Fos and nuclear factor of associated T-cells c1 (NFATc1). Mice lacking *c-fos* develop macrophages but cannot form osteoclasts.[103] The activation of NFATc1 is essential for the transcription of various essential osteoclastic markers, including genes encoding the tartrate-resistant acid phosphatase (TRAP), matrix metalloproteinase-9 (MMP-9), and cathepsin K.[104,105] The initial step of osteoclast differentiation from hematopoietic stem cells, a step toward monocytes and macrophages, requires macrophage colony-stimulating factor (M-CSF). Through the activation of extracellular signal-regulated kinases and anti-apoptotic serine/threonine kinase (AKT), M-CSF subsequently induces the proliferation and survival of osteoclast progenitor cells.[106] The next step of osteoclast differentiation requires RANKL signaling. RANKL is a member of the TNFα superfamily and is primarily expressed by osteoblasts, marrow stromal cells, and lymphocytes. RANKL signaling can be modulated by systemic hormones, including parathyroid hormone (PTH), IL-11, prostaglandins, and 1,25-$(OH)_2D_3$.[107,108] Interestingly, osteoclasts can also regulate their own formation via autocrine secretion of cytokines. For instance, IL-6 secreted by osteoclasts acts on the surrounding progenitors to promote osteoclast formation, independent of RANKL signaling.[109]

On the other hand, in inflammatory bone loss, such as rheumatoid arthritis and osteoporosis, the number and activity of osteoblasts are too low to compensate for the accelerated osteoclast action. Inflammatory responses could severely impair osteoblast differentiation via several pathways. For instance, TNFα inhibits RUNX2 expression, a master regulator for osteoblast differentiation[110] and promotes RUNX2 degradation by upregulating its E3 ubiquitin ligases Smurf1/2.[111] Conversely, inhibition of NF-κB pathway components such as IKKϒ led to increased AP-1 activation and enhanced osteoblastogenesis.[76] Furthermore, as canonical WNT signaling promotes osteoblasts, NF-κB activation interferes with WNT signaling to exert inhibitory effects on osteoblasts. NF-κB-induced Smurf1/2 upregulation promotes β-catenin degradation in mesenchymal stem cells,[112] while antagonists DKK1[113] and sclerostin[114] are induced by TNF to abrogate the osteoblastogenic effects of canonical WNT signaling.

Thus, chronic inflammation is a cardinal yet often neglected risk factor for both local and systemic bone loss.[104,115] Systemic osteoporosis and increased fracture rates are found in correlation with various rheumatological diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, as well as inflammatory bowel disease, celiac disease, cystic fibrosis, and periodontitis.[115] In addition to observing the co-incidence of inflammatory conditions, there is a temporal link between inflammation and osteoporosis

in aging, menopause, pregnancy, and steroid administration.[116] Supporting evidence is also observed in animal models of arthritis and colitis.[78,117] In summary, inflammation via the activation of NF-κB signaling uncouples the bone remodeling process. Closer examination of the shared risk factors further elucidates that systemic inflammation may also enhance immune response in the localized alveolar bone microenvironment, thereby serving as the mechanistic link underpinning the association between periodontitis and osteoporosis.

6. AGING IN OSTEOPOROSIS AND PERIODONTITIS

Advanced age is a well-established risk factor for osteoporosis.[16] The classical estrogen-centric model of osteoporosis suggested a predominant role of estrogen deficiency, as postmenopausal women presented with high incidence of osteoporotic fractures and bone loss. However, in both males and females, trabecular bone loss occurred after reaching peak bone mass, even in the presence of sufficient sex steroids, thereby implicating intrinsic age-related mechanisms at play.[69,118] Chronic inflammation is a hallmark of aging.[119] With age, the bone marrow microenvironment becomes increasingly proinflammatory with accumulation of immune cytokines, such as IL-6 and IL-1.[120] The increased production of immune cytokines and oxidative stress entail that bone metabolism is more susceptible to osteoimmunological influences. The inflammatory microenvironment may mediate the interactions between bone cells and immune cells, to directly influence bone metabolism and age-related bone loss. Studies have shown that while NF-κB signaling is activated in progeroid mice with accelerated aging,[121] and suppression of NF-κB activation could attenuate physiological skeletal aging and development of symptoms associated with accelerated aging.[121,122]

