

# Osteoporosis and periodontal disease

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Low bone mass (osteopenia) and osteoporosis are systemic skeletal diseases characterized by low bone mass and micro-architectural deterioration with a consequent increase in bone fragility and susceptibility to fracture. According to the World Health Organization, osteoporosis is considered to be present when bone mineral density is 2.5 standard deviation (SD) or more below the mean for normal young Caucasian women, i.e. a *T* score of  $-2.5$ . Osteopenia is defined as bone density levels between 1 and 2.5 SD below normal bone mineral density (63, 64).

Both osteopenia and osteoporosis are grave public-health concerns and are widely prevalent in developed countries, particularly among postmenopausal women. The World Health Organization considers osteoporosis to be second only to cardiovascular disease as a public-health concern. Osteoporosis affects an estimated 75 million people in Europe, the USA, and Japan. Worldwide, approximately one-third of women aged 60–70 years and two-thirds of women aged 80 years and older have osteoporosis (56). The National Osteoporosis Foundation estimates that 21.8 million women in the USA have low bone mass (osteopenia) and 7.8 million have osteoporosis; over 14 million men were estimated to have either low bone mass (11.8 million) or osteoporosis (2.3 million) (110). In the third National Health and Nutrition Examination Survey (NHANES III) the prevalence of osteoporosis when assessed at the femoral neck was 20% of postmenopausal Caucasian women (92). An alternative approach is to use morphological deformities in the vertebrae to define osteoporosis. The prevalence of the defined vertebral deformities was found to be 12% in both men and women. The increase in frequency with age was greater in women – from 5% for women aged 50–54 to 24% at age 75–79 years. For men aged 50–54 years this was 10%, rising to 18% for men 75–79 years old (101). The prevalence of this relatively silent disease is very high and on the rise. Future projections indicate a three-fold increase in osteoporosis-related hip fractures (69).

In the USA, 1.3 million fractures annually are the result of osteoporosis (101). One-third of women over 50 years old will experience osteoporotic fractures, as will one in five men (65, 101, 102). Between 30% and 50% of women and between 15% and 30% of men will suffer a fracture related to osteoporosis in their lifetime (118). Nearly 75% of hip, spine, and distal forearm fractures occur among patients aged 65 years or older (103).

## Diagnosis and assessment

### History and physical examination

The history and physical examination are insufficient for diagnosis of osteoporosis. However, they can be important in the screening process for osteoporosis and in directing the evaluation. The medical history will provide valuable information about factors that could influence bone mineral density, such as chronic conditions, behaviors, physical fitness, and the long-term use of medications. The history should focus on the likelihood of fractures. The physical examination should be used to aid in the screening for osteoporosis. Fractures are generally a late physical manifestation of osteoporosis. The forearm, vertebrae, femoral neck, and proximal humerus are common sites for fractures. In the elderly the presence of a dowager's hump (spinal curvature) indicates decreased bone volume and multiple vertebral fractures.

### Bone density measurement

Conventional radiographs are not sensitive enough to diagnose osteoporosis until total bone density has decreased by 50%. Bone densitometry is useful for measuring bone density (39). For assessment of bone mineral density, the most widely used techniques are dual-energy X-ray absorptiometry and quantitative computed tomography (117, 144). Single- and

dual-photon absorptiometry have been used in the past but provide poorer resolution, less accurate analysis, and more radiation exposure than X-ray absorptiometry. Both dual-energy X-ray absorptiometry and quantitative computed tomography have precision error rates of 0.5–2% (26, 42, 104, 119, 151). Of these methods, dual-energy X-ray absorptiometry is the most precise and the diagnostic measure of choice (144). Quantitative computed tomography is the most sensitive method but results in substantially greater radiation exposure than dual-energy X-ray absorptiometry.

For assessment of the peripheral skeleton, smaller less expensive systems can be used. Dual-energy X-ray absorptiometry scans of the distal forearm or the middle phalanx or quantitative ultrasound measurements can be of use for monitoring therapy when compared with baseline scans. These scans will have to be taken with the same instrument to ensure reliability. Their predictive value in assessing fracture risks for the hip or vertebrae still has to be determined. Therefore, baseline assessments of osteoporotic status and fracture risk have to be taken at a central and peripheral site.

