Literature Review

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THE INTERRELATIONSHIP BETWEEN OSTEOPOROSIS AND ORAL BONE LOSS

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Abstract
Osteoporosis is a systemic skeletal disease manifested by reduced bone strength, decreased bone mineral density, and alteration of bony architecture. It can develop when bone resorption significantly overrides bone formation, either through imbalance in the genesis and apoptosis of osteoblasts and osteoclasts or through inappropriate regulation of bone remodeling. Oral bone loss (e.g., periodontitis, tooth loss, and implant bone loss) is caused by breakdown of bone homeostasis in the oral cavity. Both osteoporosis and periodontitis are bone-resorptive, host-dependent, multifactorial diseases, and bone loss is stimulated, systemically or locally, by cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-alpha. Although some contradictory results exist, a large body of literature supports an association between systemic and oral bone loss. Individuals with systemic or oral bone loss should be closely managed with a clinical protocol that minimizes further deterioration of systemic or oral bony structures. Additional studies are needed to clarify the causality and/or association between systemic and oral bone loss and to determine the most efficacious therapeutic approach for the prevention and treatment of systemic/oral bone loss.

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Introduction

Osteoporosis is a systemic skeletal disease manifested by reduced bone strength, decreased bone mineral density (BMD), and altered macrogeometry and microscopic architecture, and resultant increased risk of fractures. A recent report revealed that osteoporosis affects more than 10 million individuals aged 50 years or more; an additional 33.6 million are affected by osteopenia (low bone mass) and consequently are at risk for osteoporosis and its complications.[1] Because of the positive relationship between age and bone loss, the prevalence of osteoporosis increases from 19% among women 65- to 74- years old to more than 50% in women aged 85 years or more.[1] As the elderly population continues to grow, the number of people aged 50 or more with osteoporosis is expected to increase to 12 million by 2010 and to nearly 14 million by 2020.[1]

In the United States (U.S.) approximately 1.5 million fractures each year are attributable to osteoporosis, as are approximately 500,000 hospitalizations, 800,000 emergency department visits, 2.6 million physician visits, and 180,000 nursing home placements.[1] Worldwide, the morbidity, mortality, and healthcare costs related to osteoporosis and resulting in low-trauma fractures are significant.[1]

Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density (BMD) that is 2.5 standard deviations (SDs) below the young normal.[2] Osteopenia is defined as a BMD between 1 and 2.5 SDs (Table 1).[2] According to the WHO assessment, the patient is assigned a score that represents a comparison to the average young (25- to 45-year-old) healthy adult of the same gender (a T-score) or to the average healthy age- and sex-matched patient (a Z-score). A

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1-unit change in T-score corresponds to a 1-SD difference in BMD from that in a young, healthy individual of the same gender. Thus, osteoporosis corresponds to a T-score of –2.5 or lower, whereas osteopenia corresponds to a T-score between –1 and –2.5.[2]

A number of methods are currently used to assess bone density, including single-photon absorptiometry, dual-photon absorptiometry (DPA), dual-energy x-ray absorptiometry (DXA), quantitative computed tomography, and radiographic absorptiometry (RA). Of these, DXA is considered the preferred technique for measurement of BMD.[3] DXA measures bone density as "area density" in units of grams per square centimeter. The sites most often used for DXA measurement of BMD include central sites such as the spine or hip, or peripheral sites such as the radius.

Although the etiology of osteoporosis has not been clearly defined, the initiation and progression of osteoporosis are known to be multifactorial. Osteoporosis is frequently seen in postmenopausal women and women who have undergone ovariectomy.[4] The incidence of osteoporosis is dependent on age, gender, menopausal status, environmental factors, and systemic health status, with Caucasian postmenopausal women representing the highest risk group.[4,5] Risk factors for osteoporosis may include, but are not limited to: genetics, aging, early menopause, physical inactivity, heavy smoking, alcohol abuse, low calcium intake, and long-term use of certain medications (e.g., glucocorticoids, antiepileptic agents, gonadotropin-releasing hormone agonists, excessive thyroxine doses, lithium, and anticoagulants). Certain systemic diseases also represent risk factors (e.g., primary hyperparathyroidism, hypogonadism, multiple myeloma, leukemia, rheumatoid arthritis, celiac disease, gastrectomy, and chronic obstructive pulmonary disease), with some of these factors being modifiable (Table 2).[6-8] The guidelines proposed by the North American Menopause Society indicate that some risk groups should be regularly assessed for osteoporosis, including all women aged ≥65 years, all women with a medical condition that can cause bone loss, and younger postmenopausal women who possess a risk factor for osteoporosis.[3]

Table 1: World Health Organization criteria for defining osteoporosis and osteopenia

Condition	Description
Normal	BMD ≤1 SD below the mean for a young, healthy adult (T ≥ –1.0)
Osteopenia	BMD >1 SD, but <2.5 SD below the mean for a young, healthy adult (–1.0 > T > –2.5)
Osteoporosis	BMD ≥2.5 SD below the mean for a young, healthy adult (T ≤ –2.5)
Established osteoporosis	BMD ≥2.5 SD below the mean for a young, healthy adult (T ≤ –2.5), with 1 or more fragility fractures

T score = 1 SD difference from the BMD in a young, healthy adult of the same gender. BMD, bone mineral density; SD, standard deviation; WHO, World Health Organization. Modified from Report of a WHO Study Group[2]

