

# Impact of Osteoporosis and Its Treatment on Oral Health

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**Abstract:** Osteoporosis has emerged as a major health problem affecting middle-aged and older individuals. It is characterized by a reduced bone mass and strength, resulting in increased susceptibility to fractures. The disease is associated with several risk factors, and increasing evidence suggests that it may be associated with oral health conditions such as periodontal disease, reduced jaw bone density and tooth loss. Besides the effect of osteoporosis on oral health, bisphosphonate-related osteonecrosis of the jaws is a major concern to the dentist. Bisphosphonate-related osteonecrosis of the jaws is a recently described adverse effect of bisphosphonate therapy. The exact mechanisms by which these drugs cause necrosis of the jaws remain unclear, and a true cause-and-effect relationship between osteonecrosis of the jaw and bisphosphonate use has not yet been established. Hence, any form of invasive dentoalveolar treatment should be performed with caution in patients taking bisphosphonates. This review discusses current evidence on osteoporosis and its treatment implications as a risk factor in the development of various oral diseases.

**Key Indexing Terms:** Osteoporosis; Postmenopausal; Periodontal disease; Tooth loss; Bisphosphonates; Osteonecrosis. [Am J Med Sci 2013;0(0):1–6.]

Osteoporosis is a skeletal disorder characterized by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and susceptibility to fracture.<sup>1</sup> It is the most common type of metabolic bone disease, characterized by compromised bone strength. Osteoporosis is commonly seen in middle-aged and older individuals, which typically goes unnoticed until fractures occur. It is a complex, multifactorial, chronic disease that represents a severe public health problem because of the high risk of low and nontraumatic fractures, especially of the vertebrae, hip and forearm bones.<sup>2</sup> Osteoporosis can be characterized as either primary or secondary type. Primary osteoporosis includes the conditions in which the decrease in bone mass can be explained by changes of aging (senile types), as well as the hormonal changes of menopause. In contrast, the term secondary osteoporosis is used for the one caused by other diseases or medications.<sup>3</sup>

Primary osteoporosis can occur in both sexes at all ages, but often women experience more rapid bone loss following menopause, which places them at a higher risk for fractures. The incidence of osteoporosis in a population is dependent on gender, age, endocrine status, and lifestyle; however, the highest risk group being postmenopausal women above the age of 50 years. In most women, the main reason of osteoporosis is the decrease in estrogen that accompanies menopause. This

decrease in estrogen levels is associated with an elevated rate of bone loss caused by the increase in several inflammatory cytokines, cooperatively stimulating osteoclast-mediated bone resorption. Production of all of these cytokines is either directly or indirectly suppressed or regulated by estrogen.<sup>4</sup>

## Pathogenesis

In living bone tissue, there is a fine balance between bone formation by osteoblast and bone resorption by osteoclast. Osteoporosis is bone reduction resulting from imbalance between resorption and bone formation, with resorption tending to increase. This disorder leads to demineralization of bones, which begins to manifest clinically in the fourth and fifth decades of life. Several risk factors for the development of osteoporosis have been identified, and these have been broadly classified as nonmodifiable and modifiable.<sup>5</sup> The nonmodifiable risk factors include age, sex, genetic factors and early menopause, while the modifiable risk factors include inadequate calcium consumption, lack of exercise and behavioral factors such as smoking and alcoholism. Besides these, other factors that can contribute to the development of osteoporosis include certain endocrine diseases such as hyperparathyroidism, chronic renal and hepatic disease, malabsorption and drugs like oral glucocorticoid therapy.<sup>5,6</sup>

The role of estrogen in the development of osteoporosis is well documented. Studies have shown that sex steroids, particularly estrogen, are important in developing peak bone mass, and estrogen deficiency is a major determinant of bone loss in both sexes.<sup>7,8</sup> In females, bone loss occurs most rapidly following menopause due to fall in estrogen levels and this observation led to the concept that estrogen deficiency is critical to the pathogenesis of osteoporosis. Although bone remodeling is accelerated at menopause, this accelerated bone remodeling is associated with increased bone loss and impaired bone formation.<sup>4</sup> Estrogen deficiency may enhance the rate of bone loss by stimulating synthesis of several inflammatory cytokines that regulate osteoclast generation, such as interleukin 1 (IL-1), IL-2, IL-6, and prostaglandin E<sub>2</sub>.<sup>9</sup>

