OSTEOPOROSIS, OSTEONECROSIS, AND ORTHODONTICS

Osteoporosis, whether senile, postmenopausal, or corticosteroid-induced, has been shown to affect orthodontic tooth movement and the periodontium. There have also been reports of osteonecrosis related to oral bisphosphonate therapy during treatment for osteoporotic bone diseases. This article summarizes the current knowledge of the relationship between osteoporosis and osteonecrosis and their effects on orthodontic tooth movements. The information will be important in orthodontic treatment planning and realization. World J Orthod 2009;10:261–271.

Key words: bisphosphonates, orthodontics, osteonecrosis, osteoporosis

Osteoporosis is a chronic, systemic, degenerative disease characterized by a decrease of bone mass, a microarchitectural deterioration of the bone, and a consequent increase in bone fragility/susceptibility to fracture.\(^1\)–\(^3\) Osteoporosis can be classed as postmenopausal or senile.\(^4\)

Osteoclastic activity plays a vital role in every orthodontic tooth movement. As force is applied to a tooth, the extracellular matrix of its periodontal ligament is distorted and the cellular shape and cytoskeletal configuration is changed. Bone remodeling is controlled by various factors.\(^5\) On the pressure side of a tooth, osteoclast progenitors are recruited and disseminated from hemopoietic tissues into bone via the circulating blood stream. The osteogenic progenitors proliferate and differentiate upon cell-to-cell interaction with osteoblasts.\(^6\) After preparation of the bone surface by osteoblasts and their proteolytic enzymes, recognition of extracellular bone matrix proteins and activation of osteoclasts takes place.\(^5,7\) Three theoretically possible regulatory mechanisms are discussed for the arrest of osteoclastic activity: (1) naturally occurring apoptosis of osteoclasts; (2) high calcium concentrations in resorption lacunae;\(^8\) and (3) release of transforming growth factor-beta or related peptides from the matrix.\(^9\)–\(^11\)

Because orthodontic tooth movement involves bone remodeling in reaction to applied forces,\(^5,12\) it follows that treatment outcome may be affected by systemic disorders such as metabolic bone diseases. Osteoporosis indeed has an influence on bone remodeling and the periodontium and can affect the speed of tooth movement.\(^13\) Nowadays, adult orthodontic treatment is widely practiced, and the perceived need and demand for such treatments has increased in the general population.\(^14,15\) Among these patients are postmenopausal women who are at risk of osteoporosis. The prevalence of osteoporosis among postmenopausal women when associated with the femoral neck\(^16\) is 20%. The prevalence of osteoporosis is 12% in both men and women when associated with vertebral deformities; this percentage increases with age.\(^1\) In addition, adults who are on a long-term medication with corticosteroids and similar substances are at risk of developing osteoporosis.\(^17\)–\(^19\)
Part of the treatment for osteoporosis and some malignancies is intravenous or oral administration of bisphosphonates. This has been reported to interfere with orthodontic tooth movement, possibly owing to the high affinity of this medication to osteoclasts and its anti-angiogenic effect. Furthermore, bisphosphonates have been shown to be related to necrosis of bone in the maxilla and mandible. Thus, there is an increasing number of patients whose orthodontic movement may be affected by osteoporosis. Understanding the effects of this disease is important in orthodontic treatment planning and execution. Thus, this paper attempts to summarize the current understanding about the relationship among osteoporosis, osteonecrosis, and orthodontics.

OSTEOPOROSIS AND ALVEOLAR BONE LOSS

Osteoporosis is considered to be a risk factor in the development of periodontal disease. The influence of osteoporosis on the periodontal condition and the alveolar bone has been studied in both animals and humans. The height of alveolar bone is important in determining the effects of applied forces. With the reduction of alveolar bone height, the center of resistance of a tooth moves apically and the resulting moment increases. Thus, the relationship between osteoporosis and alveolar bone loss has a direct impact on the basic principles of orthodontic force application.

Two animal studies showed that ovariectomy leads to a significantly lower trabecular bone volume, a greater bone resorption and formation, and deeper periodontal sulci in control animals. In a study of rats with gonadectomy-induced osteoporosis, there was more bone resorption in the maxilla than in normal rats. However, dual-energy x-ray absorptiometry used to measure bone mineral density revealed less effect on the mandible than on the femora. Sidiropoulou-Chatzigiannis et al explained this finding by suggesting that mastication leads to a constant bone remodeling, which again prevents heavier bone loss in the mandible.