While cross-sectional studies identified correlation between age and bone loss for up to 45 years of age, alveolar bone mass remained stable after 50 years of age.[123,124] This suggests that increased prevalence and severity of periodontitis is not an obligatory consequence of aging. Rather, it is likely the result of an altered disease susceptibility and host response associated with the aging as a complicating factor. Recent evidence suggests that aging promotes pathogenic microbial colonization, while evoking a pro-inflammatory microenvironment to exacerbate periodontal inflammation and bone loss.[125–127] Human studies revealed that older individuals not only had a more severe inflammatory response in an experimental gingivitis model, the gingival lesions from the older individuals contained greater composition of B-cells compared to polymorphonuclear neutrophils.[128] In a non-human primate study, the levels of systemic inflammatory mediators were significantly elevated in older animals and that this was associated with gingival inflammation and periodontal tissue destruction.[129] While the fundamental mechanisms remain unclear, emerging evidence suggests that accumulation of oxidative stress and cellular senescence are two shared, age-related mechanisms driving osteoporosis and exacerbation of periodontitis.

7. OXIDATIVE STRESS AND SENESCENCE AS SHARED MECHANISTIC LINKS

Oxidative stress in the skeletal tissue microenvironment is elevated during aging, as a result of excessive accumulation of intracellular reactive oxygen species (ROS), as

well as a depletion of enzymes for antioxidant defense.[130] ROS production takes place mostly in mitochondria-rich tissues during aerobic metabolism, fatty acid oxidation and in response to environmental stimuli, including immune cytokines.[131] With age, mitochondrial dysfunction, DNA damage, and proinflammatory cytokines are associated with increased production of ROS. In concert, elevated oxidative stress, via NF-κB signaling, triggers enhanced osteoclastogenesis, increased osteoblast apoptosis, along with decreased osteoblastogenesis.

Mounting *in vivo* evidence suggests that age-induced oxidative stress may contribute to osteoporotic bone loss. In mouse skeleton, age-dependent decline of bone mass and strength is linked with increased ROS levels and decreased antioxidant glucothiane reductase activity in the bone marrow.[132] Knockout of NADPH oxidase 4(Nox4), which is essential in ROS production, led to attenuation of osteoclastogenesis and OVX-induced bone loss, without significant impact on osteoblasts.[133] Mice deficient in antioxidants such as glutathione exacerbated OVX-induced bone loss.[134] Mice depleted with antioxidant foxhead box O (FoxO) family proteins showed rising oxidative stress that aggravated osteoclastogenesis and osteoblast apoptosis, contributing to an osteoporotic phenotype.[135,136] In humans, elevated markers of oxidative stress were found to be associated with low BMD in postmenopausal women.[137]

During the initial periodontal response to bacterial pathogens, respiratory burst of the recruited polymorphonuclear neutrophils, the primary producers of ROS, contributes to elevated ROS level, which in turn is responsible for neutrophil priming for the microbial defense.[138] However, persistent and excessive production of ROS leads to elevation of immune cytokines, triggering signaling cascades that culminates in the uncoupling of bone remodeling in periodontitis. Numerous case-control and longitudinal studies have established that the level of markers for oxidative stress or antioxidants are directly correlated to the presence, severity, or improvement of periodontitis, and have been extensively reviewed elsewhere.[71,139,140] For instance, the levels of oxidant-induced DNA damage, as measured by the biomarker 8-hydroxy-2′-deoxyguanosine (8-OHdG), are higher in patients with chronic periodontitis than in healthy controls.[141] Higher levels of total protein carbonyls, another indicator of ROS, were found in the patients with periodontal disease and correlated with increased loss of periodontal attachment.[142] Thus, excess free radicals in conjunction with reduced host antioxidant defense play a central role in the pathogenesis and progression of periodontitis.

This imbalance is extended to diabetes mellitus, another established risk factor for periodontal bone loss. Conversely, periodontitis is ranked as the sixth most common end-stage complications for type 2 diabetes.[143] Advanced glycation end (AGE) products, produced in general in conjunction with aging, are the most common product of chronic hyperglycemia. AGE products promote excessive ROS production and establish a proinflammatory state. In an environment characterized by the overproduction of free radicals, various molecules release enzymatic antioxidants in an attempt to prevent oxidative damage. Total antioxidant capacity was increased in both peripheral blood samples and gingival crevicular fluid samples from patients with type 2 diabetes and periodontitis.[71] As

such, the generation of oxidative stress may be an underlying systemic condition directly related to alveolar bone loss in periodontitis, in patients with type 2 diabetes.

