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The role of inflammatory factors in pathogenesis of postmenopausal osteoporosis

Rola czynników zapalnych w patogenezie postmenopauzalnej osteoporozy

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Summary

Osteoporosis is a metabolic disease where progressing loss of the bone mass effects from the loss of calcium compounds, associated with hormonal changes and genetic factors. Osteoporosis is three times more frequent in women which is associated with hormonal changes throughout the menopausal period. Reduced mass of the bone skeleton during ageing is caused, among other, by impaired intestinal absorption of calcium, decreased level of active vitamin D, elevated parathormone, increased activity of osteoclasts and reduced level of estrogens which activates bone resorption. Osteoporosis develops as the result of interaction between the environmental, hormonal and genetic factors which affect the bone mineral density and has a role in the risk of fracture. The environmental risk factors include the nutritional patterns: undernutrition, insufficient supply of calcium or vitamin D, lifestyle, including lack of physical activity, the use of substances, the number of pregnancies, the diseases suffered from, disorders of the bone marrow, any past inflammatory conditions or the drugs taken. Discovery of three major particles controlling osteoblasts, therefore influencing osteoporosis and other bone conditions was a turning point to start a new era of medicine. The particles are activators of the receptor of nuclear factor κ B (RANK), its ligand RANKL and the natural receptor trap for RANKL, i.e. osteoprotegerin (OPG). Osteoporosis is known to be conditioned by a number of polymorphisms, the so-called "candidate genes" for its development. The studies of the condition evaluate variability of such genes across populations, based on identification of polymorphisms of a single nucleotide (SNP). The polymorphisms may influence variability of such traits, e.g. bone mineral density. Among regulators of the signaling pathways of bone remodeling, the role of cytokines has been emphasized for their capacity to enhance or to inhibit bone resorption. Interleukin IL-17 or TNF- α increase RANKL expression, therefore they are regarded as proresorptive factors, stimulating osteoclastogenesis.

Streszczenie

Osteoporoza jest chorobą metaboliczną polegającą na postępującym ubytku masy kostnej, spowodowanym utratą związków wapnia, powiązanych ze zmianami hormonalnymi

oraz czynnikami genetycznymi. Osteoporoza trzykrotnie częściej występuje u kobiet, co jest związane ze zmianami hormonalnymi towarzyszącymi okresowi menopauzy. Obniżanie się masy szkieletu kostnego podczas starzenia się organizmu spowodowane jest między innymi: zaburzeniem jelitowej absorpcji wapnia, spadkiem poziomu aktywnej witaminy D, wzrostem poziomu parathormonu, wzrostem aktywności osteoklastów oraz obniżeniem poziomu estrogenów, co aktywuje proces resorpcji kości. Osteoporoza rozwija się pod wpływem interakcji pomiędzy czynnikami środowiskowymi, hormonalnymi i genetycznymi, które oddziałują na wartość BMD (gęstość mineralna kości) oraz wpływają na ryzyko złamań. Środowiskowymi czynnikami ryzyka rozwoju tej choroby są czynniki żywieniowe: niedożywienie, niedostateczna podaż wapnia czy witaminy D, styl życia, w tym brak aktywności fizycznej, stosowanie używek, liczba przebytych ciąż, przebyte choroby, zaburzenia dotyczące szpiku kostnego, przebyte stany zapalne czy zażywane leki. Odkrycie trzech podstawowych cząsteczek, które sterują pracą osteoklastów, a tym samym wpływają na osteoporozę i inne choroby kości, było punktem zwrotnym, który rozpoczął nową erę w medycynie. Te cząsteczki to aktywator receptora jądrowego czynnika κ B (RANK), jego ligand RANKL oraz naturalny receptor pułapka dla RANKL, czyli osteoprotegeryna (OPG).