Studies in humans using dual-photon scanning have shown greater attachment loss and lower mandibular bone mineral content in osteoporotic women. Postmenopausal females receiving estrogen therapy also had greater alveolar bone loss than healthy premenopausal women. Other studies using dual-energy x-ray absorptiometry, computed x-ray densitometry, and the Community Periodontal Index of Treatment Needs gave evidence of a correlation between bone mineral density and mean alveolar bone loss in postmenopausal women. However, again, other studies did not show any difference in probing depth or marginal bone height between women with normal and reduced bone mineral density. The different results of various studies could be attributed to small sample sizes, population differences, inadequate control of confounding factors, and common limitations of cross-sectional studies.

OSTEOPOROSIS AND ORTHODONTIC TOOTH MOVEMENT

In various studies, osteoporosis has been found to change the speed of tooth movement. Yamashiro et al showed that experimental ovariectomy resulted in an increased velocity of tooth movement. Tan et al reported a correlation between increased tooth movement and an increased number of osteoclasts in ovariectomized rats. In an immunohistochemical study, expression of interleukin-1 beta, which is important for bone remodeling, was increased when teeth of osteoporotic rats were subjected to orthodontic forces.

In a histomorphometric analysis, Arslan et al showed that in ovariectomized rats, the osteoclast counts were higher, whereas the osteoblast and osteocyte counts were lower than in the control group. However, Yamashiro and Takano-Yamamoto found that their ovariectomized rats had more osteoclasts and bone surfaces with osteoclastic but also osteoblastic activity. Although tooth movement was increased with both
bone formation and resorption, the negative balance of bone metabolism caused by this systemic hormonal imbalance could be exaggerated and thus osteopenia in the alveolar bone may still be the consequence.

Miyajima et al classified osteoporosis on the basis of the results from the study by Orimo et al into two types: (1) postmenopausal osteoporosis with accelerated bone formation but with even more accelerated bone resorption; and (2) senile osteoporosis with depressed and imbalanced bone resorption and formation. Thus, osteoporosis in experimental ovariectomized animals may be of a postmenopausal type, with accelerated tooth movement. Miyajima et al reported on a patient with slow orthodontic tooth movement, which can be explained by the fact that this patient's osteoporosis may have been of the senile variety. Without sufficient subsequent bone formation, orthodontic tooth movement may have a high tendency to relapse in patients with osteoporosis, regardless of whether it is of the postmenopausal or senile type.

ESTROGEN AND ORTHODONTIC TOOTH MOVEMENT

Estrogen supplements taken by menopausal women can reduce alveolar bone loss. This beneficial effect of estrogen results from its ability to decrease the rate of bone resorption by inhibiting production of various cytokines, mainly interleukin-1, tumor necrosis factor-alpha, and interleukin-6, which normally stimulate osteoclast formation and osteoclastic bone resorption. Compared with osteoporotic rats not receiving estrogen, those that did exhibited a decreased speed of tooth movement; however, this movement was still higher than in the controls, as were the osteoclast counts. Apart from acting on osteoclasts, estrogen can promote collagen synthesis in osteoblast-like cells and transforming growth factor-b and insulin-like growth factor and procollagen in osteoblasts, which in turn results in an inhibition of bone turnover.

In their report of a patient, Miyajima et al attributed the slow tooth movement to an estrogen supplement. Younger women taking oral contraceptives also have been found to have inhibited tooth movements. However, there are no prospective human or animal studies on the effect of estrogen supplementation on orthodontic tooth movement.

CORTICOSTEROID-INDUCED OSTEOPOROSIS AND ORTHODONTIC TOOTH MOVEMENT

A major side effect of corticosteroid administration is osteoporosis. Corticosteroid-induced osteoporosis involves the uncoupling of the normal relationship between bone formation and resorption, resulting in a net decrease in bone formation. The osteoblastic and osteoclastic function is directly inhibited by corticosteroid.

Osteoporosis induced by corticosteroids also affects the speed of tooth movement. Ashcraft et al found that corticosteroid-administered rabbits had elevated osteoclastic activity, increased alveolar bone resorption, and suppressed bone deposition. Also observed in this study was an acceleration of tooth movement with subsequent greater relapse. Histopathologic studies on male rats by Kalia et al supported this finding. In both, the chronic and acute corticosteroid treatment group, tooth movement increased when compared to controls. The force application resulted in a significant increase in the relative extension of bone resorption and formation in both treatment groups, but was more pronounced in the chronic group. Verna et al found more root resorption in an acute corticosteroid treatment group when compared with a control and a chronic group. Thus, chronic corticosteroid treatment increases the biologic reactions to mechanical perturbations, which is why orthodontic forces should be controlled and reduced. Acute corticosteroid administration reduces bone turnover but increases root resorption. Therefore, orthodontic treatment might best be postponed until a time when the patient is taken off medication.
OSTEOPOROSIS AND ORTHODONTIC CONSIDERATIONS