Bone mineral density can be used to classify patients into three categories: normal, osteopenic, and osteoporotic. For this, bone densitometry reports are expressed as a *T* score (the number of SD above or below the mean bone mineral density for sex and race matched to young controls) or a *Z* score (comparing the patient with a population adjusted for age, sex, and race). Osteoporosis is the classification for a *T* score of more than 2.5 SD below the sex-adjusted mean for normal young adults at peak bone mass. *Z* scores are of little value to the practicing clinician (10).

### Laboratory tests

When clinical history and physical examination indicate other clinical conditions influencing bone mineral density, basic chemical analysis of serum is indicated. Laboratory tests are appropriate to exclude secondary causes of osteoporosis (49). Specific biochemical markers used in research can give information about the overall rate of bone formation and bone resorption. These markers include human osteocalcin and bone alkaline phosphatase. While widely used in research they are currently not part of the basic work-up for osteoporosis (2, 34, 63, 81).

### Risk factors

Several risk factors will predispose a person to osteoporosis. Osteoporosis is usually asymptomatic

until a fracture occurs; therefore, it is important to identify risk factors and appropriate methods and timing for screening.

Risk factors for osteoporosis can be divided into non-modifiable and modifiable risk factors (Table 1) (145).

Genetic factors can explain about 80% of the variability in peak bone mass and the rate of bone loss (128). Other risk factors include hormonal factors, nutritional factors, vitamin D levels, physical inactivity, and low body weight.

### Age

Throughout life, bone mass changes can be characterized into the following phases: growth, consolidation, and involution. Peak bone mass is accumulated during the growth phase, during which up to 90% of the ultimate bone mass is deposited. This phase is followed by a consolidation phase of up to 15 years. Building peak bone mass and the influence of exercise are of great importance. Since this occurs early in life, the importance of these should be emphasized in a younger population – the prevention of osteoporosis really starts at birth. Bone loss generally starts between ages 35 and 40 in both sexes, with an acceleration of bone loss in the decade after menopause in women (122). According to data from the NHANES III, 52% of Caucasian woman older than 80 years of age had osteoporosis compared with approximately 1% of Caucasian women younger than 30 years. The proportion of women with normal bone mineral density declines sharply with increasing age (91, 92).

### Genetics

Women are more susceptible to osteoporosis than men. However, osteoporosis in men, particularly at

**Table 1.** Risk factors for osteoporosis, non-modifiable and modifiable

Non-modifiable risk factors	Modifiable risk factors
Age	Sex hormone insufficiency
Race	Calcium intake
Sex	Vitamin D intake
Family history of osteoporosis/fracture	Weight
Early menopause	Physical activity
	Cigarette smoking
	Chronic glucocorticoid use

an older age, is an important health problem in the elderly (114). One in 12 older men have osteoporosis. Of all the hip fractures in persons older than 65 years, approximately 30% occur in men. Osteoporosis-related fractures in older men are associated with lower femoral neck bone mineral density, quadriceps weakness, higher body sway, lower body weight, and decreased stature (138).

Genetic factors play an important role in regulating bone density, skeletal geometry, and bone turnover as well as contributing to the pathogenesis of osteoporotic fracture itself as evidenced by heredity studies (61, 84). Measurement of bone density in twins has shown that there is a greater concordance of bone mass between monozygotic pairs rather than dizygotic pairs, indicating the significance of genetic influence (128). There is a familial tendency for lower bone mass in young women whose mothers have sustained osteoporotic fractures. Racial differences in skeletal size, with black people having larger, heavier bones and a lower fracture risk, may also point to genetic influence (100).

Turner syndrome is an example of genetically determined osteoporosis. Osteoporosis commonly complicates this syndrome and its genetic variants. Women with this syndrome are characterized by low plasma estradiol levels and elevated gonadotropin concentration (49). Another genetic disease in which osteoporosis occurs is *osteogenesis imperfecta*.

### Hormones

Both estrogen and testosterone deficiencies have been implicated as risk factors for osteoporosis. Gonadal hormones are the most important influence on bone loss in women. The onset of menopause and subsequent estrogen deficiency can affect the rate of bone loss (19, 87, 116). Rapid bone loss in women after the menopause can be effectively prevented by hormone replacement therapy (18, 85, 87, 123). However, when hormone replacement therapy is discontinued bone loss rates similar to the rates before hormone replacement occur (19, 86).

