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IMMUNOPATHOGENETIC MECHANISMS OF PERIODONTAL DISEASE AND POSTMENOPAUSAL OSTEOPOROSIS

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Osteoporosis and periodontitis are widespread diseases among male and female population, whose incidence increases with aging. The basic pathogenic mechanism of osteoporosis and periodontal disease is a bone resorption with increased production of proinflammatory cytokines: interleukin IL-1β, IL-6, TNF-α and RANKL. The discovery of receptor activator of NF-κB (RANK), its ligand (RANKL) and osteoprotegerin (OPG) has contributed to the understanding of bone biology and mechanisms of osteoclastogenesis. RANKL-RANK interaction is critical for differentiation and maintenance of osteoclast activity. The balance between RANKL and OPG regulates osteoclastogenesis, and thus bone resorption. The disruption of the RANKL/RANK/OPG axis leads to an imbalance between bone formation and bone resorption; therefore, it is responsible for the disturbed bone homeostasis. Loss of bone density associated with decreased estrogen levels is the result of a significant increase in osteoclast activity. Menopausal bone loss may be the result of osteoclast overactivation by proinflammatory cytokines and it is associated with reduced estrogen levels. The lack of estrogen can lead to worsening of periodontal disease and it increases the rate of the gingival connective tissue damage by stimulating the synthesis of several cytokines responsible for bone resorption. Cytokines and RANKL/OPG signaling pathway involved in the pathogenesis of osteoporosis and periodontal disease can lead to the activation of osteoclasts and the stimulation of bone resorption. These findings in the future may improve the usual treatment of periodontal disease and osteoporosis therapy, including the inhibition of proinflammatory mediators and osteoclast activity with the additional use of anti-inflammatory drugs. This involves blocking the binding of different stimulating factors to their receptors on osteoclast precursors, particularly RANKL and development of new more selective drugs with fewer side effects that would act as an anti-cytokines preventing the binding of cytokines to their receptors. *Acta Medica Medianae 2012;51(4):51-57.*

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Introduction

Osteoporosis and periodontitis are widespread diseases among male and female population, whose incidence increases with aging (1).

Osteoporosis is characterized by the reduction of bone mass and a micro-architectural damage of the bone tissue. The bones of the skeleton and jaw become frail, brittle and fragile due to the pronounced loss of bone mass (2).

Numerous laboratory studies indicate that osteoporosis is likely to be caused by complex interactions among systemic and local regulators of bone cells functions. The heterogeneity of osteoporosis may be due not only to differences in the production of systemic and local regulators, but also to changes in receptors, signal transduction mechanisms, nuclear transcription factors, and enzymes that produce or inactivate local regulators. Within the last decade, the identification of many of the regulatory mechanisms that have been linked to osteoporosis has been the result of genetic studies (3).

Risk factors for osteoporosis can be divided into non-modifiable (gender, age, early menopause, physical constitution, race and inheritance) and modifiable risk factors (reduced calcium intake, physical activity, smoking, alcohol) (4).

An interesting finding is that risk factors for osteoporosis include many risk factors associated with advanced periodontal disease (4).

Having in mind that periodontal disease is defined as inflammation of the tooth-supporting apparatus followed by resorption of alveolar bone

and loss of the soft tissue attachment to the tooth (3,5,6) and that both periodontal disease and osteoporosis are bone resorptive diseases, it has been hypothesized that osteoporosis could be a risk factor for progression of periodontal disease (4).

Immunoregulation mechanisms in osteoporosis and periodontal disease

Numerous studies suggest that increased production of proinflammatory cytokines, such as interleukin IL-1β, IL-6, TNF-α and RANKL, are important factors in the pathogenesis and progression of periodontal disease and osteoporosis (7-11).

Since a large part of the immune system is located inside the bone (bone marrow), it is understandable that there is an interaction between immune and bone cells. In order to understand their mutual interaction, it is necessary to know the biology of the bone. The discovery of receptor activator of NF-kB (RANK), its ligand (RANKL) and osteoprotegerin (OPG) has contributed to the understanding of bone biology and mechanisms of osteoclastogenesis (Figure 1).