In a healthy individual, bone resorption and bone formation are in equilibrium, allowing the body to maintain bone mass and mineral density. Bone homeostasis is maintained at the cellular level by 2 highly specialized cell types, osteoclasts and osteoblasts, which are responsible for bone resorption and formation, respectively. The bone-remodeling cycle consists of a resorptive phase, which occurs over a 3- to 4-week period, followed by the reversal phase and, finally, the formative phase (Figure 1).[9] During the human life, the formation of a basic multicellular unit (BMU), which includes osteoblasts and osteoclasts, constantly takes place through the coupling of bone formation and resorption.[10] On average, the adult skeleton contains more than 1 million BMUs at any time, with almost 5-fold more located in the trabecular bone compared with the cortical bone.[11]

Bone resorption is initiated via a resorptive stimulus produced by cytokines or mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), parathyroid hormone (PTH), PTH-related protein (PTHrP), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNF-α).[12,13] In response to a specific stimulus, preosteoclasts are recruited from the hematopoietic lineage into the area of bone resorption and differentiate into active osteoclasts.[14] The active multinuclear osteoclasts form resorption pits for active bone resorption. Osteoclasts possess the ruffled membrane and clear zone that ensure the resorption process remains localized beneath the osteoclast, maintaining the pH-regulating proton pump in the bone resorptive microenvironment. Resorption gradually slows and eventually ceases as the active osteoclasts are replaced with transient mononuclear cells; this is the reversal phase. The formative phase then begins with recruitment of pre-osteoblasts (mesenchymal precursor cells) into the site. This is followed by differentiation of pre-osteoblasts into osteoblasts via the action of bone morphogenetic proteins (BMPs). In this stage, some osteoblasts are entrapped in the bone matrix and become osteocytes. Through the coupled process of bone resorption and formation, on average, an exchange of 10% of the

skeleton occurs every year over an individual's lifetime. If there is significant imbalance in the genesis and apoptosis (programmed cell death) of the bone-forming or bone-resorbing cells, osteoporosis or osteopenia may develop. Inappropriate regulation of bone remodeling can also lead to the net bone loss seen in osteopenia and osteoporosis.

Osteoporosis and oral bone loss: association versus causality

Periodontitis, a major cause of tooth loss, is clinically determined by radiographic bone loss and/or clinical attachment loss (CAL). The prevalence of periodontitis in the U.S. population, if defined as at least 1 site with CAL of >2 mm, is approximately 80% in all adults affected by bone loss, and approximately 90% in those aged 55 to 64 years.[15] Although bacterial plaque is the primary cause of periodontitis, host susceptibility or responsiveness is believed to play a major role in the initiation and progression of tissue destruction.[16,17] Both osteoporosis and periodontitis are bone-resorptive, host-dependent, multifactorial diseases, and the bone loss in both diseases is exaggerated, either systemically or locally, by the activity of cytokines (e.g., IL-1 and IL-6). In this section, studies of the relationship between systemic bone loss (i.e., BMD) and oral bone loss (e.g., alveolar bone loss [ABL] and subsequent tooth loss) are explored. A summary of these studies is given in Table 3.

The relationship between systemic BMD and tooth loss was investigated in 1,365 Caucasian early-postmenopausal women.[18] BMD was measured by DXA at the lumbar spine and proximal femur. Among the study population, 445 (33%) were osteoporotic, 694 (51%) were osteopenic, and 226 (16%) had normal BMD. The results revealed no significant correlation between tooth count and systemic BMD, showing that tooth count is not a good indicator of the risk of osteoporosis. The findings in this study correspond to those in a previous cross-sectional study by Elders and colleagues,[19] who demonstrated that there was no significant association between systemic BMD (in this case, lumbar BMD and metacarpal cortical thickness) and clinical parameters of periodontitis, including mean probing depth (PD), bleeding on probing (BOP), alveolar bone height (ABH), and number of missing teeth.

However, other studies[20-22] have shown contradictory results. Klemetti and colleagues[20] conducted a cross-sectional study in 227 healthy postmenopausal women, aged 48 to 56 years, and found a correlation between skeletal BMD and number of remaining teeth in the patient population. Individuals with high skeletal BMD appeared to retain their teeth with deep periodontal pockets more often than did those with osteoporosis. The correlation between systemic BMD and tooth loss was confirmed by a longitudinal study in which 189 Caucasian postmenopausal women were followed for up to 7 years.[22] Systemic BMD was measured at the lumbar spine, femoral neck, and whole body using either DPA or DXA, and the values measured from the 2 different instruments were adjusted. For the 7-year study period, 45 women reported tooth loss, and BMD declined as a whole body (–0.26%/year) and at the femoral neck (–0.02%/year), but increased in the spine (+0.42%/year). The relative risk of tooth loss relative to BMD changes of 1%/year was 4.83 for the body as a whole, 1.50 for the femoral neck, and 1.45 for the spine,

Table 2
Risk factors for osteoporosis

Studies	Risk relationship with osteoporosis	Modifiable with ?
Age	Older	No
Gender	Female	No
Genetics	Predilection	No
Menopause	Early menopause	No
Ethnicity	Asian or Caucasian women	No
Bone mass	Low	Treatment for osteoporosis/osteopenia
Calcium intake	Low	High-calcium diet
Physical activity	Negative	Weight-bearing exercise
Smoking	Positive	Smoking cessation
Alcohol consumption	Positive	Decreased alcohol consumption
Certain systemic diseases (e.g., hyperparathyroidism)	Positive	Treatment of the systemic disease
Certain medications (e.g., glucocorticoids)	Long-term use	Treatment modification if feasible

thus indicating a correlation between systemic BMD and tooth loss. Other independent predictors of tooth loss were years post menopause and number of teeth at baseline.