Genetic factors also contribute significantly to the risk of osteoporosis. Genetic factors influence the peak bone mass and heritability of bone mineral density (BMD) ranges from 50% to 90% in human populations.<sup>10,11</sup> Although numerous molecular association or linkage studies aiming to identify genes for BMD determination have been performed, to date, no clear consensus has been reached.<sup>11</sup>

A recent study among Swedish women has identified previous history of fragility fractures and low BMD as important factors contributing to increased hip and fragility fracture in older women.<sup>12</sup> Another similar study conducted in United States revealed that several factors such as age, self-reported health, weight, height, self-reported physical activity, history of fracture after 54 years, parental hip fracture, current smoking, current corticosteroid use and treated diabetes could be useful predictors of hip fractures.<sup>13</sup> Factors associated with increased risk for osteoporosis in men include glucocorticoid treatment, hypogonadism, excessive alcohol consumption,

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anticonvulsant use, osteomalacia, severe hyperthyroidism or bone marrow neoplasia.<sup>14</sup>

## OSTEOPOROSIS AND ORAL HEALTH

Several studies have been conducted over the last few decades to determine the relationship between osteoporosis and oral health. Majority of these investigations have studied the association between osteoporosis and periodontal disease, tooth loss and jawbone density.<sup>5,15-19</sup> According to the current concept, osteoporosis due to the estrogen deficiency represents a variety of conditions in relation to the stability of the structure of the jawbones. Given the evidence that alveolar processes provide the bony framework for teeth support, the loss of systemic bone density in osteoporosis, including that of the oral cavity, can be a negative consequence on tooth stability. It has also been found that the decline of skeletal mass can be correlated with an increased risk of oral bone loss, resulting in a host system that is increasingly susceptible to infectious destruction of periodontal tissues. In spite of these findings, osteoporosis may cause alteration in the mineral content of the alveolar bone and thus can predispose to the progression of periodontal disease<sup>6</sup> (Figure 1).

### Tooth Loss

An association between tooth loss and osteoporosis has been reported in the literature.<sup>20-24</sup> Among postmenopausal women on hormone replacement therapy, the risk of tooth loss was relatively less. Increased alveolar ridge resorption and greater alveolar crestal height loss was reported in subjects with osteoporosis and osteopenia.<sup>19,25,26</sup>

### Periodontal Disease

Recent literature suggests a possible association between osteoporosis and periodontal disease among postmenopausal females and showed a positive association between the 2 diseases.<sup>27</sup> Payne et al<sup>28</sup> in their 2-year longitudinal study evaluated the effect of osteoporosis and cigarette smoking on alveolar bone height in postmenopausal females. They reported that both smoking and osteoporosis had a negative impact on alveolar bone height. Jabbar et al<sup>29</sup> evaluated the relationship between periodontal disease and plasma cytokines, vitamin D and BMD in postmenopausal women with and without osteoporosis. They reported that periodontal disease was more common in women with osteoporosis and is associated with lower vitamin D and higher concentrations of receptor activated nuclear factor kappa B ligand and suggested that raised cytokines may play an important role in the association between these 2 conditions. Mohammad et al<sup>19</sup> in their cross-sectional

study on postmenopausal women compared various periodontal parameters in individuals with high and low bone and spine density. They reported that parameters such as gingival recession and clinical attachment level were significantly different in both the groups.