For the regulation of bone mineral density in men, testosterone is considered to be of primary importance. Estrogen also appears to play a role in the establishment of peak bone mass and maintenance of bone mineral density at a later age (13, 35, 72, 129).

In addition to sex hormones, abnormalities of calcitropic hormones are associated with bone loss (133).

### Nutrition

Nutrition is a modifiable factor and is important to bone health. Evidence suggests that calcium intake is

important during skeletal growth and peak bone mass development (52). Increasing the milk intake of adolescents has been shown to improve bone mineralization (11). Therefore, adolescents must maintain a dietary balance among calcium, protein, other calorie sources, and phosphorus. For example, phosphorus is a substantial component of carbonated drinks, and high phosphorus intake compromises calcium uptake by bone, thereby promoting decreased bone mass. In a study of carbonated beverage intake and dietary calcium-to-phosphorus ratio a strong association was reported between carbonated beverage consumption and bone fracture in girls (149). Calcium supplementation may be effective in reducing bone loss in late postmenopausal women, particularly in those with low habitual dietary calcium intake (22, 53). However, because other nutrients in addition to calcium are essential for bone health, calcium alone may be insufficient to combat osteoporosis.

The inability to maintain normal body mass promotes bone loss. The body weight history of women with anorexia nervosa is the most important predictor of the presence of osteoporosis (55). Bone mineral density in these patients does not increase to a normal range for several years after recovery and peak bone mass could be diminished compared with normal controls. Therefore, all persons with eating disorders remain at increased risk for osteoporosis.

During pregnancy, the additional demands placed on the mother by the fetus and during lactation by the infant could lead to loss of bone mineral density in the spine and hips. These losses, however, can be restored completely 6–12 months after cessation of lactation (28).

Vitamin D is essential for optimal absorption of calcium. Vitamin D deficiency contributes to osteoporosis and fractures through its effects on bone fragility and impaired muscle strength (6). The risk of vitamin D deficiency is increased with reduced sunlight exposure, as a result of strict dress codes where most of the body is covered. Other risks include low dietary intake of vitamin K (found in leafy vegetables and cheese) and high caffeine intake. Low intake of vitamin K is associated with low bone mineral density and increased risk of fracture. There is an association between high intake of caffeine and decreased bone mineral density in postmenopausal women who have low calcium intakes (96).

High consumption of fruit and vegetables and the resulting high intake of dietary alkali for skeletal integrity have beneficial effects on bone mineral density (5).

## Behavioral aspects

Current cigarette smoking is associated with low bone mineral density as well as a significantly increased risk of any kind of fracture in men and women. This effect will only slowly diminish after a person stops smoking (67). A history of smoking carries a modest but significant risk for future fractures (27, 41, 74, 143).

Heavy alcohol intake is associated with a reduction in bone density and increased fracture risk. The influence of modest alcohol consumption does not appear to have a major influence on the skeleton but can affect calcium metabolism and could lead to reduced bone mineral density. Ethanol has a direct effect on osteoblasts. Excessive alcohol consumption has been shown to depress osteoblast function and, thus to decrease bone formation. In alcoholics, relative malnutrition, lack of exercise, and impaired vitamin D metabolism will further increase the risk for osteoporosis and fractures. The lack of equilibrium and increased propensity for injury may further increase the risk for fractures.

Physical activity is important for the skeleton. Lack of physical activity is associated with an increased risk of osteoporosis; whereas weight bearing and muscular activity stimulate bone formation and increase bone mass (45). Calcium intake and vitamin D appear to be important contributors to this effect (29, 51, 132). The loading pattern and type of activity will result in site-specific responses. Starting physical activity before or at puberty provides the greatest benefits (68, 140). Bone preservation rather than addition of bone mineral density appears to be the effect in adults. The effect of exercise will not balance the effect of estrogen deficiency in the immediate postmenopausal years. Exercise in older people can improve gait, co-ordination, proprioception, and reaction time, decreasing the risk of falls (14, 135).

Low body weight and weight loss are both established risk factors for low bone mass and for an increased rate of bone loss (47, 48, 82). Bone loss can also be induced by medications, the most important of which are glucocorticoids (12). Because certain medications negatively affect bone mineral density, these drugs should be avoided, if possible, in those at risk.