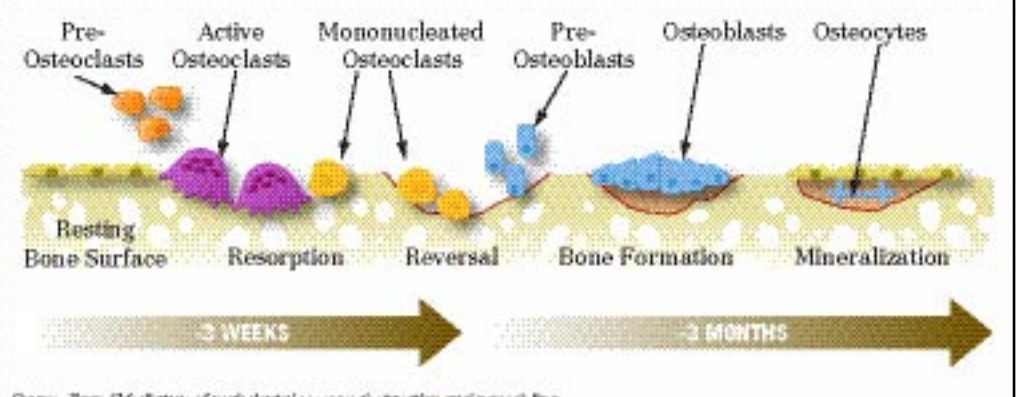
The relationship between systemic and oral bone loss has also been explored using other measures such as hip BMD, metacarpal BMD, lumbar BMD, forearm BMD, presence/absence of osteopenia/osteoporosis, CAL, ABH, and the Community Periodontal Index of Treatment Needs (CPITN).[23-30]

Tezal and colleagues,[26] in a cross-sectional study using 70 dentate postmenopausal Caucasian women aged 51 to 78, evaluated the relationship between systemic bone loss and periodontal disease. Systemic BMD was measured by DXA at the lumbar spine and femur, and periodontal condition of the study population was examined by CAL, ABL, number of remaining teeth, gingival index, plaque index, and calculus index. Multiple linear regression analyses adjusting for age, age at menopause, estrogen supplementation, bone mass index (BMI), smoking, and supragingival plaque, demonstrated that BMDs at all femoral regions and the spine were correlated with ABL (r = –0.20 to –0.27), with statistical significant correlations found for the trochanter, Ward's triangle, and total femur (r = –0.25 to –0.27). Also, CAL was consistently, though not significantly, correlated to spinal and femoral BMD (r = –0.17 and r = –0.10 to –0.16). The results of the study suggested that systemic bone loss may be a risk indicator for periodontal attachment and bone loss.

Inagaki and colleagues[30] studied the relationship between systemic and oral bone loss in 171 premenopausal (mean age: 37.9±8.0 years) and 185 postmenopausal (mean age: 63.3±7.7 years) Japanese women. Metacarpal BMD as measured by computerized radiograph densitometry was used to determine systemic bone loss, whereas CPITN (scored by examiners blinded to the subjects' metacarpal BMD status) was used to determine oral bone loss. The results demonstrated that the proportion of subjects with periodontitis (CPITN = 3 or 4) increased as metacarpal BMD decreased. The odds ratio of osteopenia/osteoporosis to periodontitis was 3.2 (2.0 when adjusted for age and menopausal status). The study also found that postmenopausal women with less than 20 teeth were more likely to have low metacarpal BMD when compared with postmenopausal women with more than 20 teeth (1.6 vs. 1.0). The study suggests that an association may exist between systemic bone loss and periodontitis, independent of age and menopausal status, and that systemic bone mineral status might be related to tooth count in postmenopausal Japanese women.

Causality between systemic and oral bone loss has been tested in several longitudinal studies.[28,29,31] In a 2-year longitudinal study exploring the association between cigarette smoking and ABL in 59 postmenopausal females (38 nonsmokers and 21 smokers), both smokers and osteoporotic/osteopenic subjects experienced mean ABL during the study period.[28] Mean alveolar bone gain was noted only in nonsmokers with normal bone BMD. The results suggest that smoking and osteoporosis/osteopenia can be risk factors for ABL. Recently, Yoshihara and colleagues[29] conducted a 3-year longitudinal study in 179 gender-matched Japanese community-dwelling elderly to investigate the relationship between periodontal disease and systemic BMD. Patients did not smoke or have diabetes, had more than 20 teeth, and were not taking medications for osteoporosis. BMD was measured at the heel using an ultrasound bone densitometer, and the presence/absence of osteopenia was determined by stiffness values (a combination of speed-of-sound and broadband ultrasound attenuation as the signal travels through bone). Stiffness was indicated in the bone densitometer as a percentage of the value for a healthy younger individual. Osteopenia

Figure 1: Bone-remodeling cycle



Source: From "Mediators of periodontal osseous destruction and remodeling: Principles and implications for diagnosis and therapy," published in J Periodontol.

The bone-remodeling cycle begins with the resorptive phase, during which preosteoclasts are recruited and differentiated into active osteoclasts, leading to bone resorption. After active bone resorption, multinucleated osteoclasts are replaced by mononucleated osteoclasts lining the resorption lacunae; this is followed by recruitment of preosteoblasts through coupling (the reversal phase). The recruited preosteoblasts are differentiated into active matrix-secreting cells, forming bone and undergoing mineralization (the formative phase). Recreated from McCauley and Nohutcu.[9]

was defined as a stiffness value ≤85 for 70-year-old males and ≤69 for females. Periodontal disease status was examined by periodontal probing using a pressure-sensitive periodontal probe[i]. At the 3-year follow-up, the number of progressive sites (CAL ≥3mm during the 3 years) was significantly higher in the osteopenic group than in the non-osteopenic group (P< .05). Also, multiple linear regression analysis showed that BMD was associated with the number of progressive sites (CAL ≥3mm during the 3 years) (P=.001), suggesting a significant relationship between periodontal attachment loss and systemic BMD.

