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Periodontitis and osteoporosis

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Abstract

Today's knowledge and studies show a firm correlation between osteoporosis and periodontitis, particularly in postmenopausal women. This review study deals with epidemiological and etiopathogenetic association between chronic periodontitis and an osteoporosis. A special emphasis is put on explanation of possible relations between a premature tooth loss and decrease of length and density of jaw bones, particularly their alveolar prolongations. The second part of the paper deals with principles of treatment in patients suffering of osteoporosis. Osteoporosis reduces density of jaw bones and decreases a number of teeth in jaws, but it does not affect other clinical signs and markers of periodontitis such as inflammation, bleeding and the depth of periodontal pockets and microbial plaque.

INTRODUCTION

Osteoporosis is currently presented as a systemic disease of osseous tissue and several studies and research now consider it as a possible etiopathogenetic factor of severe periodontitis. Previous research stated that generalized osteoporosis did not play a role in etiology of destructive periodontitis. However, now it has been shown that total body calcium and bone density correlated with mandibular bone density and several studies have demonstrated a close association between systemic osteopenia and edentulism (Gera 2002). Nowadays there is presented knowledge that also jaw bones, including their alveolar prolongations, are subject to osteoporotic processes (Kribbs 1990; Van Wovern *et al.* 1994). It is suggested that periodontal tissue loss including alveolar bone and also tooth loss can be associated with osteoporotic and osteopenic systemic changes, particularly in postmenopausal women (Mohammad *et al.* 2003; Payne *et al.* 1999).

Osteoporosis is a systemic disease of bone structures resulting in low bone mass and its micro architectural deterioration. Osteoporosis and osteopenia are characterized by reduction in bone mass resulting from imbalance between the rate of bone formation and resorption. Increased resorption results in demineralization, deformities and pathological fractures in various locations. Reduction of bone mineral density is normally measured by means of osteodensitometry, which gives us a bone density in g/cm^2. According to the WHO, osteoporosis is considered to be present

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when bone mineral density (BMD) is expressed as a T-score reflecting the value of 2.5 of standard deviations (SDs) below maximum levels of young healthy adults. In osteopenia, BMD values range between 1.0 and 2.5 of standard deviations (SDs) of BMD in young healthy adults. Reduced BMD values associated with fractures are called "osteoporosis with fractures" (fracture of 1 to 3 vertebrae) and "advanced osteoporosis" with multiple fractures of the skeleton (Blake *et al.* 2007; AAP 1989).

Osteoporosis is a serious health problem with strong economic and social impacts. The latest diagnostic studies presented the fact that in 70-year-old Scandinavian women osteoporosis may be detected in 49 up to 72% of subjects (Persson *et al.* 2011). In the USA osteoporosis affects more than 20 million patients and treatment of osteoporosis in the USA requires the amount of 7 to 10 billion dollars per year (AAP 1989).

CLASSIFICATION AND ETIOPATHOGENESIS

Etiopathogenetic classification divides osteoporosis into primary and secondary forms.

Primary forms of the disease do not associate with other diseases and they largely relate to involutionary changes in postmenopausal women. Other forms of primary osteoporosis include an idiopathic form (of unknown etiology) and postsurgical form (after ovariectomy). Primary osteoporosis affects both genders in all age categories. *The most common form is known as involutionary* and is represented by **postmenopausal osteoporosis.** *Postmenopausal osteoporosis is caused by estrogen deficiency, which accompanies changes in climacterium.* Estrogen deficiency results in increased bone resorption through cytokine dysregulation affecting activity of osteclastogenesis. Cytokines affected by estrogen include particularly: PGE2, M-CSF (macrophage-colony stimulating factor), IL-1, IL-2, IL-6, TNF and RANK-ligand (Kanis *et al.* 1994, Marques *et al.* 2003). Under experimental conditions there was found increased expression of a key mediator of osteoclast differentiation where the values of RANKL (Receptor activator of nuclear factor kappa-B ligand) were the highest in a group of laboratory animals with periodontitis and osteoporosis which may explain a mutually enhancing effect of both diseases (Allam *et al.* 2010). During measuring the spectrum and number of bacteria, levels of cytokines IL-1-beta and IL-6, and also highly sensitive hsCRP in elderly people, statistically significant correlates with the following risk factors were found in a group of patients with active periodontitis and osteoporosis: ethnicity, depth of periodontal pockets, female sex, serum concentrations of hsCRP and the presence of *Peptostreptoccocus micros*, *Tannerella forsythia*, *Prevotella intermedia* and *Streptococcus mutans* (Swoboda *et al.* 2008). The above mentioned facts constitute a mechanism that interprets an association between periodontitises and osteoporotic changes, as chronic inflammatory diseases of the periodontium activate proinflammatory cytokines, which stimulate osteoclastic mechanisms (Golub *et al.* 2006).