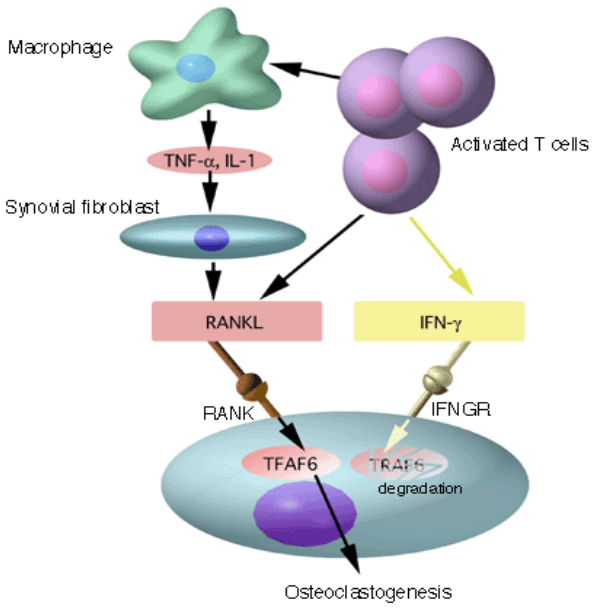

Figure 1. RANK/RANKL interaction (Available at: www.sciencemag.org/site/ feature/data /pharmacia/2002/takayanagi.xhtml on 27 March 2012)

Osteoclasts are the cells responsible for bone resorption. These are large multinucleated cells originating from a multipotent hematopoietic stem cells, so they are closer to the immune than the connective tissue cells (12). First, the interaction between these cells and T cells has been documented. One of the important factors of osteoclast differentiation is RANKL, which is produced by activated T cells. RANKL binds to RANK on osteoclast precursor and leads to the formation of osteoclasts.

Namely, RANKL is transmembrane protein that belongs to the tumor necrosis factor (TNF) superfamily, which is expressed by a large set of different cell types, including osteoblasts and activated T cells. RANKL constitutes an essential prerequisite for osteoclast differentiation, thereby triggering enhanced local bone resorption (13-15). RANKL is essential for the final differentiation steps of osteoclasts, as well as for their bone resorbing capacity (16). Consequently, RANKL deficient mice display severe osteopetrosis, which is characterized by an increased density and thickness of bones due to the lack of osteoclasts. Moreover, osteoblasts of RANKL-/- mice cannot support osteoclastogenesis (15).

RANKL-RANK interaction is critical for differentiation and maintenance of osteoclast activity and thus could represent the final common pathway of pathogenicity factors acting, in both osteoporosis and periodontal disease, leading to increased bone resorption. Besides, it is now well known that bone loss evident in osteoporosis and periodontal disease is accompanied by the inflammatory events (17,18). Possible missing link between inflammation and bone resorption in both these diseases could actually be the modulation of RANKL expression. It was shown that cultured periodontal ligament fibroblasts after lipopolysaccharide (LPS) treatment, that mimics proinflammatory environment, enhances RANKL mRNA expression, what could promote bone resorption (19). Up-regulation of RANKL expression by LPS was also observed in primary osteoblasts cocultured with bone marrow cells (20). Furthermore, certain pro-inflammatory cytokines, such as interleukin IL-1, IL-6, IL-17 and especially TNF-α, can also induce and enhance RANKL expression (21-24).

OPG is a decoy receptor of RANKL, produced by osteoblasts and dendritic cells. It highly specifically binds to RANKL and by competitive inhibition, prevents its binding to RANK and thus inhibits osteoclast differentiation and activation. The balance between RANKL and OPG regulates osteoclastogenesis, and thus bone resorption. The disruption of the RANKL/RANK/OPG axis leads to an imbalance between bone formation and bone resorption, and it is responsible for the disturbed bone homeostasis (15).

Studies in transgenic mice have shown that over-expression of OPG leads to serious osteopetrosis, while OPG-knockout mice had a phenotype of severe osteoporosis with a high incidence of fractures (25). However, it is difficult to demonstrate the role of OPG deficiency in the pathogenesis of osteoporosis, since the levels of OPG are changing, even increasing with age. Increased OPG production may be considered as a homeostatic response in order to limit the bone loss that occurs with an increase in other bone-resorbing factors (26,27). In contrast to previous data, in vitro studies demonstrated that OPG mRNA in osteoblasts was suppressed by the prolonged LPS treatment; it is even postulated

that suppression of OPG production in osteoblasts is more important than the induction of RANKL expression for stimulation of osteoclastogenesis and bone loss (20).

Stimulation of proinflammatory cytokines by decreased estrogen levels

About 80% of osteoporotic patients are women in menopause because estrogen level decreases as a result of the ovarian function loss (11). Loss of bone density associated with decreased estrogen level is the result of a significant increase in osteoclast activity. However, so far, it has not been shown that estrogen has a direct effect on osteoclast activity (28), so it is understandable that it acts indirectly to decrease osteoclast activity.

There is evidence obtained from experimental studies that suggests that bone loss associated with menopause may be the consequence of over-activation of osteoclasts by proinflammatory cytokines (11). Pacific et al. (29) reported that in premenopausal women, ovariectomy had been associated with a significant increase in pro-inflammatory cytokines, IL-1 and TNF-α, with a simultaneously increase in bone resorption. Increased production of IL-1 and TNF-α by poly-morphonuclear leukocytes (PMNL) was associated with decreased estrogen levels and a concomitant increase in bone resorption.