Wiadomo, że osteoporoza jest chorobą uwarunkowaną występowaniem licznych polimorfizmów tzw. „genów kandydujących” do jej rozwoju. W badaniach na ten temat ocenia się zmienność tych genów w populacjach ludzkich, opierając się przy tym na identyfikacji polimorfizmów pojedynczego nukleotydu (SNP). Polimorfizmy te mogą wpływać na zmienność takich cech, jak gęstość mineralna kości.

Wśród regulatorów szlaku sygnalizacyjnego przemiany kostnej podkreśla się rolę cytokin, które mogą wspierać lub hamować resorpcję kości. Interleukina IL-17 czy TNF- α zwiększają ekspresję RANKL i dlatego uznaje się je za czynniki proresorpcyjne, stymulujące osteoklastogenezę.

Osteoporosis is a metabolic disease where progressing loss of the bone mass effects from the loss of calcium compounds, associated with hormonal changes and genetic factors. It is characterized by impairments of bone microarchitecture and the osseous tissue metabolism. Misdiagnosing and delayed treatment, both contribute to frequent fractures bringing dangerous consequences. Osteoporosis appears as a growing social issue, therefore it has been classified by the World Health Organisation as a civilization disease.

Today WHO defines the condition as a generalized metabolic disease of bones, characterized by low bone mass, impaired microarchitecture of bones, and in consequence, increased fragility and susceptibility to fractures. The definition of osteoporosis has been complemented by the value of T-score (SD – standard deviation from the average scores for the peak bone mass at the age 20-29 years). It has been accepted that the T-score value indicative of osteoporosis is below 2.5 SD from the average scores for the peak bone mass at the age 20-29 years (1).

The present number of inhabitants of Europe and the United States affected by osteoporosis exceeds 75 million, contributing to more than 2.5 million bone fractures each year. Contrary to Caucasian population, the prevalence of the condition in Afro-Americans is much lower. Osteoporosis is three times more frequent in women which is associated with hormonal changes throughout the menopausal period. Men show the bone mass higher than women, therefore significant loss of the bone mass in them is less frequent. Statistical data on osteoporotic fractures are alarming. Fractures of the hip bone in white women at advanced age have been estimated at least at 3% in year (2).

Defining the ageing process one should observe that it is characterized by reduced general physiological efficiency of the body, where catabolic changes predominate the anabolic ones and susceptibility to illness grows for both, acute and chronic conditions (3).

Ageing is also associated with structural changes within a bone, both a dense and a spongy one. Reduced mass of the bone skeleton during ageing is caused, among other, by impaired intestinal absorption of calcium, decreased level of active vitamin D, elevated parathormone, increased activity of osteoclasts and reduced level of estrogens which activates bone resorption (4).

A breakthrough in woman's life is the perimenopausal period and the menopause itself. This time is defined as a stage characterized by gradual extinction and eventual exclusion of the ovarian function and regression of menstruation. Throughout that time the female body adapts to altered conditions associated with the lack of hormonal activity of the ovaries, the deficiency of estrogens and failure to secrete such hormones as gonadoliberin (GnRH), the folliculotropic hormone (FSH) and the luteinizing hormone (LH) (5). Reduced production of estrogens contributes not only to impaired metabolism of the osseous tissue and development of osteoporosis, but also to the growing risk of neoplastic diseases. Abrupt loss of the bone mass is experienced during a few years following the menopause. Beyond the age of 65, the loss of the bone mass reaches approximately 25% of the maximum bone mass, while during the following years the decrease is remarkably lower (6).

Osteoporosis develops as the result of interaction between the environmental, hormonal and genetic factors which affect the bone mineral density and has

a role in the risk of fracture. The environmental risk factors include the nutritional patterns: undernutrition, insufficient supply of calcium or vitamin D, lifestyle, including lack of physical activity, the use of substances, the number of pregnancies, the diseases suffered from, disorders of the bone marrow, any past inflammatory conditions or the drugs taken.