Both osteoporosis and periodontal diseases are bone resorptive diseases. Osteoporosis is characterized by reductions in bone mass and may lead to skeletal fragility and fracture. Periodontitis is characterized by resorption of the alveolar bone and is a major cause of tooth loss in adults. Because loss of alveolar bone is a prominent feature of periodontal disease, severe osteoporosis could be suspected of being an aggravating factor in the case of periodontal destruction. Therefore, it has been hypothesized that the breakdown of periodontal tissue may, in part, be related to systemic diseases, including osteoporosis. In addition, literature has proposed the role of osteoporosis in the onset and progression of periodontitis and tooth loss. Bando et al<sup>30</sup> reported that lower spinal BMD was positively correlated with tooth loss. In a study to determine the risk factors for tooth loss in elderly people, Xie and Ainamo<sup>31</sup> found that tooth loss was associated with a history of bone fracture that was used as an indicator of osteoporosis.

### Loss of Bone Density

Osteoporosis also results in loss of BMD throughout the body, including the maxilla and the mandible. The resulting low density in the jawbones leads to increased alveolar porosity, altered trabecular pattern and more rapid alveolar bone resorption following invasion by periodontal pathogens. The systemic factors affecting bone remodeling may also modify the local tissue response to periodontal infection, such as increased systemic release of IL-1 and IL-6. However, chronic infection around multiple teeth could contribute significantly to elevated production of cytokines associated with periodontal diseases. This could accelerate systemic bone resorption by modulating the host response. Proinflammatory cytokine IL-6, produced by osteoblasts, may play a pivotal role in this potential mechanism. In normal bone homeostasis, IL-6 production stimulates osteoclastic activity resulting in bone resorption.<sup>32</sup> Many of the effects on BMD may also be modulated through IL-6.<sup>33</sup> Animal studies have proved that elevated levels of IL-6 were found in the serum and gingival tissue adjacent to deep periodontal pockets.<sup>34</sup> Therefore, it is at least theoretically possible that chronic periodontitis may contribute to the development or progression of osteoporosis. However, clinical reports have failed to find this correlation.<sup>33</sup>

## ORAL IMPLICATIONS OF OSTEOPOROSIS THERAPY

Several medications are available to increase BMD, which include hormone replacement therapy, bisphosphonates (BPs), calcitonin, selective estrogen receptor modulators, recombinant human parathyroid hormone (teriparatide of ribosomal DNA origin: Forteo, Eli Lilly and Company, Indianapolis, IN) or combination of these medications.<sup>6</sup> Recently, a new bone antiresorptive agent Denosumab (Prolia, Amgen Inc, Thousand Oaks, CA) has been approved by Food and Drug Administration in the treatment of osteoporosis and metastatic cancer to the bones. Denosumab targets and binds to RANK ligand, inhibiting osteoclast formation, function and survival.<sup>35</sup> There is sufficient evidence in the literature to demonstrate that most of the medications used for the treatment and prevention of osteoporosis have the potential to reduce systemic as well as oral bone loss.<sup>15</sup> It has been shown that estrogen used in



FIGURE 1. Orthopantomogram of a 60-year-old patient with osteoporosis. Note the area of low bone density, alveolar bone loss and tooth loss.

hormone replacement therapy of postmenopausal women is associated with reduced gingival inflammation and a reduced frequency of gingival attachment loss in osteoporotic women in early menopause.<sup>17</sup>

### BP Therapy

BPs are nonhydrolyzable analogues of pyrophosphate that potently inhibit bone resorption, a property that has led to their widespread application in the treatment of bone diseases characterized by excessive resorption, including postmenopausal osteoporosis, Paget's disease and tumor-induced osteolysis.<sup>36</sup>

BPs are the standard of care for increasing or maintaining bone mass and reducing excessive bone turnover, and they have proven to be effective in reducing osteoporosis complications.<sup>37</sup> By inhibiting osteoclast-mediated bone resorption, BPs contribute to an increase in BMD and lead to a marked reduction in the risk of bone fractures.<sup>38,39</sup> They have also been shown to inhibit tumor cell proliferation and inhibit angiogenesis. These added features have made BPs useful in the management of bone metastases.<sup>40</sup> They are derived chemically from pyrophosphates that are agents that prevent calcium and phosphorous precipitation. Several clinical trials have shown that BPs reduce skeletal tumor burden in patients with multiple myeloma, breast cancer and prostate cancer, leading to an increase in the use of BPs in the management of metastatic disease.<sup>41</sup>