Orthodontic forces for osteoporotic patients should be carefully planned and adjusted because the risk of alveolar bone loss is higher as discussed earlier. Osteoporotic patients should be thoroughly examined for periodontal diseases before and during orthodontic treatment. If they are receiving medications such as corticosteroids or estrogen, the medications may need to be temporarily ceased during orthodontic space closure, after the patients’ physician has considered the risks and benefits of a possible discontinuation of the medication. The individual orthodontic treatment plan may be less extensive, especially as far as extractions are concerned because orthodontic root uprighting is problematic. Long-term retention with a highly effective retention regimen should be planned because these patients have a elevated tendency of relapse.

OSTEOPOROSIS, BISPHOSPHONATES, AND OSTEONECROSIS

Bisphosphonates are synthetic analogs of inorganic pyrophosphates that have a high affinity for calcium. They have been used in the management of systemic metabolic bone diseases including osteoporosis and osteopenia in postmenopausal women, corticosteroid-induced osteoporosis, multiple myeloma, bone metastasis of various cancers, hypercalcemia, and severe Paget’s disease. High-potency bisphosphonates used for cancer therapy are injected, whereas those used for treatment of osteoporosis are administered per os. Recently, there have been increasingly more reports of osteonecrosis and slowed orthodontic tooth movement associated with the use of bisphosphonates, whether intravenously or orally administered.

Oral bisphosphonates have been increasingly used in Western cultures, and they are the most regularly prescribed class of drug in the United States. Commonly used oral bisphosphonates include alendronate, sometimes with colecaltiferol and risedronate. Pamidronate and zoledronic acid are the commonly injected bisphosphonates used in the United States. The various types of bisphosphonates are listed in Table 1. Bisphosphonates bind to the mineral bone matrix and target areas of high bone turnover, especially exposed hydroxyapatite actively undergoing bone resorption. They are potent inhibitors of osteoclastic activity, and their ingestion after phagocytosis by osteoclasts triggers osteoclastic apoptosis and programmed cell death. Osteoclastic recruitment is inhibited, and osteoblast-mediated osteoclastic resorption is restricted.

Thus, in patients with periodontal disease, bisphosphonates have been applied locally after mucoperiosteal flap elevation to control bone resorption and encourage alveolar bone growth. Bisphosphonates have also been used clinically to promote bone formation during the regeneration of peri-implant defects. Paradoxically, animal and human studies have shown that this drug possesses an anti-angiogenic effect, and it may therefore reduce the healing potential of the already compromised bone.

In recent years, osteonecrosis has often been described as a major adverse effect of bisphosphonate therapy. The definition of bisphosphonate-induced osteonecrosis according to the American Association of Oral and Maxillofacial Surgeons Task Force is as follows: (1) current or previous treatment with bisphosphonate; (2)
exposed necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws.66

Ruggiero et al.49 reported that 54 of 63 patients who had received intravenous bisphosphonate injection and recently undergone procedures such as tooth extractions, flap surgery, or medication for oral infection, developed osteonecrosis. Marx et al.67 reviewed 119 individuals with osteonecrosis in relation to bisphosphonates and found that many osteonecrotic sites were related to extractions, existing periodontal diseases, periodontal surgeries, placement of dental implants, and apicectomies. Beside this, spontaneous osteonecrosis occurred in 30 of the 119 patients. Similarly, Woo et al.68 reported in a systematic review spontaneous bisphosphonate-induced osteonecrosis (BON) in 39% of patients.

The relationship between jaw osteonecrosis, intravenous or oral bisphosphonate therapy, and previous invasive dental treatment was confirmed by several patient reports and cohort studies.69–74 Although oral bisphosphonate therapy is considered as having a low risk of BON, recent publications have shown BON in patients who were receiving oral bisphosphonates, either spontaneously75,76 or as a result of pressure from a denture, even though this is noninvasive and considered a low risk factor for BON.77

Osteonecrosis is often progressive and orally manifested as mucosal dehiscence with exposure of the underlying bone of the mandible or maxilla. The lesion itself can cause discomfort in the adjacent soft tissues or be painful due to the constant abrasion of exposed bone. There may be soft tissue swellings, tooth hypermobility, and exudation. When the lesion is acutely infected, patients often complain of severe pain and paresthesia; peripheral nerve compression may be indicated in such a situation.78