Jeffcoat and colleagues[23] examined mandibular basal BMD and hip BMD in 158 postmenopausal women (mean age: 62.2 years) using quantitative digital intraoral radiography and DXA, respectively. The study found a significant correlation between mandibular basal BMD and hip BMD, and suggested that intraoral radiography could serve as a screening tool for osteopenia.

In an older, ethnically diverse population (1,084 subjects aged 60 to 75 years), Persson and colleagues[32] studied the prevalence of self-reported history of osteoporosis, the

Table 3
Studies on the relationship between systemic and oral bone loss

Studies	Population	Oral Measure	Systemic Measure	Study Type	Results
Earnshaw and colleagues[18]	1,365 Caucasian women (45-59 years old	Tooth count	Lumbar/proximal femur/BMD	CS	No relationship
Elders and colleagues[19]	286 women (46-55 years old)	ABH/tooth count	Lumbar BMD/MCT	CS	No relationship
Klemetti and colleagues[20]	227 PM women (48-56 years old)	ABH/tooth count	Skeletal BMD	CS	Correlation
Mohammad and colleagues[21]	30 PM Asian-American women	CAL/tooth count	os calcis BMD	CS	Correlation
Krall and colleagues[22]	189 Caucasian PM women	Tooth loss	Skeletal BMD	7-year LS	Correlation
Jeffcoat and colleagues[23]	158 PM women 62.2±7.6 years	Mandibular basal BMD	Hip BMD	CS	Correlation
Hildebolt and colleagues[24]	135 PM women (41-70 years old)	CAL	Lumbar/proximal femur BMD	CS	Correlation between years of PM and CAL
Kribbs[25]	112 women (50-85 years old)	CAL	OP (yes/no)	CS	No relationship
Tezal and colleagues[26]	70 PM Caucasian women (51-78 years old)	CAL/ABH	Skeletal BMD	CS	Correlation
von Wowern and colleagues[27]	12 OP and 14 normal women	CAL	Forearm BMD	CS	Correlation
Payne and colleagues[28]	38 PM women	ABH/ABD	Normal vs. OP/osteopenia	2-year LS	Correlation
Yoshihara and colleagues[29]	179 Japanese women and men (70 years old)	CAL	Normal vs. osteopenia	3-year LS	Correlation

ABD, alveolar bone density; CS, cross-sectional; LS, longitudinal study; MCT, metacarpal cortical thickness; MRRH, mandibular residual ridge height; OP, osteoporosis; PM, postmenopausal; PRM, premenopausal.

[i]VIVACARE TPS PROBE®, Schaan, Lichtenstein

agreement between panoramic radiographic findings of mandibular cortical index (MCI) and self-reported osteoporosis, and the likelihood of having both a self-reported history of osteoporosis and a diagnosis of periodontitis.[32] The study results demonstrated a positive MCI (indicative of bone loss) in 38.9% of the subjects, whereas only 8.2% of the subjects self-reported osteoporosis. The intraclass correlation between MCI and self-reported diagnosis of osteoporosis was marginal, but statistically significant (0.20, P<.01), and the likelihood of an association between MCI and osteoporosis was 2.6 (P<.01), suggesting an association between osteoporosis and periodontitis. The study also suggests that oral health practitioners can screen osteoporotic elderly individuals by means of dental panoramic radiographs taken for diagnosis of the teeth and jawbones.

In interpreting the above studies, risk indicators must be differentiated from risk factors. A risk indicator is defined as a probable or putative risk factor, detected in case-control or cross-sectional studies, but not confirmed by longitudinal studies. A risk factor is defined as any environmental, behavioral, or biological factor confirmed by a temporal sequence. Risk factors are verified by longitudinal studies and indicate a part of a causal chain. With regard to the relationship between systemic and oral bone loss, primarily cross-sectional studies have been performed, and the findings are somewhat contradictory. These contradictory results may be the result of differing populations, small sample sizes, different methods used to assess BMD, and lack of adequate control of confounding factors (e.g., smoking or concurrent therapies).

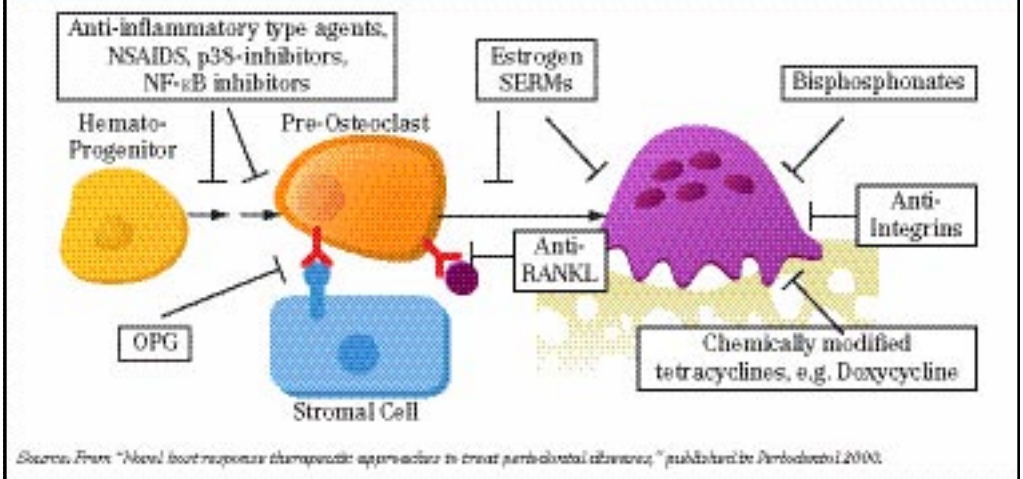
In summary, although the causality between systemic bone loss and oral bone loss has not been determined, the evidence demonstrates a plausible association between the 2 disease entities. Study results imply that individuals with either systemic or oral bone loss should be closely managed with a clinical protocol that minimizes further deterioration of systemic or oral bony structures. Additional randomized, controlled clinical trials are needed to clarify the causality and/or association between systemic and oral bone loss.