## Therapy

Therapy can be based on the classification of bone mineral density. Patients with normal density

measurements need no further therapy. In osteopenic patients, emphasis should be on counseling and prevention of future bone loss. Follow up will be needed to monitor potential changes in bone mineral density. In osteoporotic patients, active therapy should be aimed at increasing bone density and decreasing fracture risk. Treatment of established osteoporosis, irrespective of the patient's age, is cost-effective (66). Therapies with proven rapid efficacy may offer important value to healthcare funders, providers, and patients (89). Correctly diagnosing, identifying, and treating patients at risk of fracture, before sustaining a fracture, will have a significant impact on the long-term burden of osteoporosis. The risk of the first fracture can be reduced from 8% to 2% and the 5-year fracture incidence can be reduced from approximately 34% to 10% (90). However, there is evidence suggesting that many women who sustain a fragility fracture are not appropriately diagnosed and treated for probable osteoporosis (37, 127). Of the majority of individuals at high risk, a large proportion will experience a fracture before being diagnosed and treated, and they will have an inadequate or non-existent prevention strategy (111). This highlights the importance of proper screening, early diagnosis, and the institution of appropriate prevention and treatment strategies.

## Prevention strategies

It is important to identify risk factors for individual patients and develop prevention strategies for the specific situations of patients. There are general principles and recommendations for prevention that were formulated by the National Osteoporosis Foundation.

- All women should be counseled on the risk factors for osteoporosis. Osteoporosis is a 'silent' risk factor for fracture, just as hypertension is for stroke; one in two Caucasian women will have an osteoporotic fracture at some point in her lifetime.
- To determine the diagnosis and disease severity, an evaluation of bone mineral density should be performed on all postmenopausal women who present with fractures.
- Bone mineral density testing is recommended for all postmenopausal women younger than 65 years who have one or more risk factors for osteoporosis, in addition to menopause.
- Bone mineral density testing is recommended for all women 65 years and older regardless of additional risk factors.

- All diagnosed patients are counseled to obtain an adequate dietary intake of calcium (at least 1200 mg/day), including supplements if necessary.
- Regular weight-bearing and muscle-strengthening exercises, to reduce the risk of falls and fractures, are recommended.
- Patients should be advised against smoking and smoking cessation should be advocated. Alcohol intake should be at a moderate level (i.e. up to one drink per day for women and up to two drinks per day for men).
- All postmenopausal women who present with vertebral or hip fractures should be considered candidates for osteoporosis treatment.
- Initiate therapy to reduce fracture risk in women with bone mineral density *T* scores below  $-2$  in the absence of risk factors and in women with *T* scores below  $-1.5$  if other risk factors are present.
- Pharmacological options for osteoporosis prevention and treatment are hormone replacement therapy, alendronate (Fosamax) and raloxifene (Evista) for prevention; and calcitonin (Calcimar) for treatment (109).

All postmenopausal women and men of older age should be aware of their risk for developing osteoporosis and be familiar with the range of non-pharmacological approaches to maintain bone health, bone mineral density, and to prevent osteoporotic fractures. Clinicians, including dentists, should be a resource of this information and motivation to make and sustain lifestyle changes relating to diet, exercise, tobacco, and alcohol use, and approaches to fall prevention.

Adequate intake of calcium and vitamin D is probably the easiest lifestyle modification. The National Osteoporosis Foundation, as well as the National Academy of Sciences, recommends a daily intake of 1200 mg dietary calcium and 400–800 IU of vitamin D. Well-balanced nutrition to ensure this is preferred; however, supplements should be suggested if diet alone cannot provide the recommended daily intake. In a large multicenter trial 36,282 postmenopausal women, aged 50–79 years, were randomly assigned to receive either 1000 mg calcium with 400 IU vitamin D<sub>3</sub> daily or placebo. After a 7-year follow-up period, a small but significant improvement in hip-bone density was found. Hip fracture rates were not significantly reduced and an increased risk of kidney stones was reported (57).

Tobacco use should be discouraged and current smokers should be encouraged to quit on their own or participate in a smoking cessation program. Excessive alcohol consumption adversely impacts

bone health. Counseling and treatment should be offered to patients with excessive alcohol consumption as part of the lifestyle modifications to prevent osteoporosis (112).