To date, there is no uniform treatment for BON as it does not seem to respond to any known treatment. Relevant randomized controlled trials are still missing. Therapeutic strategies include surgical debridement, bone curettage, local irrigation with antibiotics, and hyperbaric oxygen therapy.49,68,78 However, surgical debridement can result in further bone necrosis. Even termination of bisphosphonate administration may not improve the situation immediately because of the drug’s long half-life. Hyperbaric oxygen administration is of limited benefit.67,79

A prospective study by Montebugnoli et al.80 compared surgical debridement and sequestrectomy to continuous antibiotic therapy as two treatment choices in patients with BON. The goal of the antibiotic therapy was to interrupt the vicious cycle of BON. The bony, vascular, and connective tissue structures necessary for repair are impaired during BON, resulting in a failure of osteoclasts, which normally remove necrotic bone. This condition is superimposed by a bacterial infection, which leads to sequestrum formation. In all, Montebugnoli et al.80 did not find any significant difference in the dimensional change of the exposed bone between the two treatment modalities. However, the extent of osteonecrosis in the two groups was different before initiation of therapy. Thus, current consensus favors a conservative approach.49,81–83

Because the treatment response of BON seems to be unsatisfactory, its prevention is important. An American Academy of Medicine position paper78 gives detailed recommendations for preventive measures but also for therapy in patients with BON. Similar recommendations were given by an expert panel of the Novartis Pharmaceutical Corporation84,85 and in 2006 by the American Dental Association.86 Nevertheless, these recommendations are not supported by scientific studies. Research is also needed to elucidate the pathologic mechanism of BON development after traumatic dental procedures in patients receiving bisphosphonate treatment. Current evidence suggests that markers of bone resorption and formation are suppressed during this therapy.87–89

Marx et al.80 published a paper correlating C-terminal telopeptide (CTX) in morning fasting serum with the risk of developing BON. They found that patients with CTX values of less than 100 pg/mL had a high risk of developing BON, those with 100 to 150 pg/mL had a moderate risk, and those with greater than
150 pg/mL had a minimal risk. Thus, the CTX test may be used as an indicator of BON risk among patients taking oral bisphosphonates. Also, it may be used as an indicator to determine when traumatic oral procedures can be performed with the lowest risk of BON.

**BISPHOSPHONATES AND ORTHODONTIC TOOTH MOVEMENT**

The effect of bisphosphonate therapy on orthodontic tooth movement has been documented in various animal studies and patient reports. Igarashi et al. found that topical administration of bisphosphonates in rats inhibited tooth movement. Rinchuse et al. reported that in patients undergoing bisphosphonate administration for either osteoporosis or cancer, orthodontic tooth movement took longer and bodily movements were limited. Also, radio-opaque sclerotic lines were found around the roots of teeth near an extraction site in the mandible but not in the corresponding site in the maxilla. Similar sclerotic lines were seen by Markiewicz et al., who also observed that space closure was extremely difficult owing to the limited osteoclastic activity and a possible anti-angiogenic effect that allowed only tipping space closure.

**BISPHOSPHONATES AND ORTHODONTIC CONSIDERATIONS**

Orthodontists need to bear in mind that impeded tooth movement can occur during bisphosphonate therapy due to reduced osteoclasia and decreased microcirculation; in addition, the risk of BON increases. Accordingly, the following recommendations by the American Dental Association Council on Scientific Affairs, as by Zahrowski and Rinchuse et al., should be considered although they reflect only expert opinions.

First, it is important to ask any new patient whether she/he is or was taking any bisphosphonates and for what reason. If this is or was the case, the patient should sign a consent form that details the relevant risks and concerns. It is essential to find out about the risks of osteoclastic inhibition and BON according to:

- **Form of administration.** The risk for oral administration is 0.7 per 100,000 persons per years of exposure because only 1% of the bisphosphonate is absorbed by the gastrointestinal tract. However, if bisphosphonate is administered intravenously, 50% of it will be incorporated into the bone matrix.

- **Duration of administration.** The mean duration before osteonecrosis detection ranges from 9 to 14 months after intravenous administration and up to 3 years after oral administration.

- **Administered dose.** No solid guidelines are available, but it is widely accepted that higher doses pose a higher risk. However, this risk is associated with the concomitant use of estrogens or glucocorticoids, advanced age (65 years or older), and bisphosphonate treatment duration.