The bones change throughout the human life, where the process comprise bone resorption by osteoclasts and synthesis of the matrix by osteoblasts. It is estimated that the whole human skeleton in replaced every 10-25 years. This is necessary to adapt to the changing pressures on the skeleton throughout daily routines and to repair any microfractures or microdamages. Impaired balance between the osteoclasts and the osteoblasts may effect from hormonal changes or increased production of inflammatory cytokines or growth factors which results in reduced bone mass (osteoporosis) or the increased one (osteopetrosis). While osteopetrosis is a heterogenic group of rare hereditary diseases, osteoporosis, or the bone loss, is a common condition observed in numerous diseases, such as chronic infections, parodontosis, rheumatoid arthritis, leukæmia, postmenopausal osteoporosis or lytic bone metastases. Recently, it has become apparent that the im-

munological cells may have a role in bone physiology which gave birth to a new scientific discipline, named osteoimmunology.

Osteoclasts originate from the line of monocytes/macrophages are specialized cells responsible for bone decay (7). In normal bone remodeling the resorptive function of osteoclasts is coupled with formation of osteoblasts (8, 9). Bone remodeling is the basic process indispensable to preserve appropriate condition of the osseous tissue. The course of the process in physiological conditions in upon inflammation is presented in figure 1a, b.

Numerous studies carried out throughout the recent years have significantly extended our knowledge of mechanisms underlying bone mass loss. Understanding of such processes is needed to design new therapeutic methods, which would slow down the disease progression in patients with bone mass loss. Discovery of three major particles controlling osteoblasts, therefore influencing osteoporosis and other bone conditions was a turning point to start a new era of medicine. A diagram showing their role in bone physiology is presented in figure 2 and the mechanism regulating osteoclastogenesis is illustrated in figure 3.