Implants and osteoporosis

Osteoporosis results in decreased bone quality and therefore may affect the outcome of dental implant therapy. In an animal study[33] evaluating the effect of glucocorticoid-induced osteoporosis on implant osseointegration, animals received intramuscular injections of glucocorticoids (7.5 mg/kg) for 8 weeks before, simultaneous with, or after implant placement, with a fourth group serving as the control. Although there was no difference in interfacial strength between the test and control groups, bone-to-implant contact (BIC) was significantly lower in the osteoporosis groups (range, 24%±16% to 42%±16%) compared with the control group (49%±10%). Similarly, another study[34] utilizing an ovariectomized rat model found that an osteoporotic state resulted in decreased BIC compared with controls. Furthermore, the greatest decrease in BIC was noted when an osteoporotic state was induced after osseointegration had occurred (BIC = 50% compared with 79% in the control group). The results of these studies imply that although osseointegration of implants in osteoporotic bone is possible, the long-term stability of the implants may be compromised by the disease.

Several studies[35-37] in humans have reported successful implant placement in osteoporotic individuals, although 1 case report[38] revealed that 5 implants failed in a patient 6 months after diphosphonate therapy was initiated. Becker and colleagues[39] conducted a case-control study in 98 patients, half of whom had osteoporosis, and found no correlation between DXA scores and implant failure. This study suggested that an assessment of bone quality at the implant site may be more valuable in predicting implant

Figure 2: Chemotherapeutics for treating systemic/oral bone loss



Source. From "Novel host response therapeutic approaches to treat periodontal diseases," published in Periodontol 2000.

Current approaches to treatment encompass 2 main categories of drugs: anti-resorptive agents and anabolic agents. NSAIDs, anti-RANKL agents, and OPG agents inhibit osteoclast differentiation and formation, whereas estrogen and SERMs inhibit osteoclast activity and promote osteoclast apoptosis. In addition, bisphosphonates promote osteoclast apoptosis, and anti-integrins block matrix adhesion, preventing osteoclastic bone resorption. Tetracyclines and their derivatives reduce MMP activity and consequent degradation of the organic matrix. Recreated from Kirkwood and colleagues.[42]

failure than DXA scores. A retrospective study[40] analyzing 16 osteoporotic patients who received implant therapy showed an overall implant survival rate of 97% in the maxilla and 97.3% in the mandible with a follow-up time of 6 months to 11 years. In addition, the marginal bone loss observed was consistent with that in other studies conducted in nonosteoporotic patients, indicating that osteoporosis does not adversely affect implant success. In contrast, von Wowern and Gotfredsen[41] evaluated whether the presence of mandibular osteoporosis increased marginal bone loss around implants over a 5-year period. No implant failures occurred in any of the 7 osteoporotic and 11 healthy patients, although marginal bone loss increased around the implants placed in patients with osteoporosis.

This literature review demonstrates that dental implants are a viable treatment option for patients with osteoporosis, although less BIC is attainable and there is a higher risk for marginal bone loss. More studies are needed to determine the long-term effects of osteoporosis in this patient population.

Chemotherapeutic agents for treatment of systemic/oral bone loss

Current approaches to treating systemic/oral bone loss with chemotherapeutic agents encompass 2 types of agents: anti-resorptive agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], matrix metalloproteinase [MMP] inhibitors, and bisphosphonates) and anabolic agents (e.g., estrogen and selective estrogen receptor modulators [SERMs] and teriparatide [PTH]). Anti-resorptive agents alter the host response by targeting various cell types in order to minimize net bone resorption. Frequently this involves inhibiting osteoclast activity through numerous mechanisms. Conversely, anabolic agents act to increase net bone deposition, through both stimulation of osteoblast activity and inhibition of osteoclastic bone resorption. Both therapeutic strategies target various steps in the osteoclast differentiation and resorption pathways (Figure 2).[42] These include inhibiting early differentiation signals, such as those from cytokines and inflammatory mediators (e.g., PGE_2 and cyclo-oxygenase 2 [COX-2] inhibitors). Other approaches include preventing osteoclast differentiation by manipulating the receptor activator of the NF-κB ligand (RANKL) pathway through decoy receptors such as osteoprotegerin (OPG), anti-RANKL therapeutic agents, or estrogen/SERMs. Finally, many chemotherapeutic agents are designed to prevent osteoclastic bone resorption by altering osteoclast function. This may include preventing osteoclast adhesion to the bone substrate, preventing formation of the resorptive sealing zone, or inducing premature osteoclast apoptosis. Other types of therapeutic agents, such as PTH, have unknown mechanisms of action. This section will briefly discuss the chemotherapeutic agents used for systemic/oral bone loss along with relevant studies of those agents (Tables 4a and 4b).