Cellular senescence, the halting of proliferation for damaged and dysfunctional cells, is critical in the pathogenesis of age-related chronic diseases, including diabetes and osteoporosis.[144–147] Mesenchymal stem cells (MSCs) possess self-renewal ability and multiple lineage potentials that contribute to osteoblasts and adipocytes in the adult bone marrow.[148–150] Prolonged age-induced stressors, such as oxidative stress, drives chronic cellular senescence. The exhaustion of the MSC pool through senescence represents one of the hallmarks for skeletal aging.[151–153] In the bone microenvironment, age-induced senescence was found in all stages of the osteoblast lineage in the vertebrae and long bones.[154] Clearance of senescent osteocytes, but not osteoclast progenitors, significantly alleviated age-related bone loss, including osteoporosis.[146,155] Therefore, targeting senescence in the mesenchymal lineage through senolytic agents is a promising strategy for treating osteoporosis.[147,156]

The negative impact of cellular senescence on tissue homeostasis is twofold: the loss of regenerative potential in progenitors and altered immunomodulation in the microenvironment. Senescent MSCs lose potential for proliferation, self-renewal, and osteogenic differentiation, contributing to the impaired bone mass and delayed repair in long-bone.[122,152,153] Cellular senescence is also associated with inflammation and extracellular matrix remodeling through the secretion of proteins termed as senescence-associated secretory phenotype (SASP). The pro-inflammatory microenvironment would in turn increase the cellular stress to trigger senescence in the neighboring cells as a positive feedback loop. In the oral cavity, aging, hyperglycemia, and bacterial lipopolysaccharide (LPS) have been demonstrated to induce cellular senescence in various subpopulations of the periodontal tissues to exacerbate the adaptive immune response and periodontal inflammation.[126,144,157]

As a unitary theory, advanced age drives the establishment of proinflammatory tissue microenvironment through accumulation of oxidative stress and senescence. In the respective contexts of systemic and local bone microenvironments, the elevated inflammation disrupts the balance between osteoclasts and osteoblasts to cause uncoupling of bone remodeling (Figure 1).

8. NUTRITIONAL DEFICIENCY AND SMOKING AS SHARED RISK FACTORS

Calcium and vitamin D deficiency are major risk factors for osteoporosis[158] and periodontitis.[159,160] Inadequate vitamin D intake resulting in insufficiency (<25 nmol/L serum concentration) can lead to decreased calcium intestinal absorption and ultimately release of calcium from the skeleton in order to maintain calcium homeostasis.[161] Serum level of 25-$(OH)_2D_3$ was reportedly associated with BMD.[162] A total of 5 out of 9 interventional studies of vitamin D supplementation alone, and 16 of 22 studies of vitamin D combined with calcium supplementation, have reported positive effects on the systemic BMD and reduced fracture risks.[163] On the other hand, large cohort cross-sectional studies

revealed that women with a low intake of dietary calcium have more severe periodontal disease, and a more modest relationship is suggested for men.[159]

Vitamin D3 is a pleiotropic hormone, the main activities of which are the result of the interaction of its active metabolite (1,25-$(OH)_2D_3$, or calcitriol), in concert with PTH to modulate bone homeostasis and calcium/phosphate balance.[164] Vitamin D stimulates intestinal absorption of calcium, regulates PTH release by the chief cells, and mediates PTH-induced bone reabsorption. Administration of vitamin D derivatives promoted osteoclastogenesis *in vitro*, but inhibited osteoclast fusion and function *in vivo*.[161,165,166] Also, 1,25-$(OH)_2D_3$ is a potent inducer of RANKL secretion in immature osteoblasts and a suppressor of osteoprotegerin (OPG) synthesis.[167] Through regulation of the RANKL/OPG ratio, vitamin D controls bone remodeling. On the other hand, PTH is well known to enhance differentiation of committed osteoblast precursors, prolonging osteoblast lifespan via inhibition of apoptosis.[168] From an immunological perspective, 1,25-$(OH)_2D_3$ and intermittent administration of PTH downregulates cytokine production, including IL-6 and TNF-α, especially in postmenopausal women.[169,170] Therefore, aside from their physiological roles, both vitamin D and PTH exert direct and indirect influences over the differentiation and function of bone cells to modulate bone remodeling.