Secondary osteoporoses represent forms particularly related to endocrinological diseases such as hyperparatyreosis, hypertyreosis, in patients with diabetes, in renal diseases, in hepatopathies and osteoporosis induced by long-term use of glucocorticoids, which with the participation of growth factors such as IGF-1, inhibit osteoformation and stimulate osteoresorption (Gera 2002; AAA 1989; Kanis *et al.* 1994).

RISK FACTORS FOR OSTEOPOROSIS

1. Advanced age. Bone metabolism in the body has three major phases. Growth, consolidation and involution. A phase of involution starts at the age of 35 to 40 years.
2. Genetic predisposition. Genetics plays a crucial role in regulation of bone density and bone rebuilding and in skeletal geometry as well (Jin *et al.* 2005).
3. Subtle body framework with fragile, hypovolemic skeleton, which does not produce adequate bone tissue reserve.
4. Ethnicity.
5. Female sex hormones significantly affect bone loss. Postmenopausal hypoestrogenemia and amenorrhea after ovariectomy cause large bone loss (Andreoli *et al.* 2011; Tezal *et al.* 2000).
   Testosterone level in the body directly affects bone density.
6. Low calcium and vitamin D intake and physical inactivity.
7. Smoking may associate with decreased bone density and may increase a risk of pathological fractures (Kotuganti *et al.* 2009).
8. Long-term medication with glucocorticoids (Cannalis *et al.* 1996).

ASSOCIATIONS BETWEEN SYSTEMIC OSTEOPOROSIS AND PERIODONTITISES

Correlations between systemic and local osteoporosis and destructive periodontitises can be divided into more morphometric, metric and clinical groups and parameters. Comparison of particular categories can in many aspects and mechanisms predicate of and demonstrate mutual relations between both diseases. In terms of correlations between osteoporosis and inflammatory periodontal diseases the following partial interrelations and parameters are frequently researched.

a) Systemic osteoporosis and osteoporotic changes in jaws

Several studies have found that the total bone mass and skeletal density are in a close correlation with the density of alveolar bone particularly in healthy, but also in osteoporotic women (Kribbset 1990; Payne *et al.* 1999;

Klemetti *et al.* 1996). In postmenopausal women systemic osteopenia with interproximal loss of alveolar prolongations occurred most, whereas the basal portion of jaws remained relatively intact (Klemetti *et al.* 1996). Some other results show that osteoporosis decreases mineral density in jaw bones and height of alveolar bones, which affects the loss of posterior teeth (Payne *et al.* 1999). Reduction of mineral density in alveolar bone was found also in a group of osteoporotic patients with hypoestrogenemia in a 2-year longitudinal clinical study (Payne *et al.* 1999). While monitoring the total body calcium, bone mass at radius and mineral density at the spine, there was found a correlation with a total mandibular mass (Kribbs *et al.* 1989). In healthy women the density of maxillary alveolar process bone was related to the density of the mandibular alveolar process, and also to the density of lumbar spine, hip bones and radius. However, BMD of the maxillary alveolar process bone declined with age (Southard *et al.* 2000). In a group of healthy women aged 20–90 years the mandibular bone mass strongly correlated with the bone mass at spine and wrist (Kribbs *et al.* 1990).