Marx et al. reported that CTX values improved after oral bisphosphonate treatment was ceased for 6 months and suggested that this protocol reduces the risk of developing BON. However, this report needs confirmation with further scientific research. It seems plausible that the lower the bisphosphonate concentration, the fewer anti-angiogenic effects will manifest. The half-life of bisphosphonate can be as long as 12 years. Therefore, it is debatable whether the temporary discontinuation of bisphosphonate treatment before orthodontic therapy is useful. It also remains unknown whether cessation of bisphosphonate administration has a significant effect on bone resistance to fracture. In any case, the risks and benefits of interrupted bisphosphonate therapy have to be discussed with the patients’ physician before planning any orthodontic treatment. Although risks seem to be lower when bisphosphonate is administered orally instead of intravenously, this view may change as more scientific research is published. Overall, routine dental treatments should not be modified,
but patients should be informed of the risks of any invasive procedure.

Advice for patients receiving both bisphosphonates and corticosteroids is also needed but not existent. Marx et al\(^90\) recommended CTX testing for patients who have been taking bisphosphonates orally for more than 3 years and for those who received bisphosphonates less than 3 years but concomitantly corticosteroids or chemotherapeutic medication. It is recommendable before any elective dental procedures (including orthodontic treatment) to have the respective patient take a drug holiday until CTX values reach 150 pg/mL.

Discussion of the orthodontic treatment plan with the patient’s physician is recommended. During treatment planning, orthodontists should try to avoid or minimize elective surgery, laser therapy, microimplants,\(^81\) and extractions but favor procedures such as interproximal enamel reduction, which is noninvasive and reduces the amount of necessary tooth movements. These movements may be slowed or even stopped during the first 3 years of oral bisphosphonate exposure because of its antiresorptive (antiresorptive effect).\(^20,90,91\) Primary space closure should be attempted if extraction is unavoidable. Bone covering soft tissues should not be compressed. Thus, for retention, tooth-borne appliances are to be preferred. In case removable retainers have to be used, they should not compress the tissue over the maxillary or mandibular bone. Bodily tooth movement is difficult, so extraction sites are mostly closed by tooth tipping. Because of the concomitant incorrect angulation that increases the relapse tendency, prolonged retention is advisable.

### CONCLUSION

The relationships among osteoporosis, osteonecrosis, and bisphosphonate administration are summarized in Tables 2 to 4.

There is increasing evidence that osteoporosis and medications for its treatment affect orthodontic tooth movement and stability of orthodontic therapy. Even spontaneous osteonecrosis has been reported among patients undergoing oral bisphosphonate therapy. Thus, orthodontic patients may be at risk of this serious side effect, so their orthodontic treatment should be carried out with caution. Continuing research may lead to alternative therapy regimens in the future that could induce apoptosis of osteoclasts and thus replace the current medication. Nuclear factor NF-κB was involved in the activation of genes critical for osteoclast differentiation and activity. Penolazzi et al\(^94\) injected into animals a decoy oligonucleotide targeting NF-κB that could induce apoptosis of osteoclasts after the application of orthodontic forces. Thus, they succeeded in regulating alveolar bone resorption during orthodontic tooth movement. If this approach could be improved, excessive osteoclastic activity in pathologic conditions such as osteoporosis, periarticular osteolysis, inflammatory arthritis, Paget’s disease, and tumor-associated osteolytic metastases could be controlled.

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<th>Table 2</th>
<th>Osteoporosis and side effects with impact on orthodontic interventions</th>
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<td>Postmenopausal osteoporosis</td>
<td>Alveolar bone loss</td>
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<td>Periodontal disease</td>
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<td>Increased orthodontic tooth movement</td>
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<td>Senile osteoporosis</td>
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<td>Increased orthodontic relapse</td>
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<td>Corticosteroid-induced osteoporosis</td>
<td>Increased orthodontic tooth movement</td>
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<td>Inhibition of bone formation</td>
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<td>Increased orthodontic relapse</td>
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<td>Estrogen supplementation</td>
<td>Reduced orthodontic tooth movement</td>
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<td>Bisphosphonate therapy (oral)</td>
<td>Reduced orthodontic tooth movement</td>
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The effects of dental and orthodontic procedures in osteoporotic patients require further research to develop reliable recommendations. Also, prospective studies are needed to enlarge the contemporary knowledge of the pathogenetic mechanisms of BON development and related risk factors. In the mean time, physicians need to stay up-to-date by reading any research articles on this relatively new topic.

REFERENCES