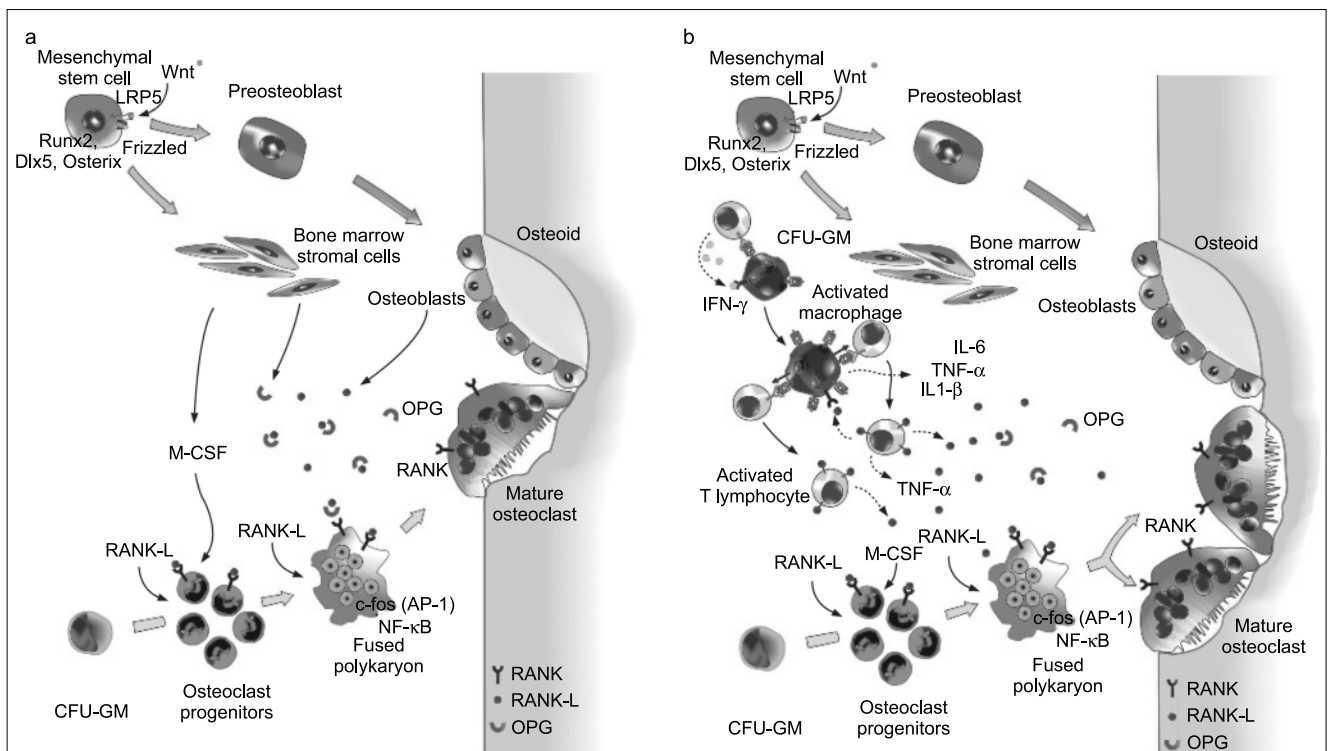


Fig. 1a, b. Bone remodeling under physiological conditions (homeostasis) (10) (a) and bone remodeling in chronic inflammation (10) (b). a) Bone remodeling involves several types of cells: osteoblasts (OBs) which form the organic bone matrix; the bone marrow stromal cells and osteoclasts (OCs) resorbing a bone. Osteoblasts originate from the mesenchymal matrix cells. An important role in induction of osteoblastogenic transcription factors Runx2, Dlx5 and Osterix is played by the pathways Wnt10 and LRP5. Osteoclasts are formed from the myeloid precursors influenced by RANK pathway and several transcription factors, e.g. NFκB i AP-1 (c-fos). RANK is activated by RANKL, member of TNF superfamily, which is a key osteoclastogenic cytokine, produced mainly by bone marrow cells and osteoblasts. RANKL activity is inhibited by osteoprotegerin, which is a soluble decoy receptor for RANKL. Bone homeostasis is regulated by the balanced resorptive activity of RANKL and the protective one of OPG. b) Active lymphocytes T produce RANKL and its soluble form, therefore have a direct role in bone loss through induction and activation of OCs via RANKL. The quantity of RANKL exceeds the protective capacity of OPG. In addition, the proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, promote osteoclastogenesis and bone resorption, cooperating with RANKL. Gamma interferon (IFN-γ) promoted indirectly the bone decay through its capacity to trigger antigene presentation and activation of lymphocytes T through gene presenting cells

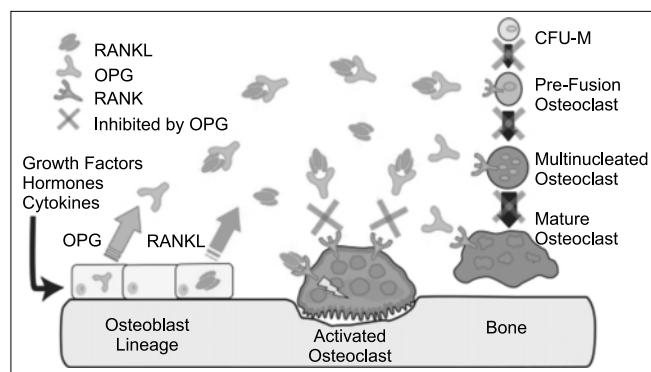


Fig. 2. The mechanism of OPG, RANKL and RANK activity (11). RANKL is expressed by osteoblasts, bone marrow stromal cells and other cells, affected by a number of proresorptive growth factors, hormones and cytokines. Osteoblasts and stromal cells express OPG which, binding with RANKL, inhibits its activity. The main binding complex is most probably a single OPG homodimer effecting at high affinity upon RANKL single homodimer. At the absence of OPG, RANKL activates its receptor RANK on osteoclasts and their precursors. Such activity of RANK-RANKL effects in:

- recruitment of preosteoclasts and their fusion into multinuclear osteoclasts,
- activation of osteoclasts,
- survival of osteoclasts.