Two routes of administration of the drug are commonly used, oral and intravenous. BPs act almost exclusively on bone when administered at physiological doses because of specific affinity to bone, where they deposit both in newly formed bone and in proximity to the osteoclasts. The half-life of BPs in the circulation is quite short, ranging from 30 minutes to 2 hours.<sup>42</sup> However, once incorporated into bone tissue, they can persist for up to 10 years, depending on the skeletal turnover time.<sup>43</sup>

Oral BPs are commonly used in the treatment of osteoporosis, Paget's disease and osteogenesis imperfecta, whereas the intravenous BPs are used in the treatment of osteolytic tumors, hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors and other tumors.<sup>37,44</sup> The most common oral BPs are alendronate (Fosamax, Merck & Co, Inc, Whitehouse Station, NJ), risedronate (Actonel, Procter and Gamble Pharmaceuticals, Cincinnati, OH) and ibandronate (Boniva, Roche Pharmaceuticals, Nutley, NJ). The chances of developing bisphosphonate-related osteonecrosis of the jaw (BRONJ) depends on the potency and duration of BP exposure.<sup>45</sup>

### Mechanism of Action of BPs

BPs are classified as nitrogen-containing and non-nitrogen-containing categories.<sup>46</sup> Nitrogen-containing BPs, such as zoledronate, are potent inhibitors of osteoclastic bone resorption through inhibition of synthesis of farnesyl pyrophosphate, a key enzyme in the mevalonate pathway.<sup>47</sup>

BPs can both decrease osteoclast activity and decrease osteoclast numbers. The first is exemplified by internalization by osteoclasts, causing disruption of osteoclast-mediated bone resorption,<sup>48</sup> and the second by inhibiting osteoclast recruitment and accelerating programmed cell death (apoptosis) of osteoclasts, thus reducing osteoclast numbers. Both mechanisms lead to reduction of bone resorption and to a decrease in bone turnover.<sup>49</sup> BPs bind avidly to exposed bone mineral around resorbing osteoclasts, resulting in very high levels of BPs in the resorption lacunae. Because bone-incorporated BPs are not metabolized, these high concentrations are maintained within bone for long periods.<sup>48</sup>

### BP-Related Osteonecrosis of the Jaw

BRONJ is defined as a condition characterized by nonhealing exposed necrotic bone in the mandible or maxilla persisting for more than 8 weeks in a patient who has taken or is currently taking a BP and who has no history of radiation therapy on the jaws.<sup>45,50</sup> Incidents of osteonecrosis of the jaw have been reported in persons using BPs and undergoing invasive dental treatment procedures, including tooth extractions, dental implants and surgical and nonsurgical periodontal treatment (Figure 2).<sup>51,52</sup>

Although BPs have been reported to cause oral mucosal alterations,<sup>53,54</sup> the changes occurring in the jawbones are of a greater significance to the dentist. BRONJ is a serious oral complication occurring in 1.8% to 12.8% of the cases with intravenous BP administration.<sup>48,55</sup> However, the rate of occurrence of this complication and the factors that predispose to its occurrence are not well understood. A true cause-and-effect relationship between osteonecrosis of the jaw and BP use has not yet been established. Most of the reported cases (95%) have been associated with zoledronic acid or pamidronate given intravenously to control metastatic bone disease.<sup>56,57</sup> Osteonecrosis of the jaw has developed far less often among patients who have received oral BPs at the lower doses used for osteoporosis than among patients who received the higher doses used for metastatic cancer. Even though the exact incidence of BRONJ is unknown, reports have estimated it to be about 1 in 10,000 for intravenous use of BPs. There is also an incomplete understanding of how BP therapy may affect tissue healing and the success rate of dental implants.<sup>58,59</sup>