Smoking is a dose-dependent risk factor for periodontal disease[171] and has also been implicated in osteoporotic bone loss.[172] The mechanisms through which cigarette smoking influences periodontal destruction are complex. Evidence is unclear on the effect of smoking on the gingival crevicular fluid cytokine profile, as related to periodontal inflammation.[173,174] Nonetheless, a suppressive effect on OPG level in serum and gingival crevicular fluid was observed in smokers.[175–178] The resultant imbalance in the RANKL/OPG ratio has been positively associated with increased osteoclastic resorption and bone loss in smoking-related periodontitis patients.

In addition to RANKL-induced destruction of tooth-supporting tissue, there is evidence of smoking-induced oxidative stress caused mainly by increased generation of ROS within gingival tissues.[179] The results of screening tests for markers of DNA (8-OHdG) and protein (C-reactive protein) oxidation have been compared with the smoking status of periodontally diseased patients, as well as the formation of antioxidant compounds, such as superoxide dismutase, catalase, and glutathione peroxidase. Recent cohort studies showed that oxidative stress is higher in smokers with chronic periodontitis than in nonsmokers with chronic periodontitis.[179,180] Conversely, when the effects of periodontal treatment on oxidative biomarkers were evaluated, a significant interaction between smoking status and salivary superoxide dismutase levels at baseline and after treatment was reported.[181] Smokers had significantly lower reductions in superoxide dismutase levels after treatment in comparison with nonsmokers and former smokers. The authors implied that cigarette smoking influences redox homeostasis and alters antioxidant levels in favor of ROS.[181] Consistently, superoxide dismutase levels were found to be significantly lower in smokers than in nonsmokers and, most interestingly, the antioxidant levels of heavy smokers differed from those of light smokers, implicating that tobacco consumption influences superoxide dismutase levels in a dose-dependent manner.[182] In systemic bone health, smoking elicits similar effects on the RANKL/OPG ratio and, thus, disrupts the balance in bone remodeling.[183] In summary,

smoking accelerates bone turnover and resorption via increasing RANKL/OPG ratio in both systemic and alveolar bone; smoking is also associated with a build-up of oxidative stress from diminished antioxidant capacity, thereby rendering the periodontal tissue more susceptible to damage.

9. INTERDISCIPLINARY MANAGEMENT AND THERAPEUTIC IMPLICATIONS

While osteoporosis may be considered a risk modifying factor for periodontitis,[184] there is insufficient evidence to suggest periodontitis influence systemic BMD. However, the correlation between alveolar bone loss/CAL and systemic BMD could serve as the basis for dentists to screen for potential fracture risk when treating patients with severe periodontitis. Osteoporosis is a “silent bone killer,” which is often undiagnosed until the first osteoporotic fracture. Early detection and diagnosis of osteoporosis will be instrumental for prevention of debilitating fractures. It should be advisable for dentists to identify patients with multiple shared risk factors, such as aging and smoking, and based on the periodontal status, recommend these patients to perform fracture risk assessment with their primary care physicians. Several groups have devised digital assessment tools to analyze intraoral and panoramic radiographs for alveolar bone loss, with the intent that routine dental radiographs could serve as a low-cost tool to screen and predict fracture risk.[32,33] Conversely, it should also be recognized that patients with fracture risk beyond the intervention threshold are at greater risk for developing severe periodontitis and undergo tooth loss.[185] Routine dental care should be recommended for patients who are under treatment for osteoporosis and possess shared risk factors for periodontitis.