Physical activity and the beneficial affects of weight-bearing exercise have been well studied in a multitude of randomized, controlled clinical trials (32, 36, 71). Postmenopausal women participating in aerobic, weight-bearing, strength-training, and stretching exercises, who received calcium and vitamin D supplements, increased lumbar spine bone mineral density by 1.3%, compared with a 1.2% decrease in the control group (71). To motivate currently sedentary women to exercise and increase physical activity is a difficult challenge. The average older woman is not likely to exercise to the level needed to actually build bone. Additional benefits of exercise are strengthening of muscles, improvement of balance, and prevention of falls. On a weekly basis, a minimum exercise program should include three sessions lasting from 30 to 60 minutes each.

An increased fall risk is associated with dizziness, balance problems, poor co-ordination, muscle weakness and poor vision. Several medications, including sedatives, narcotic analgesics, antidepressants, anticholinergics, and antihypertensive agents, can affect awareness, alertness, and balance and should be viewed as additional risk factors for falls.

Individual approaches to identify these risk factors and steps to address these could include correcting vision, evaluating any neurological problems, reviewing prescription medications for side effects that affect balance, and evaluating home safety (112). Vitamin D deficiency is associated with increased body sway and an increased risk of falls and fall-related fractures. Vitamin D and calcium supplementation has been shown to reduce the risk of falling in elderly women (38, 150).

## Pharmacological intervention

Several pharmacological strategies are available to increase bone mineral density and therefore treat or prevent osteoporosis and reduce the risk of fractures. They include hormone replacement therapy, bisphosphonates, calcitonin, selective estrogen receptor modulators, parathyroid hormone or combinations of these medications. There is sufficient evidence in the literature to demonstrate that, depending on the drug and the patient population, treatment reduces the risk of vertebral fracture by 30–65% and of non-vertebral fractures by 16–53%

(25). On the other hand, poor compliance of patients with drug therapies for osteoporosis over a year leaves them at risk for fractures and higher health-care costs (25).

## Hormone replacement therapy

Rapid loss of bone density is observed because of estrogen deficiency in the early postmenopausal years. The rationale for hormone replacement therapy is to delay this bone loss. Estrogen therapy can have a dual effect that results in increased bone density. It can inhibit osteoclast formation and function and can also extend the lifespan of osteoblasts and osteocytes (93).

Randomized trials provide strong evidence that hormone replacement therapy prevents bone loss at both trabecular and cortical sites. The evidence for hip-fracture reduction comes primarily from case-control and cohort studies (9, 15, 73, 97, 108).

A meta-analysis evaluated data on all estrogen therapy and hormone therapy trials performed up to 1999 (147). The main focus was the impact of hormone replacement therapy on bone density and fractures. The combined data of this analysis suggest a strong impact of hormone replacement therapy on bone density at both trabecular and cortical sites after 1 and 2 years of therapy. A dose-response in bone density with hormone replacement therapy, in particular for the lumbar spine and femoral neck, was observed. There was a significant difference at 2 years between low-dose estrogen, defined as equivalent to 0.3 mg of Premarin, and high-dose estrogen, equivalent to 0.9 mg Premarin. Since that meta-analysis, several double-blind, randomized trials have been conducted. All the trials studied the effect of two, three or four doses of estrogen therapy and hormone therapy against placebo on bone mineral density. These studies in general found similar increases in spine bone mineral density for estrogen therapy and hormone therapy as reported in the meta-analysis (3, 7, 20, 23, 83, 88, 99, 113, 125, 130, 146).

In a randomized clinical trial as part of the Women's Health Initiative trial, in those women randomly assigned to receive conjugated estrogens, with or without a progestin, the reduction in hip fracture was 33% (124). Hormone replacement therapy increased total hip bone mineral density and reduced the risk of fractures at the hip, vertebrae, and wrist (16). When studying women with a hysterectomy in the estrogen-alone component of the Women's

Health Initiative, a reduced rate of hip fracture was found (1).

Discontinuation of estrogen results in measurable bone loss, although it is not certain whether discontinuation results in a greater fracture risk than continuation (44). Until recently, hormone replacement therapy was considered the primary therapy for postmenopausal women with osteoporosis. In 1999, it was used for approximately 38% of postmenopausal women in the USA (70). Forty-six million prescriptions were written in 2000 for conjugated estrogen. That made it the second most frequently prescribed medication in the USA. Recently, concern has been raised about the non-skeletal risks associated with long-term use of estrogen. Evidence of an increased risk of breast cancer and of cardiovascular outcomes during the course of the estrogen plus progestin trial of the Women's Health Initiative prompted early termination of this trial in 2002 (124). In 2004, an increased risk of stroke and failure to lower the incidence of coronary heart disease led to the early termination of the estrogen-alone trial.