### Pathogenesis

The mechanism by which BPs may cause or promote the occurrence of osteonecrosis of the jaws remains uncertain.<sup>60</sup> The potent BP-mediated inhibition of osteoclastic function leads to decreased bone resorption and inhibits normal bone turnover remodeling, resulting in areas of microdamage, accumulation and a reduction in some mechanical properties of the bone (Figure 3).<sup>61</sup> The mandible and maxillary bones normally offer a high level of resistance to infection by oral microorganisms during dental infections or extractions or when a foreign body (eg, an implant) is inserted. This resistance to infections, together with an ability to heal rapidly, is thought to stem in part



FIGURE 2. BRONJ in a 63-year-old woman subsequent to extraction of mandibular molar. The patient was on intravenous zoledronate for 1 year.



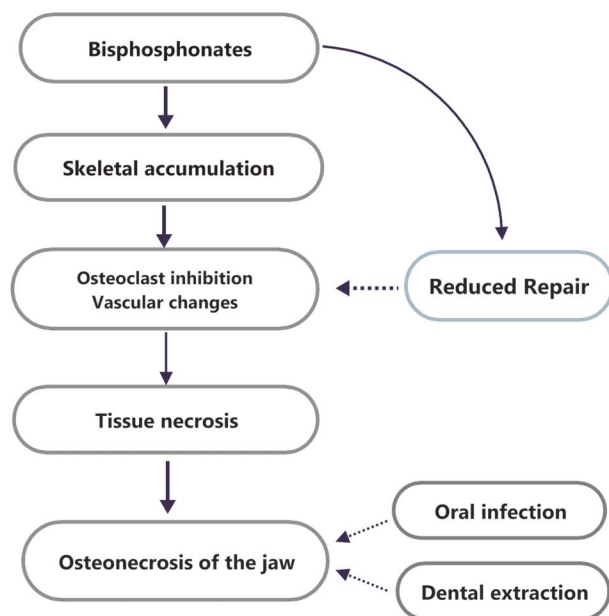


FIGURE 3. Schematic diagram showing the possible mechanism of development of BP-associated osteonecrosis. BP, bisphosphonate.

from the high blood flow that characterizes the mandibular and maxillary bone.<sup>62</sup>

Animal studies have reported the possibility of angiogenesis inhibition by BPs.<sup>63,64</sup> This is mediated primarily through inhibition of vascular endothelial growth factor and other angiogenic factors, which may be an underlying mechanism of BRONJ. Infection is a dominating component of osteonecrosis of the jaw, and a pronounced overlap between jaw osteomyelitis and osteonecrosis exists. Delayed epithelialization may result in exposed bone that, in the presence of oral bacteria, increases the risk of infection. BPs may contribute to the pathogenesis of osteonecrosis of the jaw by being toxic to the oral epithelium at pharmacologic concentrations.<sup>65</sup>

### Clinical Features

Clinically, BRONJ presents as an area of exposed alveolar bone that occurs spontaneously or becomes evident following an invasive surgical procedure such as extraction of a tooth, periodontal surgery, apicoectomy, or dental implant placement.<sup>66</sup> The 3 most common sites for BRONJ are (1) non-healing dentoalveolar sites; (2) traumatized tori (palatal and/or mandibular) and (3) exposures of portions of the mylohyoid ridge.

In a review of 368 reported cases of BRONJ, it was found that 65% of cases involved the mandible only, 26% involved the maxilla only and 9% involved both the jaws.<sup>67</sup> There was a slight female predilection of 3:2. Multifocal or bilateral involvement was more common in the maxilla than in the mandible. Most of the reported lesions were on the posterior lingual aspect of the mandible near the mylohyoid ridge. Among the reviewed cases, 60% occurred after tooth extraction or dentoalveolar surgery.