Anti-resorptive agents

NSAIDs. Inflammation-induced bone resorption is mediated in part by arachidonic acid metabolites, including prostaglandins and COX-2. These substances are increased in areas of inflammation, notably in the gingiva of periodontitis patients, and they stimulate bone resorption by enhancing expression and potentiating the effects of RANKL.[43-45] NSAIDs inhibit the production of these inflammatory mediators and consequently are used to inhibit osteoclast formation and thereby decrease oral bone loss.[46,47] Williams and colleagues[48] studied the effects of flurbiprofen on naturally occurring periodontitis in a canine model. In this study, beagle dogs were treated with either surgical or nonsurgical periodontal therapy in combination with either flurbiprofen or placebo. For up to 12 months, flurbiprofen significantly decreased the rate of radiographic ABL; this same result did not occur in the placebo group. A human case-control study of 22 patients taking NSAIDs for other medical conditions (e.g., arthritis) found that these patients, when compared with matched controls, displayed lower Gingival Index (GI) scores and shallower pocket depths.[49] A 3-year longitudinal trial[50] assessed the effects of NSAIDs on periodontal disease progression in 44 adult patients with advanced periodontitis. Following periodontal therapy, patients self-administered 50 mg flurbiprofen or placebo twice daily (bid) for 24 months. After 3 years, 33 compliant patients were available for follow-up. Flurbiprofen significantly arrested the progression of bone loss in these patients when compared with controls. Use of these drugs for prevention of oral bone loss has decreased in recent years because of the need for long-term systemic administration and the resultant side effects,[51] although local-delivery applications are being pursued with some success.[52]

MMP inhibitors. MMPs are enzymes that play an important role in extracellular matrix remodeling. MMP activity is increased in areas of inflammation, including periodontitis, leading to unwanted amounts of tissue destruction.[53] Studies have shown that reducing MMP levels in areas of periodontal destruction results in positive clinical outcomes.

Therapeutically, several medications are available to decrease MMP levels. These include bisphosphonates (discussed in the next section), tetracyclines and tetracycline derivatives, and synthetic anticollagenases (e.g., low-dose doxycycline [LDD]). Tetracyclines and their derivatives have the ability to chelate the cations of MMPs, inhibiting their function.[54] Tetracyclines can also inhibit neutrophil and osteoclast activity, thereby limiting their destructive capabilities.[54] MMP inhibition by tetracyclines occurs independently of the antibiotic properties of these agents.

Consequently, chemically modified tetracyclines have been developed that inhibit MMP activity without antimicrobial properties and their resultant side effects.[55] Alternatively, low-dose tetracyclines can also be used to achieve the same therapeutic goal.[56] One randomized 12-month study[57] of patients with chronic periodontitis examined the effects of nonsurgical periodontal therapy administered with and without LDD on MMP-8 levels in gingival crevicular fluid (GCF) and other clinical parameters. Patients who received LDD demonstrated significantly reduced MMP-8 levels for up to 6 months and also significantly reduced probing depths (PD) and GI scores for up to 12 months when compared with patients who did not receive LDD. Low-dose and chemically modified tetracyclines show promise as a therapeutic treatment for oral bone loss.

LDD therapy has also been shown to reduce oral fluid levels of MMP-8 and MMP-13 as well as levels of bone collagen breakdown fragments (cross-linked carboxyterminal telopeptide of type I collagen [ICTP]) when compared with placebo in patients with severe periodontitis and oral bone loss.[57-60] MMP-8 is the predominant type of collagenase found in diseased periodontal tissues and initiates the degradation of collagen.[61,62] Although MMP-8 reduction was also observed after mechanical periodontal therapy, LDD further suppressed MMP-8 levels, confirming the host-modulation effect of LDD. MMP-13 and ICTP are related to bone resorption, and their decrease after LDD therapy is consistent with the ability of LDD to function as a bone-sparing agent for potential applications in the management of osteoporosis.[59,63]

Table 4a
Chemotherapeutic agents for systemic/oral bone loss — anti-resorptive agents

Therapy	Mechanisms of action	Studies	Outcome
Anti-inflammatory agents	Inhibit inflammatory mediator production (PGE_2 and COX-2)	Williams and colleagues[48]	Flurbiprofen decreased radiographic bone loss at 12 mo.
		Waite and colleagues[49]	Lower GI and PDs in patients taking NSAIDs
		Williams and colleagues[50]	Flurbiprofen arrested bone loss progression over 3 yrs.
Bisphosphonates	Inhibit formation and resorptive capacity of osteoclasts Increase osteoclast apoptosis Inhibit MMP production Inhibit inflammatory mediator production	Reddy and colleagues[68]	Alendronate increased bone mass in dogs, but had no effect on periodontal parameters
		Tani-Ishii and colleagues[69]	Incadronate increased BMD and decreased PMN infiltration in rats
		Lane and colleagues[71]	Bisphosphonates improved CAL, PD, and BOP but did not increase BMD
		El-Shinnawi and El-Tantawy[72]	Alendronate increased BMD, but no effect on periodontal parameters
		Takaishi and colleagues[73]	Etidronate increased BMD density and decreased tooth mobility and PDs
MMP inhibitors	Inhibit MMP production Inhibit neutrophil and osteoclast activity	Emingil and colleagues[57]	LDD significantly reduced MMP-8 levels up to 6 mo. and significantly reduced PDs and GI indices up to 12 mo.
OPG	Inhibits osteoclast development	Bolon and colleagues[94]	Adenoviral delivery of OPG reduced bone loss in ovariectomized mice
		Bekker and colleagues[97]	A single injection of OPG reduced bone turnover in postmenopausal women for up to 6 wks.