Intriguingly, while osteoporosis and periodontitis are managed independently, treatment for osteoporosis has shown to improve alveolar bone loss and periodontal attachment loss, such as in a longitudinal study on the effect of hormone replacement therapy.[186,187] Modifiable, shared risk factors, such as nutritional deficiency and smoking, could be proactively managed via supplementation of vitamin D and smoke cessation programs, respectively. While the optimal dosage is still unclear, the beneficial effect of oral supplementation of vitamin D and/or calcium on periodontal conditions is well supported.[188–191] Smoke cessation has significant impact on both prevention of vertebral fracture[172,192] and improvement of periodontal conditions.[193]

Other Food and Drug Administration (FDA) -approved treatment modalities for osteoporosis have, to various extent, shown positive impact on the treatment of periodontitis. Antiresorptive therapies such as oral bisphosphonates, as an adjuvant therapy to non-surgical management of periodontitis, showed promising efficacies.[194,195] However, emerging evidence suggests significant risks for complications of medication-related osteonecrosis of the jaw (MRONJ) arising in patients using bisphosphonates or the RANKL antibody Denosumab who undergo invasive dental treatments or even occasionally non-surgical debridement.[196,197] As such, the risks for these complications are deterrent for the therapeutic application of antiresorptives in periodontal treatment. Bone anabolic agents such as PTH (teriparatide) is approved for treatment of osteoporosis. Limited evidence

on rodent models suggests that PTH administration may also attenuate periodontal inflammation and bone loss, suggesting a promising therapeutic option.[198–200] Another bone anabolic agent Romosozumab, a SOST antibody was recently approved for osteoporosis treatment. In rodent models, Romosozumab stimulated periodontal bone regeneration after experimental periodontitis and promoted peri-implant osseointegration.[201–204] While these anabolic agents could restore the inflammation-induced uncoupling of bone remodeling, further studies are required to assess their potentials in periodontal treatment as an adjunct therapy.

10. CONCLUSION

Osteoporosis and periodontitis are both inflammation-driven, age-related bone disorders. Increasing evidence strongly supports a correlation between systemic and alveolar bone loss, while moderately suggesting a correlation between systemic BMD and periodontal attachment loss. In both diseases, age-related oxidative stress and senescence are underlying mechanisms that drive a pro-inflammatory tissue microenvironment, thereby causing an uncoupling of bone remodeling process. These mechanistic links are at play in their shared risk factors including vitamin D deficiency and smoking. Understanding these factors and their interplay calls for well-controlled longitudinal studies to examine the interdisciplinary management and potential therapeutics to address both diseases.

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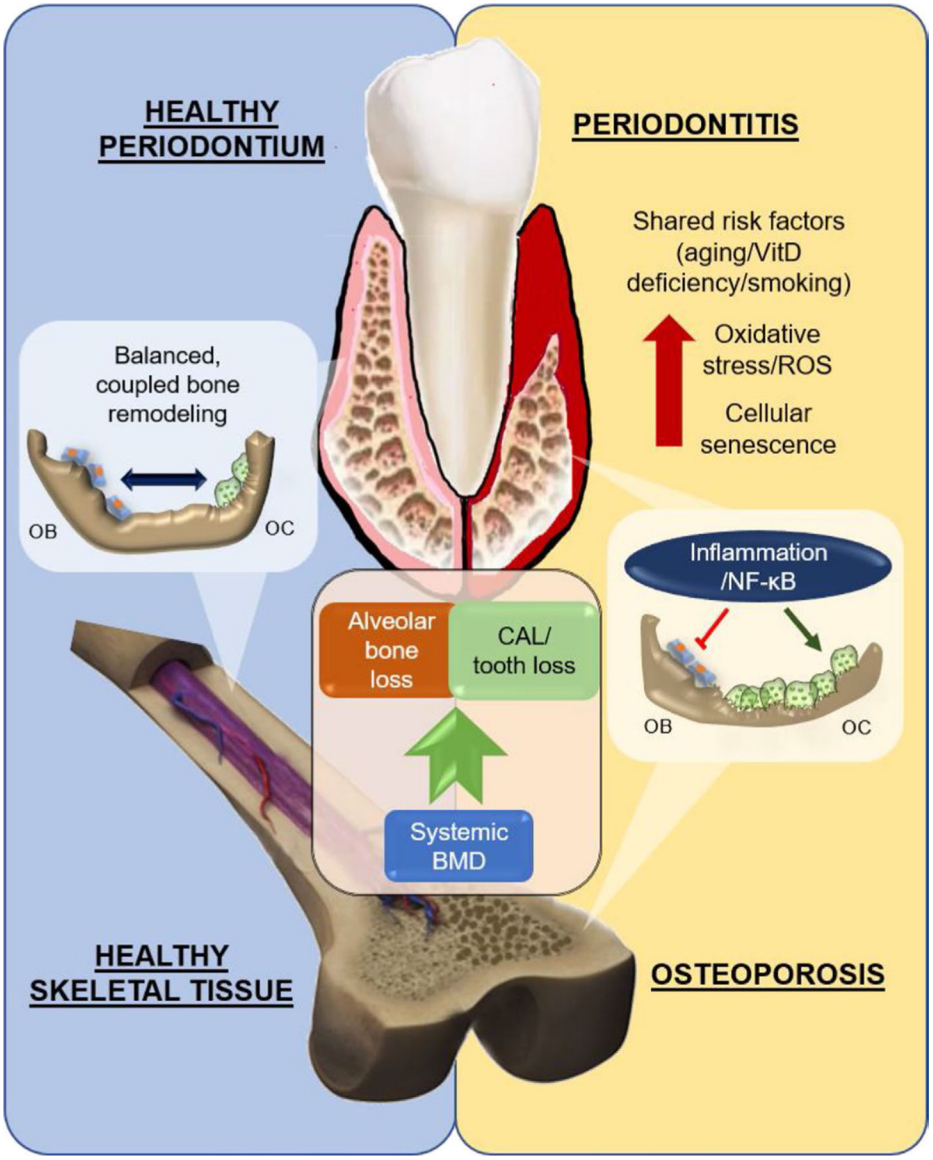