This has led to a re-evaluation of the role of hormone replacement therapy in the treatment and prevention of osteoporosis. It should not be recommended for prevention of osteoporosis in postmenopausal women unless the woman is at significant risk of osteoporosis and other osteoporosis medications are unable to be considered (33). Since the publication of the Women's Health Initiative findings in 2002 about the risks of combined estrogen/progestin, a substantial decline has been observed in women receiving hormone replacement therapy (33). The result of this could be an increase in the incidence of osteoporosis in women who discontinued hormone replacement therapy and did not start another form of anti-resorptive therapy; especially when data concerning the rate of bone loss after withdrawal of estrogen therapy are considered. An accelerated rate of bone loss is observed, resulting in reductions in bone mineral density of up to 4.5% at the lumbar spine and up to 3.3% at the hip, during the first year after therapy discontinuation (33). When comparing women who had never used hormone replacement therapy to women who had discontinued hormone replacement therapy during the previous 5 years, the rate of hip fracture was 65% higher (150).

It is, therefore, important that women discontinuing hormone replacement therapy receive appropriate screening for their risk for complications of osteoporosis and should be counseled regarding alternative forms of therapy to prevent fracture (4).

## Selective estrogen receptor modulators

Selective estrogen receptor modulators were developed to provide the benefits of estrogen therapy without its unwanted side effects. Their mechanism of action, such as that of raloxifene, is similar to that of the estrogens (121).

Although less potent than conjugated equine estrogens and bisphosphonates, the selective estrogen receptor modulators decrease bone turnover (115). Raloxifene increases spine bone mineral density slightly and decreases the risk of vertebral fracture by 40% in women with osteoporosis, but it has no effect on the risk of non-vertebral fracture.

The Multiple Outcomes of Raloxifene Evaluation trial in 7705 women with postmenopausal osteoporosis evaluated the efficacy of raloxifene. In 4 years of therapy with raloxifene with high and low doses, the risk of vertebral fracture was reduced by 43% and 36%, respectively. Reduction in fractures was observed in the first year of treatment but no effect was found on the risk of non-vertebral fractures. Adverse events include hot flashes and leg cramps. Similar to estrogen therapy, an increase in the incidence of deep vein thrombosis was observed (24). A reduction in the risk of breast cancer is observed with long-term use of raloxifene. The drug, however, is not approved for this indication (21).

New selective estrogen-receptor modulators are being researched and may be available in the near future.

## Bisphosphonates

Bisphosphonates, analogs of pyrophosphate, bind selectively to bone mineral. During bone resorption they are taken up by osteoclast, resulting in osteoclast deactivation and apoptosis. Bone resorption is suppressed, followed by a secondary mineralization resulting in increased bone mass, improving bone strength, and a reduction in fractures (120).

Bisphosphonates are often considered the first-line therapy for the treatment of postmenopausal osteoporosis. They are the most widely prescribed anti-resorptive agents. Randomized trials of alendronate and risedronate, two second-generation bisphosphonates, demonstrated increased bone mineral density in postmenopausal women with osteopenia or osteoporosis. In women with osteoporosis a reduction in the incidence of hip, vertebral, and non-

vertebral fractures of nearly 50% was found. This effect was noted early in therapy (8, 31, 50, 98).

Long-term use of alendronate can be safe for at least 7 years without adverse affects on bone strength. Upon discontinuation of long-term (5 years or more) alendronate therapy, minimal amounts of bone loss were observed in the following 3–5 years (31, 44). The high rate of drug-induced esophagitis led to development of once weekly regimens.