Bisphosphonates. Bisphosphonates inhibit bone resorption through multiple mechanisms, although the main mechanisms involve inhibiting the formation and resorptive capabilities of osteoclasts and promoting osteoclast apoptosis.[13] Bisphosphonates also downregulate levels of several MMPs, including MMP-1, -3, -7 through -9, and -12 through -14,[64] even in the periodontal ligament cells.[65] Furthermore, some bisphosphonates have anti-inflammatory properties and inhibit the release of inflammatory mediators such as IL-6, TNF-α , and IL-1Beta.[66] Other research[67] suggests that secretion of osteocalcin by osteoblasts may also be affected by these drugs.

Preclinical studies[68,69] evaluating the effect of bisphosphonates on the periodontium reveal that although bisphosphonates prevent oral bone loss compared with controls, they provide no additional benefits in terms of reducing inflammation or PDs. Reddy and colleagues[68] studied the effects of alendronate on oral bone loss in 16 beagle dogs with naturally occurring periodontitis. At 6 months, alendronate resulted in a statistically significant difference in bone mass, although no differences in gingival inflammation, plaque, tooth mobility, or CAL were found when compared with controls. Similarly, another study[69] evaluated the ability of incadronate to prevent oral bone resorption in *Porphyromonas gingivalis*–induced periodontitis and found that it increased BMD and decreased polymorphonuclear leukocyte infiltration compared with controls. Human trials[70-73] have also provided conflicting results. A recent study[72] evaluating the effect of alendronate on ABL in 24 periodontitis patients over 6 months found that the use of this agent increased BMD, but provided no additional benefit for clinical parameters such as PD, CAL, and GI. However, a 12-month randomized controlled trial[71] found different results: Bisphosphonate therapy improved clinical parameters (CAL, PD, and BOP) when compared with placebo, but did not affect periodontal bone mass. In contrast, a long-term study[73] of 4 women receiving intermittent cyclical doses of etidronate revealed that bisphosphonates increased BMD and decreased tooth mobility and PDs. Bisphosphonates are highly concentrated in bone tissue and remain in the body for as long as 10 years.[74] Given this long half-life and recent reports of significant side effects such as osteonecrosis of the jaw,[75] additional research is urgently needed to determine appropriate uses for these drugs. Discussion and a case report on bisphosphonate-related osteonecrosis of the jaw are presented elsewhere in this issue.[76]

Receptor Activator of NF-κ (RANK), RANKL, and OPG. Osteotrophic factors such as hormones (e.g., vitamin D3, PTH, PTHrP), cytokines (IL-1, -6, -11, and -17), growth factors (TNF-α, and BMP-2) and other molecules (PGE_2, CD40L, and glucocorticoids) all enhance the expression of

Table 4b
Chemotherapeutic agents for systemic/oral bone loss — anabolic agents

Therapy	Mechanisms of action	Studies	Outcome
HRT/SERMs	Prevent cytokine production	Lopez-Marcos and colleagues[99]	HRT resulted in decreased PDs, less tooth mobility, and less dental pain
		Norderyd and colleagues[101]	Estrogen supplements decreased gingival bleeding
PTH	Specific mechanism unknown; anabolic actions in bone at intermittent low doses	Miller and colleagues[104]	PTH significantly increased crestal bone levels in ovariectomized rats
		Barros and colleagues[105]	PTH decreased bone resorption and inflammatory cell infiltrate in dogs
		Padbury and colleagues[106]	Hyperparathyroidism patients had increased tori and exostoses, but not increased periodontal disease
		Schneider and colleagues[107]	Intramembranous bone more amenable than endogenous vertebral bone to regeneration with PTH treatment

BOP, bleeding on probing; PMN, polymorphonuclear leukocyte; PTH, parathyroid hormone

the RANKL gene in bone-forming cells.[77,78] The RANKL–RANK interaction is responsible for the differentiation and maturation of osteoclast precursor cells to activate osteoclasts. OPG acts as a decoy receptor expressed by osteoblastic cells that binds to RANKL and inhibits osteoclast development.

Several studies have shown the opposite effect of RANKL and OPG in bone modulation. In pathologic bone resorption observed in bone metabolic conditions, inflammatory diseases, and certain types of cancer, the equilibrium of this interaction is dysregulated. In periodontal disease, the role of RANKL in alveolar bone resorption was first investigated by Teng and colleagues.[79] Several previous studies had suggested that T cells could modulate inflammation and/or alveolar bone resorption, but the mechanism by which host immune responses contribute to alveolar bone destruction remained unclear. Teng and colleagues orally inoculated severe combined immunodeficiency (SCID) mice with the periodontal pathogen, *Actinobacillus actinomycetencomitans*, which resulted in the upregulation of RANKL and alveolar bone destruction. This result suggests that RANKL expression by T cells plays a significant role in the bone destruction observed in periodontitis. Liu and colleagues[80] and Crotti and colleagues[81] demonstrated an overexpression of RANKL in inflamed periodontal tissues, suggesting expression by inflammatory cells. Also, the RANKL:OPG ratio was increased in subjects with periodontitis when compared with healthy subjects, suggesting that this molecular interaction may play an important role in modulating local bone loss. The RANKL:OPG ratio was found to be significantly increased in the GCF of patients with periodontitis when compared with healthy patients.[82] Delivery of OPG has been shown to be beneficial in blocking bone resorption in experimentally induced periodontitis.[83]