FIGURE 1.

Schematic of the association between periodontitis and osteoporosis. Low systemic bone mineral density (BMD) is linked to alveolar bone loss and clinical attachment loss (CAL). In healthy periodontium and skeletal tissue, osteoblasts (OB) and osteoclasts (OC) function in an orchestrated balance to achieve bone homeostasis. In both periodontitis and osteoporosis, shared risk factors, such as aging, vitamin D deficiency, and smoking, escalate the oxidative stress and cellular senescence in the tissue microenvironment. Mechanistically, the exacerbation of inflammatory response, through activation of NF-κB signaling, inhibits osteoblasts while promoting osteoclasts, resulting in a net bone loss

TABLE 1

Summary of literature on the correlation between alveolar bone loss and systemic BMD

Study	Year	Sample size	Oral bone loss determinant	Osteoporosis determinant	Age (years)	Patient population	Correlation: ABL and systemic BMD
Okabe et al[17]	2008	659	MCW (pano)	DXA heel	80	262 men and 397 women	Yes
Brennan et al[18]	2008	1256	ACH (intraoral)	DXA forearm, hip, spine	66.6 ± 7.0	Postmenopausal women	Yes (among women <70 years)
Ishii et al[19]	2007	54	MCW, ABL (pano)	DXA femur	56.8 ± 7.7	Postmenopausal women	Yes (MCW); not strong (ABL)
Taguchi et al[20]	2007	450	MCW (pano)	DXA spine	57.2 ± 8.1	Postmenopausal women	Yes
Takaishi et al[21]	2005	40	alveolar BMD (intraoral)	DXA spine, ultrasound	59.4 ± 5.6	Postmenopausal women	Yes
Hilderbolt et al[22]	2002	49	ACH (intraoral)	DXA spine, femur	60 ± 5.5	Postmenopausal women	Yes
Jonasson et al[23]	2001	80	alveolar BMD (intraoral)	DXA forearm	47 ± 27	Mixed	Yes
Tezal et al[24]	2000	70	ABL (intraoral)	DXA spine and femur	62.1 ± 7.1	Postmenopausal women	Yes
Taguchi et al[25]	1999	90	MCW, ABL (pano)	QCT spine	54.1 ± 7.4	Mixed	Yes (MCW); no(ABL)
Payne et al[26]	1999	38	ACH, alveolar BMD (intraoral)	DXA spine	53.9 ± 0.4	Postmenopausal women	Yes (ACH and alveolar BMD)

TABLE 2

Summary of literature on the correlation between periodontal attachment loss and systemic BMD