Of concern to the dental community is the occurrence of osteonecrosis of the jaws. Within the last 3–4 years, reports in the literature have described osteonecrosis of the jaw as a potentially serious complication, which is suspected of being associated with the use of intravenous bisphosphonates. After initial observations by Wang at the University of California, San Francisco, Marx and Migliorati reported similar findings in a new set of patients (94, 105, 126, 142). The clinical aspects and behavior of the osteonecrotic lesions in these patients showed a striking resemblance to osteoradionecrosis with exposed bone, sequestration, and questionable/delayed response to conventional surgical management. Many of the initial observations point to the potential role of intravenously administered bisphosphonates, such as pamidronate and zoledronate, in the development of this condition. In a detailed paper, the findings in an additional 63 patients were outlined. Fifty-six patients had received intravenous bisphosphonates for bone metastasis and seven had undergone chronic oral bisphosphonate treatment for osteoporosis (126). In a 2004 editorial, Greenberg (43) further underscored the importance of this largely unrecognized destructive lesion, and alerted oncologists and dentists of its potential association with intravenous bisphosphonates. While these case series and editorials implicate the role of bisphosphonates, a consistent definition of the etiology of osteonecrosis of the jaw remains unclear. The problem is further complicated by reports that it may also be induced by fungal infections, trauma, herpes zoster virus infection, and necrotizing sialometaplasia, and potentially by other drugs and chemotherapeutics, which are commonly utilized in the management of this population. Regardless of the lack of a clearly defined process, a relationship between bisphosphonates and osteonecrosis of the jaw appears to exist.

Osteonecrosis of the jaw occurs more commonly in the mandible but has also been reported in the maxilla. It appears to be highly associated with periodontitis, other oral infections and extraction of infected teeth in a majority of the reported cases. In addition, the signs and symptoms that may occur

before the appearance of clinically evident osteonecrosis include changes in the health of periodontal tissues, non-healing mucosal ulcers, loose teeth, and unexplained soft-tissue infection. As such a small number of patients taking oral bisphosphonates for osteoporosis actually develop osteonecrosis, it seems logical that multiple etiological factors or potentiators may play roles in the onset of osteonecrosis. More than half of the subjects reported to have osteonecrosis of the jaw were on high-dose corticosteroids in addition to bisphosphonates, and some patients may have had impaired bone marrow blood flow, leading to chronic marrow ischemia and infarction (137). One hundred and nineteen patients who had bisphosphonate-related bone exposure after being treated with intravenous bisphosphonates for approximately 1 year were described (95). Common findings were periodontitis (84%), dexamethasone use (59.7%) and other maintenance chemotherapies. The most common identifiable precipitating events were tooth extraction (37.8%) and periodontitis (84%), with approximately one-quarter of bone exposures occurring spontaneously in patients with edentulous mandibles.

Most of the 263 reported cases suspected of being osteonecrosis of the jaw had common findings. The osteonecrosis of the jaw occurred most commonly in patients with existing periodontitis following tooth extraction. Most patients were receiving intravenous bisphosphonate as an adjunct to chemotherapy and, in addition, were or had been taking corticosteroids. The role of oral bisphosphonates in osteonecrosis of the jaw needs to be further evaluated.

## Calcitonin

Calcitonin is an inhibitor of osteoclast activity. Nasal calcitonin and subcutaneous calcitonin are available for treatment of postmenopausal osteoporosis. Treatment of women with osteoporosis with nasal calcitonin has been shown to reduce the incidence of vertebral fractures, in a single randomized study, by 33% when compared with placebo (17).

Calcitonin is not a first-line treatment for osteoporosis and it is now considered preferable to treat osteoporosis with more potent agents.

## Future developments

A dramatic increase in the incidence of osteoporosis is predicted. Several factors play a role in this. Life

expectancy is increasing and the population is aging. The National Osteoporosis Foundation estimates that 61.4 million men and women in the USA will have low bone mass or osteoporosis by 2020. With the aging population, the number of people at risk for fragility fractures is projected to increase. The worldwide incidence of hip fracture is projected to increase by 310% in men and by 240% in women by the year 2050 (46). The largest increases are anticipated in Asia (118). Over the last 40 years, a fivefold increase in the incidence of annual hip fractures has been observed. In the European Union, fracture rates related to osteoporosis are expected to double by 2050 (101).

## Osteoporosis and oral health

The risk factors for osteoporosis include many risk factors associated with advanced periodontal disease. Since both osteoporosis and periodontal diseases are bone resorptive diseases, it has been hypothesized that osteoporosis could be a risk factor for the progression of periodontal disease. The correlation between systemic bone mineral density and oral bone mineral density has been studied.

Kribbs was the first to address the relationship between systemic bone mineral density and mandibular density when measured by quantitative analysis on intraoral radiographs. The osteoporotic group had less mandibular bone mass and density and a thinner cortex at the gonion than the normal group (77). Most studies reported to date concerning this relationship are cross-sectional and relate systemic bone mineral density with mandibular mineral density. In general, a correlation is reported between systemic and oral bone mineral densities (58, 60, 131, 134, 148).