The data gathered on various types of studies appear to indicate a direct relationship between BMD of jaw bones and quantity of bone mass and BMD in healthy and also osteoporotic individuals. We can also say that osteoporosis occurs in jaw bones as well.

b) Associations between osteoporosis and tooth loss

Patients with osteoporosis often present with premature loss of teeth. This loss is in correlation with decreased BMD in the upper and lower jaw. Partially dentated lower jaws had zones with adequate density and zones with decreased density in a direct correlation with the presence of teeth. The lowest BMD values were found in edentulous jaws. However, locally highest BMD values in the mandible were detected at the sites of enormous functional load, which denotes a significant argument for sustained tooth preservation in these groups of patients (Straka 2002). Reduction of BMD appears particularly in women in climacterium after the age of 50 years. A mutual correlation of decreased BMD in jaw bones and skeletal bones was found in femur, shoulder and metacarpal bones and spinal vertebrae (Straka 2002; Hildebolt *et al.* 1997).

In a group of postmenopausal women there was detected a relationship between systemic BMD and premature tooth loss, where tooth loss correlated with reduced BMD in the upper and lower jaws (Straka 2002; Hildebolt *et al.* 1997; Krall *et al.* 1994). Postmenopausal osteoporosis, premature tooth loss and reduced BMD are etiologically related to hypoestrogenemia, which was confirmed by studies in the groups of patients with ovarian insufficiency or after ovariectomy (Straka 2002; Močil *et al.* 1991).

b) Associations between osteoporosis and some clinical symptoms of periodontitises

Local osteoporotic changes in jaw bones can be subject to several clinical symptoms of periodontitises that largely are not related to inflammatory changes. For example, systemic skeletal reduction of BMD correlated with a decreased clinical attachment loss (CAL) and interproximal alveolar bone loss and also attachment loss resulting in larger gingival recessions (Tezal *et al.* 2000; Mohammad *et al.* 1996). Increased attachment loss was found also in osteoporotic women with the mean age 68 years (Von Wovern *et al.* 1994). Following-up of osteoporotic individuals who were in addition smokers revealed a decreased bone loss presented by gingival recessions (Payne *et al.* 2000).

However, some studies in this field failed to confirm positive correlations of both diseases. When comparing some parameters evaluated in periodontitises by means of bite-wing radiographs and by assessment of lumbar spine BMD, a correlation between both diseases was not confirmed (Elders *et al.* 1992). Another study compared pocket depth, gingival recession, gingival bleeding and marginal bone level in patients with normal BMD and with osteoporosis. When comparing particular parameters, no statistically significant differences were observed (Lundstrom *et al.* 2001). The results of various other studies have not shown clearly a positive correlation between some indices and parameters of periodontitises in the groups of osteoporotic and healthy individuals, largely in the parameters related to periodontal inflammation.

d) Osteoporosis, periodontitis and pathological fractures

Osteopenia and osteoporosis result in bone demineralization, which is clinically presented by pain, bone deformities and pathological fractures. The risk of fractures directly correlates with total mineral bone density. With advancing bone demineralization the risk of pathological fractures also increases and some studies suggest that present periodontal disease may increase the risk of fractures (Moedano *et al.* 2011; Clark *et al.* 2009).

A Latin American osteoporotic study revealed that in women at the age of 50 years and more the prevalence of radiographically detected fractures accounted for 19.2%. In Mexico City the prevalence of osteopenia accounted for 63.7% and osteoporosis 22.7% in women at the age ranging from 60 to 64 years. Ageing of the population increases the risk of pathological fractures and causes increased mortality after one year following the first hip fracture up to 20% of subjects (Moedano *et al.* 2011; Clark *et al.* 2009). The risk of osteoporosis and pathological fractures was associated with the severity of some clinical signs of periodontitises and tooth loss (Moedano *et al.* 2011).

Some studies stated that osteoporotic individuals with at the same time present periodontitis had significantly aggravated PIXI calcaneus T-values than the sub-

jects without periodontitis (Swoboda *et al.* 2008). It was also found that osteoporotic patients with periodontitis were at higher risk of pathological hip and hand fractures than osteoporotic patients without periodontitis (Persson *et al.* 2011).

The results of these studies suggest that a concurrent disease of osteoporosis and periodontitis deteriorates BMD and at the same time may increase a risk of pathological fractures at various sites, although their causal relationship remains unclear (Persson *et al.* 2011; Moedano *et al.* 2011; Clark *et al.* 2009; Swoboda *et al.* 2008). It should be noted that not all studies showed a positive correlation between osteoporosis and periodontitis (Phipps *et al.* 2007).