The role of proinflammatory cytokines as mediators of bone loss due to declining estrogen levels has also been investigated using many animal models (11). Ovariectomy in rats is accompanied by increased secretion of pro-inflammatory cytokines and a tenfold increase in osteoclast formation leading to reduced bone density. Administration of antibodies to IL-6 or implantation of estrogen pellets abolished this effect (30). These data suggest that lack of estrogen is associated with an increased production of pro-inflammatory cytokines, which increases the osteo-clast activity resulting in a profound bone loss (11).

Estrogen deficiency can lead to worsening of periodontal disease (31). Lack of estrogen increases the rate of gingival connective tissue damage by stimulating the synthesis of several cytokines responsible for bone resorption. In these terms, increase of IL-6 concentration occurs in the bone marrow (32-34), serum (26,35), and gums (31,32), which together leads to the activation of osteoclasts and, consequently, to bone resorption.

A cross-sectional study of pre- and post-menopausal women suggests a significant corre-lation between alveolar and metacarpal bone mineral density (BMD) and increased IL-6 concen-trations in saliva of postmenopausal women (36). This would indicate that osteoporosis or lower systemic BMD should be considered a risk factor for periodontal disease progression (4). A recent study has shown that skeletal BMD is related to interproximal alveolar bone loss (ABL) and clinical attachment loss (CAL), though not to a statistically significant level, implicating the postmenopausal osteopenia as a risk indicator for periodontal disease (37).

Therapeutic implications

RANK/RANKL/OPG system also represents an attractive, new therapeutic approach in the treatment of osteoporosis and periodontal disease.

RANKL expression is significantly higher in post-menopausal compared to pre-menopausal women, and post-menopausal women treated with estrogen (38). Estrogen supplementation is associated with reduced gingival inflammation and reduced frequency of attachment loss in osteo-porotic women in early menopause is docu-mented clinically (36). Postmenopausal hormone replacement therapy negative (HRT-) women had a greater chance of having periodontitis than premenopausal women. In contrast, postmeno-pausal HRT+ women and premenopausal women had similar periodontal status. HRT may have a beneficial effect on periodontal health (39). However, there are contrasting views on effects of hormone therapy on periodontal status in post-menopausal women. Pizzo et al. have shown that long-term hormonal therapy was not associated with relevant effects on periodontal status and clinical measures of periodontal disease (40). Since an increase in RANKL is detected in peripheral blood cells of patients with osteoporosis undergoing menopause (38), returning RANKL to its premenopausal level using hormone substitution therapy may represent a promising therapeutic option worth investigating (11).

The phytoestrogens, which are known to bind to the estrogen receptor sites of the cell and trigger the components and processes of estrogenic activity, have a promising role in the treatment of osteoporosis. Such pharmacological effects of 'green medicines' would be useful for prophylaxis or treatment of inflammatory bone disease (41).

Cytokines and RANKL/OPG signaling pathway involvement in the pathogenesis of osteoporosis and periodontal disease in the future may improve the usual treatment of periodontal disease and osteoporosis therapy in a way different than the hormone substitution, including the inhibition of proinflammatory mediators and osteoclast activity with the additional use of anti-inflammatory drugs (42,43). This involves blocking the binding of different stimulating factors to their receptors on osteoclast precursors, particularly RANKL and development of new more selective drugs with fewer side effects that would act as an anti-cytokines preventing the binding of cytokines to their receptors (14).

As a therapeutic drug for preventing bone loss, OPG has recently been evaluated in preclinical studies relating to estrogen deficiency, skeletal tumors, and specific cancers, and it has been shown that it has significant effects on the inhibition of bone loss (44). Inhibition of RANKL function with OPG treatment significantly reduced the number of

osteoclasts and alveolar bone loss (45,46). It seems that both alveolar bone height as well as loss of BMD induced by experimental periodontitis can be rescued by OPG. In contrast to long-lasting bisphosphonate therapy, which is proved beneficial in patients with osteoporosis, OPG treatment does not increase the risk for the development of osteonecrosis of the jaw, which could be OPG advantage compared to bisphosphonates in periodontal disease treatement (44).