Low bone mineral density has been associated with higher tooth loss (59, 76, 134, 136). Other reports fail to find this correlation (30, 75, 106). Tooth loss could serve as a surrogate evaluation for periodontal disease, assuming that 100% of attachment is lost when the tooth is lost. There are some concerns with this assumption. The underlying reason for loss of teeth is often unknown and could include reasons other than terminal periodontal disease. The extent of disease around the remaining teeth is also not taken into account in these analyses. Therefore, an accurate measurement of the extent of periodontal destruction cannot be made by using tooth loss as a variable in the analysis of the relationship between osteoporosis and periodontitis. Cross-sectional studies have used a

variety of parameters to evaluate the periodontal disease severity in subjects with decreased bone mineral density. Most studies showed a correlation between reduced bone mineral density and increased severity of periodontal disease (54, 58, 60, 77–80, 107, 134, 139, 141, 148).

Von Wowerm assessed osteoporosis using bone mineral content of the mandible and forearm, determined by dual-photon scanning, and found greater amounts of loss of attachment in osteoporotic women in a small population with a mean age of 68 years (148).

In a study population of 70 postmenopausal Caucasian women aged 51–78 years, skeletal systemic bone mineral density was assessed by dual-energy X-ray absorptiometry. Clinical attachment loss and interproximal alveolar bone loss represented periodontal disease severity. Mean alveolar bone loss significantly correlated with systemic bone mineral density. A trend for a correlation between clinical attachment levels and bone mineral density was found (139).

In contrast, some studies failed to report this correlation (30, 75). Elders used lumbar bone mineral density and metacarpal cortical thickness compared with alveolar bone height measured on bite-wing radiographs and clinical parameters of periodontitis. No significant correlation was observed between the bone mass measurements and alveolar bone height or periodontal parameters (30). The mean age in this group was relatively young, between 46 and 55 years of age, and could have contributed to the lack of correlation.

Cross-sectional studies have limitations. No information about the diseases studied before the examination is available. Although both osteopenia and periodontal disease are chronic diseases and can be assumed to have been present before the observations, it is incorrect to conclude that both diseases have been present. Larger prospective longitudinal studies are needed to further evaluate osteoporosis as a risk factor for periodontal disease progression. The oral ancillary study of the Women's Health Initiative was designed to determine if there is an association between systemic osteoporosis and oral bone loss. In postmenopausal women hip-bone mineral density was confirmed with dual-energy X-ray absorptiometry. Alveolar bone height changes over a period of 3 years were assessed with subtraction radiography. Subjects with osteoporosis presented with greater progression of alveolar bone loss than subjects with no osteoporosis over the 3-year period. Subjects with

periodontal disease at baseline exhibited greater amounts of alveolar bone loss than subjects with periodontal disease. This indicates a greater propensity to lose alveolar bone in subjects with osteoporosis, especially in subjects with pre-existing periodontitis (40). Further evaluation of this relationship is needed to better understand the true correlation. To date, limited information is available for a male population.

## Osteoporosis and dental management

The effects of osteoporosis on both systemic health and oral health need to be well understood. As a healthcare provider, the dentist could serve as a pre-screener of patients with the potential for osteopenia or osteoporosis. Familiarity with the risk factors could help identify these individuals and aid in earlier diagnosis. Proper counseling of the need for prevention and treatment together with referral for further evaluation of their bone status could greatly benefit our patients. An additional tool for pre-screening may lie in the information obtained on our dental radiographs. The usefulness of the alveolar trabecular pattern analysis and mandibular alveolar bone mass for prediction of skeletal bone mineral density was evaluated (62). An index to assess the alveolar trabecular patterns was developed and a significant correlation was found with skeletal bone mineral density. Evaluation of the coarseness of trabeculation of alveolar bone, as seen on intraoral radiographs, could be a helpful clinical indicator of skeletal bone mineral density and better than densitometric measurements of the alveolar bone. Dense trabeculation is a strong indicator of high bone mineral density, whereas sparse trabeculation may be used to predict low bone mineral density. Further studies are being conducted to develop protocols for pre-screening our patients for reduced bone mineral density on dental radiographs.

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