TREATMENT OF OSTEOPOROSIS

In practice, there are often presented opinions that adequate bone mineralization can be saturated by increased calcium intake in a diet. However, some research found that increased calcium intake does not have to correlate with total skeletal density, since it does not have to be related to its increased gastrointestinal absorption (Tellez *et al.* 1995; NIH 1994). Minor improvement of skeletal BMD was found in concurrent medication with calcium and vitamin D. Synchronized supplementation of calcium dose of 500 mg and vitamin D of 5.0 μg shows a partial therapeutic effect in benign osteopenias; nevertheless, in the therapy of postmenopausal osteoporoses it is not sufficient (Straka 2002; Straka *et al.* 2014; Tellez *et al.* 1995). Particularly in children we can advise milk intake, while in indicated patients a parallel supplementation of calcium and vitamin D together with sufficient UV radiation is beneficial (Straka 2002).

The most frequent cause of osteoporosis is postmenopausal hypoestrogenemia. Decreased skeletal density affects also jaw bones with premature tooth loss in this group of women. Though, estrogen deficiency caused by insufficient ovarian functions leads also to gynecological, cardiological, psychiatric or psychological disorders (Straka 2002). Hormone replacement therapy (HRT) substitutes inefficient ovarian production of estrogens and currently it represents a dominant pharmacological treatment for the above mentioned complications. In a review study that assessed 20 published studies involving 13,735 postmenopausal women it was summarized that individuals treated with HRT had better dental parameters and they spent considerably lower costs for dental care than a comparable group of untreated women (Straka 2002; Allen *et al.* 2000). Another research showed that HRT with estrogens provided maintenance of several teeth in jaw bones and improved a condition of mandibular bone mass (Straka 2002; Straka *et al.* 2013; Birkenfeld *et al.* 1999; Jacob 1996 *et al.* 1996). Once having been aware of the facts involved, it is clear that HRT application in postmenopausal patients is beneficial also for a general oral status.

Today's standard pharmacological treatment of osteoporosis is with bisphosphonates, which affect bone remodeling by decreased function of osteoclasts. Thus a remodeling process involves mostly formation of bone tissue and its increased density and weight. Bisphosphonates are derivatives of inorganic pyrophosphates with low intestinal absorption. Renal excretion is the only route of their elimination in a non-metabolized condition. Bisphosphonates are characterized by their high affinity for hydroxylapatite crystals and they incorporate into bones unchanged with the half-life in bone in the human body up to 12 years (Straka 2002; Straka *et al.* 2012; Harris *et al.* 1993; Lin *et al.* 1999; Reddy *et al.* 1995). According to a pharmacodynamic effect bisphosphonates are divided into aminobisphosphonates and non-aminobisphosphonates. Aminobisphosphonates are more potent and they also have anti-tumor effects (they stimulate cell apoptosis, inhibit tumorus invasiveness, inhibit cell adhesiveness to extracellular matrix), they also cause anti-angiogenesis and are used in treatment for various types of tumors metastasizing into bone and multiple myeloma (Santini *et al.* 2003; Vincenz *et al.* 2005; Woo *et al.* 2006).

A serious complication of bisphosphonate application is osteonecrosis of jaw bones, where the prevalence only in the lower jaw bone accounts for about 65%, only in the upper jaw bone 26% and in both jaws together 9%. A majority of patients (94%) was treated with intravenous bisphosphonates and in 86% of patients there was diagnosed multiple myeloma or metastasizing lung cancer, the rest of patients were subjects with oral application of antiosteoporotics or patients with Paget's disease (Woo *et al.* 2006). Interestingly, in 60% of patients osteonecrosis occurs after a tooth extraction or another surgical dentoalveolar procedure. Relatively frequent osteonecroses occur in patients with various types of removable dentures, which can pose less physiological loading of bone. The same etiopathogenesis can be observed on localization within bone exostoses (Woo *et al.* 2006; Marx *et al.* 2005). It should be noted that intravenous doses of antiosteoporotics for treating malignancies are 12-fold higher than doses used for the therapy of osteoporosis. Particular types of antiosteoporotics are responsible for a risk of developing osteonecroses, especially from the group of zoledronic acid, whereas with increasing duration of use this risk is intensified. A possible cause of increasing risk is a long life-time of the medicament (Woo *et al.* 2006). Up to 94% of patients with osteonecrosis received antiosteoporotics from the group of zoledronic acid and pamidronates. Treatment with non-aminobisphosphonate antiosteoporotics from the group of clodronates generally does not induce development of osteonecroses.