Promising results in osteoporosis and periodontal disease treatment are also accomplished by denosumab, a fully human monoclonal antibody that binds to and inhibits RANKL and thus inhibits bone resorption by inhibiting osteoclast formation, function and survival. Compared with OPG, denosumab binds RANKL more specifically (it is less likely to affect the immune and other regulatory systems), it does not have the potential for autoimmunization against a vital regulatory protein, and it has a longer half-life, which permits less frequent dosing. Each of these attributes makes denosumab a more attractive therapeutic agent than forms of OPG (47). In preclinical studies, anti-RANKL antibody treatment inhibited A. actinomycetemcomitans-specific T cell induced periodontal bone resorption in mice by blockade and reduction of tissue RANKL, suggesting an immunological approach to ameliorate immune cell-mediated periodontal bone resorption (48). It has also been reported that inhibiting RANKL with an anti-RANKL antibody in estrogen-deficient older monkeys prevented the loss of cancellous bone and preserved indices of bone strength (49). In human trails, denosumab proved to be highly efficient in osteoporosis treatment; in postmenopausal women with low BMD, treatment with denosumab for 2 years was associated with sustained increases in BMD and reductions in bone resorption markers compared with placebo (50). Futhermore, denosumab was generally well-tolerated in clinical trials and in the large phase III FREEDOM study reduced the risk of vertebral, nonvertebral and hip fractures compared with placebo over three years (51). Clinical use of denosumab in periodontal disease still awaits an approval by large clinical trials.

Considering a plenty of evidence that links inflammation to osteoporosis and periodontal disease, the possibility of anti-cytokine therapy usage in these pathological conditions seems real. The bone resorption activity in ovariectomised rats is reduced with anticytokine therapy such as IL-1 receptor antagonists and TNF-binding protein implicating this therapy in postmenopausal osteoporosis (52). In periodontal research, the effects of soluble receptors and receptor antagonists of IL-1 and TNF- α have been studied during experimentally induced periodontitis in a non-human primate models (53,54). The clinical and biochemical findings of these experiments established that IL-1 and TNF- α antagonists blocked the progression of the alveolar bone inflammatory cell infiltrate, the osteoclastogenesis and periodontal attachment and bone loss. Accordingly, anti-cytokine therapy can act as a host response modulator in the control of inflammatory diseases of the tooth-supporting apparatus and may provide the basis for new molecular therapeutic approaches to the treatment of periodontitis.

Conclusion

Recognition of RANK/RANKL, IL-1β, IL-6, IL-17 and TNF-α important role in the pathogenesis of chronic inflammatory diseases may have practical significance in order to develop the most effective therapeutic procedures for periodontal disease and osteoporosis.

Understanding the association between periodontal disease and osteoporosis as well as their pathogenic mechanisms can improve the prevention, diagnosis and treatment of these very common diseases of bone tissue.

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IMUNOPATOGENETSKI MEHANIZMI PARODONTOPATIJE I POSTMENOPAUZALNE OSTEOPOROZE

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Osteoporoza i parodontopatija su široko rasprostranjene bolesti među muškom, kao i ženskom populacijom, čiji se intenzitet povećava sa starenjem. Osnovni patogenetski mehanizam u osteoporozi i parodontopatiji je resorpcija kosti uz povećanu produkciju proinflamacijskih citokina: interleukina IL-1β, IL-6, TNF-α kao i RANKL-a. Otkriće receptor aktivatora NF-kb (RANK), njegovog liganda (RANKL) i osteoprotegerina (OPG) doprinelo je razumevanju biologije kosti kao i osteoklastogenetskih mehanizama. RANKL-RANK interakcija je kritična za diferencijaciju i održavanje osteoklasne aktivnosti. Ravnoteža između RANKL-a i OPG-a reguliše osteoklastogenezu, a time i resorpciju kosti. Narušavanje RANKL/RANK/OPG ose dovodi do neravnoteže između formiranja i resorpcije kosti i odgovorno je za poremećenu koštanu homeostazu. Gubitak kosti u menopauzi može biti posledica aktivacije osteoklasta proinflamacijskim citokinima i povezan je sa padom nivoa estrogena. Nedostatak estrogena može dovesti do pogoršanja parodontopatije i povećava stopu oštećenja vezivnog tkiva gingive stimulacijom sinteze nekoliko citokina odgovornih za koštanu resorpciju. Citokini i RANKL/OPG signalni put, uključeni u patogenezu osteoporoze i parodontalne bolesti, mogu dovesti do aktivacije osteoklasta i stimulacije resorpcije kosti. Stoga, ova saznanja, u budućnosti mogu dopuniti uobičajenu terapiju parodontopatije i osteoporoze terapijom usmerenom ka inhibiciji proinflamacijskih medijatora i osteoklastne aktivnosti, uz dodatno korišćenje antiinflamacijskih lekova. To podrazumeva blokiranje vezivanja različitih stimulišućih faktora za receptore na prekursorima osteoklasta, pre svega RANKL-a i razvoj novih lekova koji će delovati kao anticitokini, sprečavajući vezivanje citokina za njihove receptore i na taj način, što selektivnije i sa što manje nuspojava, blokirati dejstvo određenog citokina. *Acta Medica Medianae 2012;51(4):51-57.*

Ključne reči: *postemenopauzalna osteoporoza, parodontopatija, inflamacija, citokini*