Preclinical studies[84-87] demonstrated a potential therapeutic role for OPG in the prevention and reduction of lytic bone lesions associated with skeletal tumors, prostatic carcinoma metastases, hypercalcemia of malignancy, and breast cancer. OPG blocked the increased osteoclast formation responsible for resorptive processes in patients with rheumatoid arthritis[88-90] and in periprosthetic bone tissue.[91-93] Gene therapy to provide life-long OPG delivery has also been proposed as a more practical treatment for chronic inflammatory diseases. OPG-expressing adenoviral (Ad) vectors provided sustained and efficacious levels of circulating OPG that enhanced BMD and reduced the number of osteoclasts for an extended period of time (18 months) in ovariectomized animals.[94] A gene therapy vector co-expressing OPG and administered in a single injection demonstrated complete inhibition of bone breakdown in a periprosthetic bone resorption model[95] and reversed osteopenia in ovariectomized animals, without resulting in liver toxicity.[96] OPG administered by single injection to postmenopausal women resulted in a significant decrease in bone collagen degradation products measured in urine, without adverse side effects, suggesting a potential use for OPG in osteoporosis treatment.[97] The anti-resorptive effect of a genetically engineered OPG-Fc construct was shown to be effective in inhibiting bone resorption in lytic bone disease associated with multiple myeloma.[98] In summary, based on preclinical animal studies and preliminary human studies, the OPG-RANKL-RANK axis is a new target for the treatment of destructive periodontal disease and other bone resorption–related diseases. Additional studies are needed to determine the most efficacious therapeutic approach to that molecular interaction.

Anabolic agents

Estrogen and SERMs. Estrogen functions to maintain bone mass, and its withdrawal leads to accelerated bone resorption, increased osteoclast activity, and subsequent bone loss. This loss of bone mass associated with estrogen deficiency may also occur in the oral cavity. Many studies have linked features characteristic of oral bone loss (tooth loss, decreased oral bone density, and crestal ABL) to both osteoporotic and estrogen-deficient states (see Table 3). Hormone replacement therapy (HRT) using estrogen is well established as a first-line treatment for osteoporosis and is being studied as a way to prevent oral bone loss. SERMs, a class of drugs modified from estrogen, have been developed to provide the specific therapeutic effects of estrogen therapy without unwanted side effects. In terms of treating oral bone loss, the therapeutic goals include blocking cytokine production to decrease osteoclast resorption, which results in increased bone mass. In 1 study[99] evaluating the effects of HRT on the periodontium, patients who received HRT had decreased probing depths, less tooth mobility, and less dental pain compared with controls. Another study[100] found similar results: osteoporotic/osteopenic patients who received estrogen supplementation had a reduced frequency of CAL compared with those who did not receive supplementation.

However, the benefits of HRT remain controversial. In 1 study,[101] 228 women were evaluated for estrogen intake and periodontal status. After controlling for confounding variables, the only significant effect of estrogen on the periodontium was decreased gingival bleeding. Although more controlled studies are needed, SERMs appear to have excellent therapeutic potential for minimizing oral bone loss.

PTH. PTH is an endogenous hormone with potent anabolic and catabolic actions in bone. Clinically, it increases BMD and prevents osteoporotic fractures, and consequently, it is used in the treatment of osteoporosis.[102,103] Although the effects of PTH on the oral cavity are largely unknown, ani-

mal studies suggest that oral bone structure is responsive to the anabolic actions of PTH.[104] Miller and colleagues[104] examined the ability of intermittent PTH therapy to stimulate bone formation in the mandible and humerus of ovariectomized rats. PTH significantly increased crestal bone levels in the mandible, particularly on the buccal surface, when measured at 1 year post ovariectomy. Furthermore, a recent animal study[105] showed that PTH was able to reverse periodontal bone loss in a rodent model. In the study, experimental periodontitis was induced in rats. Animals in the test group were administered PTH in a dose of 40 µg/kg. Histologic examination revealed a significant decrease in bone resorption and decreased inflammatory cell infiltrate in these animals compared with control animals. A study[106] of patients with hyperparathyroidism revealed that these patients did not have an increase in periodontal disease as measured by attachment levels, but they had a higher prevalence of tori and exostoses, indicating an increased level of osseous activity. These findings suggest that the oral cavity is not adversely affected by increased circulating levels of PTH. In fact, the oral cavity may respond more favorably than other areas of the body to PTH therapy. One study[107] found that intramembranous bone was more amenable to regeneration than endogenous vertebral bone when both were treated with PTH. Although PTH is not used specifically to treat oral bone loss, systemic administration may have positive benefits on the oral cavity. Current knowledge of PTH suggests that such treatment may have a positive impact on osseous healing in the oral cavity.

Summary and future research

Both osteoporosis and periodontitis are common bone-resorptive, host-dependent, multifactorial diseases that generally affect older patients. Both diseases are stimulated by bone-resorptive proinflammmatory cytokines such as IL-1 and TNF-α, but the end result of this stimulation differs in the 2 diseases. Osteoporosis results in bone loss that is generalized throughout the skeleton, whereas periodontitis results on bone loss that is localized to the alveolus. Current studies suggest a plausible association between these 2 diseases; however, the causality between them must be clarified with additional randomized controlled clinical trials. There are 2 types of chemotherapeutic agents for the treatment of systemic/oral bone loss: anti-resorptive agents (which inhibit bone loss) and anabolic agents (which increase bone formation). Anti-resorptive agents include NSAIDs, MMP inhibitors, bisphosphonates, RANKL, RANK, and OPG agents. Anabolic agents include SERMs and PTH. Preclinical animal studies and preliminary human trials suggest that these chemotherapeutic agents possess a high potential for use in the treatment of destructive periodontal disease and other bone resorption–related diseases, but additional studies are needed to determine the most efficacious therapeutic approach.

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