Currently, we can summarize the risk factors of developing bisphosphonate-induced osteonecroses into several groups. One group of risk factors includes total dose and type of bisphosphonate used and another one includes dental surgery, history of trauma and dental

infection. Some possible etiopathogenetic relations of arising such complications stem from these risk and predisposing factors. Posterior mandibular lingual area is extremely loaded and is sheltered with only a thin layer of mucosa; minor forms of osteonecrotic lesions suggest a condition of a so-called "lingual mandibular sequestration", where in the elevated mylohyoid area there detach the spicules of bone ranging from 1 to 3 mm that resorb spontaneously. In this localization, apparently due to large mechanical load and disordered metabolism on the application of bisphosphonates, there often occur also drug-associated osteonecroses (Woo *et al.* 2006). Another possible etiopathogenetic factor is a fact that dental and periodontal tissues are often infected, which may be transferred also to adjacent bone structures. Chronic stress trauma, infection, accumulation of the drug and metabolic suppression in the form of dysregulated bone modification may cause local bone necrosis.

In the prevention of bisphosphonate-induced osteonecroses there plays a key role early identification of such patients, particularly those with implants, and avoidance of dentoalveolar surgical procedures in them. In case of scheduled procedures it is recommended to postpone the procedure for 24 months after discontinuation of treatment (Zadik *et al.* 2012). In conclusion, it is clear that treatment of osteoporosis is at the same time an active measure for preserving adequate bone density in jaw bones, which has a positive impact on maintenance and sufficient function of the teeth and dental apparatus.

CONCLUSIONS

1. Osteoporotic changes in skeletal bones affect also jaw bones, particularly their alveolar prolongations, where they significantly decrease their length and density. Basal parts of the upper and lower jaw remain relatively well preserved (Straka 2002).
2. Osteoporosis and adverse BMD values on jaw bones are directly correlated with premature tooth loss, especially in gerontological patients, postmenopausal women in particular (Renvert *et al.* 2011).
3. Osteoporosis reduces density of jaw bones and decreases a number of teeth in jaws, but it does not affect other clinical signs and markers of periodontitises. In addition to decreased values of BMD in jaw bones and increased loss of teeth, osteoporotic process does not affect significantly other symptoms of periodontitis such as inflammation, bleeding and the depth of periodontal pockets and microbial plaque (Straka 2002).
4. Estrogen deficiency in climacterium affects adversely skeletal BMD and jaw bones in this group of women and significantly increases a risk for pathological fractures and premature tooth loss. In the group of postmenopausal women HRT (hormone replacement therapy) is an important therapeutical method which in addition to antiosteoporotic effect has also several beneficial effects on other postmenopausal complications (Allen *et al.* 2000).
5. Another group of antiosteoporotics includes bisphosphonates, whose oral application in treatment of osteoporosis poses a minimal risk of formation osteonecrosis in jaw bones. However, such risk is significantly increased after their intravenous application in treatment of malignancies. Treatment with bisphosphonates increases density of jaw bones and decreases loss of teeth (Jacob *et al.* 1996; Harris *et al.* 1993; Lin *et al.* 1999).
6. In prevention of osteoporosis and maintaining adequate mineral bone density and in treatment of minor osteopenias, we indicate supplementation with calcium of 500 mg/24 hours and concurrent medication with vitamin D in a dose of 5.0 μg. Slightly raised intake of calcium and vitamin D is important particularly in children and elderly people over 65 years of age.
7. Dentists encourage administration of various groups of antiosteoporotics indicated by other experts, particularly in postmenopausal women and gerontological patients. Antiosteoporotic treatment is a good therapeutical preventive measure for maintaining appropriate mineral density of jaw bones, which protects the skeleton against pathological fractures and premature loss of teeth (Straka 2002).

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