Symptoms may occur spontaneously in the bone or at the site of previous tooth extraction. Symptoms include pain, soft tissue swelling, infection secondary to dead bone, loosening of teeth and, in some cases, the ragged bone surfaces cause ulceration of the contacting soft tissues. There are associated

sinus tracts, and in severe cases, a cutaneous fistula may develop. A typical lesion begins in the alveolar bone and occurs more frequently in mandibular than maxillary sites by the ratio of 2:1.<sup>68</sup>

Radiographically, osteolytic changes are frequently seen and the bone lesion may appear less or more radiodense than the unaffected bone, providing a radiographic appearance similar to that observed in bone metastasis. The disease can result in a long-term debilitating condition. Advanced cases of BRONJ have developed pathological fractures especially in edentulous patients with long-standing oral implants.<sup>69</sup>

Dental treatment seems to be a precipitating event in the development of most cases of BP-related osteochemonecrosis. It is therefore imperative that osteoporosis patients for whom BP therapy is being contemplated should have their dental status assessed prior to initiation of the BP therapy. This includes control of dental caries and periodontal disease, avoiding dental implant placement, using soft liners on dentures and to recommend an alternative to tooth extractions for patients with history of receiving BP therapy. This is because withdrawal of BP therapy before major dental procedures does not appear to hasten recovery of osteonecrosis due to their persistence in bone.<sup>68</sup>

### Dental Implants and BP Therapy

BPs are the most widely prescribed medication for the management of osteoporosis. They are pyrophosphate analogues containing a phosphate-carbon-phosphate bond, which is stable to chemical and enzymatic hydrolysis; they strongly bind to hydroxyapatite crystals and potentially inhibit osteoclast-mediated bone resorption while minimally inhibiting osteoblast activity.<sup>70</sup> There are conflicting reports regarding dental implants and BP therapy.<sup>58,71</sup> Experimental studies show a positive effect of BPs on the bone around implants in experimental animals.<sup>72,73</sup> Although some studies have reported that BPs have no effect on implant stability,<sup>74</sup> few other reports suggest that BPs may have a negative impact on osseointegration. Failure of osseointegration in a patient on BP therapy has been reported.<sup>59,75,76</sup> Current advice is that placement of implants may be avoided if the patient has serious bone disease and are on potent doses of the drug. Osteoporotic patients on lower doses need a full informed consent before proceeding with treatment. Patients on BP therapy with existing implants should be regularly monitored. Increased bone density around the implant may occur. If bone pain or loss of integrity occurs, the superstructure should be removed and the implant left submerged.<sup>77</sup> Bone surgery must be avoided as the bone is exceedingly dense and avascular necrosis may occur.

It is important to make health care professionals and patients aware of the potential risk of BP treatment. Once the therapy has commenced, regular dental monitoring of oral health and a preventive approach should be adopted. Patients should be educated regarding good oral hygiene practices and to report having come across any symptoms. There should be a greater collaboration between oral health providers, physicians and surgeons alike to minimize the complications of this therapy, thereby keeping patient morbidity at check. The goal of this approach should be, like elsewhere, to harness the intrinsic reparative drive to the judicious pharmacokinetic intervention aimed at avoiding treatment-related health risks.

### CONCLUSIONS

Osteoporosis results from an imbalance in the rates of bone formation and resorption that cause bones to lose mineral mass. Along with the loss of minerals, they also lose strength and the ability to withstand low-level trauma. Although

osteoporosis can affect people of all ages, they occur most often in middle-aged and elderly people, the same segment of the population that has the highest risk of chronic periodontal disease and tooth loss. The association between osteoporosis and periodontitis is biologically plausible as well. However, a growing body of literature has been restricted to postmenopausal women regarding the role of estrogen deficiency in the onset and progression of periodontal disease. There is consistency of results of most studies, suggesting that an association likely does exist, but whether there is a causal nature to that association is not firmly established. Moreover, available scientific data suggest that patients with osteoporosis who are on BPs require special care during dental treatment, especially in regard to dental implants, due to a risk of occurrence of BRONJ. Further studies are needed to assess the role of osteoporosis in various oral conditions, to determine the clinical implications of osteoporosis therapies on oral health and to elucidate whether dental examination might be of value for initial screening for signs of osteoporosis.

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