Study	Year	Sample size	Periodontitis determinant	Osteoporosis determinant	Age (year)	Patient population	Correlation between CAL and BMD
Mashalkar et al[39]	2018	94	CAL > 5 mm on 30% site	DXA spine	45–60	Postmenopausal women	Yes
Passos-Soares et al[40]	2017	492	PD > 5 mm with CAL > 6 mm	None	66.6 ± 7.4	Postmenopausal women	Yes (osteoporosis treatment with CAL)
Penoni et al[41]	2016	134	PD > 5 mm with CAL > 6 mm	DXA femur, spine	69.8 ± 3.9	Postmenopausal women	Yes
Juluri et al[42]	2015	100	CAL, PD	DXA spine	60.2 ± 2.1	Postmenopausal women	Yes
Singh et al[43]	2014	78	PD, CAL, tooth loss	DXA femur, spine	46–54	Postmenopausal women	Yes (CAL and PD), No (tooth loss)
Tak et al[44]	2014	2990	CAL, tooth loss	DXA femur, spine	64 ± 8	Postmenopausal women	Yes (spine BMD only)
Gondim et al[45]	2013	148	tooth loss, CAL	DXA femur, spine	58.9 ± 4.3	Postmenopausal women	Yes
Passos et al[46]	2013	521	PD>5mm with CAL>6mm	DXA femur, spine	60.6 ± 7.3	Postmenopausal women	Yes
Iwasaki et al[47]	2013	397	CAL, tooth loss, BOP	DXA femur, spine	68.2	Postmenopausal women	Yes
Marjanovic et al[48]	2013	380	PD > 5.5 mm or CAL > 7 mm	DXA femur, spine	58 ± 4.7	Postmenopausal women	No
Moeintaghavi et al[49]	2013	60	PD, CAL, tooth loss	DXA femur, spine	50.8–56	Postmenopausal women	No
Grocholewicz et al[50]	2012	37	CAL, tooth loss	DXA femur, spine, and forearm	59.4 ± 5.6	Postmenopausal women	Yes
Al Habashneh et al[51]	2010	400	PD > 5 mm with CAL > 6 mm	DXA femur, spine	62.5 ± 6.4	Postmenopausal women	Yes
Nicopoulou et al[63]	2009	665	tooth loss	DXA spine, femur	45–70	Mixed	Yes
Brennan et al[18]	2007	1329	CAL	DXA spine, femur, forearm	66.6 ± 7.0	Postmenopausal women	Yes (without subgingival calculus)
Gomes-Filho et al[52]	2007	139	PD > 4 mm with CAL > 3 mm	DXA femur, spine	58.8 ± 6.4	Postmenopausal women	Yes
Taguchi et al[53]	2004	1298	tooth loss	DXA femur, spine	70.8 ± 9	Mixed	Yes (femur BMD only)
Mohammad et al[54]	2003	30	tooth loss; CAL	DXA calcenaous	63.4 ± 8.6	Postmenopausal women	Yes
Pilgram et al[55]	2002	135	PD, CAL	DXA femur, spine	41–70	Postmenopausal women	No (weak)
Lundstrom et al[56]	2001	36	BOP; PD; recession;	DXA femur	70	Mixed	No
Tezal et al[24]	2000	70	CAL, PD, BOP	DXA femur, spine	62.1 ± 7.1	Postmenopausal women	No
Weyant et al[57]	1999	293	CAL, PD, BOP	DXA femur and spine;	75.5 ± 4.4	Mixed	No
Taguchi et al[25]	1999	90	tooth loss	CT spine	54.1 ± 7.4	62 postmenopausal	Yes (posterior teeth only)
Mohammad et al[58]	1997	44	tooth loss; CAL; PD	DXA spine	65.2 ± 1.6	Postmenopausal women	Yes (CAL) No (PD and tooth loss)
Hildebolt et al[59]	1997	135	tooth loss; CAL; PD	DXA femur, spine	59 ± 6.2	Mixed	No
Mohammad et al[60]	1996	42	CAL; recession	DXA spine	68 ± 6.8	Postmenopausal women	Yes (gingival recession)
Krall et al[64]	1996	189	tooth loss	DXA femur, spine	60 ± 6	Postmenopausal women	Yes

Study	Year	Sample size	Periodontitis determinant	Osteoporosis determinant	Age (year)	Patient population	Correlation between CAL and BMD
May et al[65]	1995	874	tooth loss	DXA femur, spine	65–76	Mixed	Yes in men, No in women

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment loss; DXA, dual energy X-ray absorptiometry; PD, probing depth.