Each of the responses may be inhibited by OPG

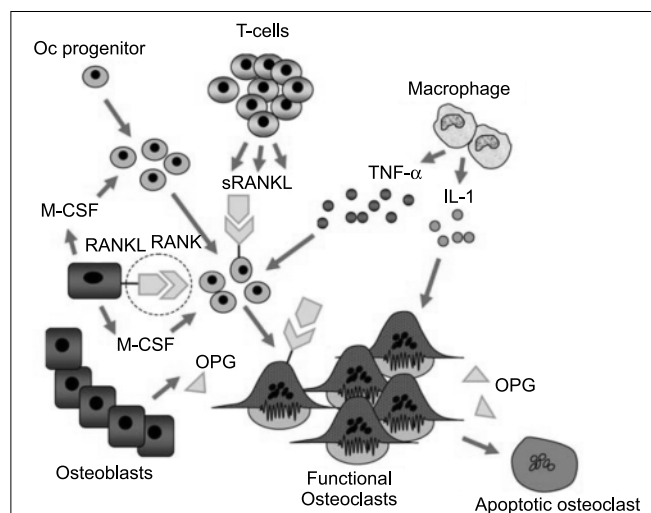


Fig. 3. Regulation of osteoclastogenesis (18). Differentiation of osteoclasts is regulated by osteoblasts. The process involves membrane-bound RANKL and soluble V-CSF. Expression of RANKL by osteoblasts is supported by the hormones, e.g. parathormone or cytokines, such as IL-6 and parathormone related protein (PTHrP) and reduced by estrogens. OPG is inhibited by glucocorticoids or PTH. (s)RANKL is also expressed by active lymphocytes T. TNF-α stimulates M-CSF and release of RANKL from osteoblasts which enhances osteoclastogenesis in inflammatory conditions. RANKL and IL-1 affect osteoclasts preventing their apoptosis. RANKL-RANK interaction (circled) may be therapeutically interfered by specific monoclonal antibodies of RANKL

The particles are activators of the receptor of nuclear factor κ B (RANK), its ligand RANKL and the natural receptor trap for RANKL, i.e. osteoprotegerin OPG) (12-14). Although the studies showed that hormones associated with calcium metabolism and cytokines, such as PTH-related Peptide (PTHrP), vitamin D₃, interleukin IL-1 β or TNF- α (tab. 1) have a role in

osteoclastogenesis during individual stages of development (15), it is worth noting that only RANKL proved absolutely indispensable to develop osteoclasts *in vivo* (16, 17). Table 2 specifies conditions, the development of which involves the OPG/RANKL/RANK pathway.

Tab. 1. Factors which may affect expression of RANKL, OPG and/or RANK

	RANKL	OPG	RANK
Hormones			
Vitamin D ₃	↑	↑	↑
PTH	↑	↓	
PTHrP	↑		
Estradiole		↑	
Testosterone		↑	
Prolaktin	↑	↓	
Cytokines			
TNF- α	↑	↑	
TNF- β		↑	
IL-1 α		↑	
IL-1 β	↑	↑	
IL-6	↑	↑	↓
IL-11	↑	↑	
IL-17	↑		
CD40L		↑	
Growth factors			
TGF- β	↓	↑	↓
BMP-2	↑	↑	
IGF-I	↑	↓	
VEGF			↑
Glucocorticoids			
Dexamethasone	↑	↓	↑
Hydrocortisone		↓	
Immunosuppressants			
Rapamycin	↑	↓	
Cyklosporine A	↑	↓	
FK-506	↑	↓	
Other			
Prostaglandine E ₂	↑	↓	↑
Calcium	↑	↑	
LPS	↑	↓	
Ascorbinic acid	↑		

The diseases and nutritional deficiencies throughout childhood well as reduced exposure to sex steroids during maturation frequently lower accumulation of peak body mass.

Various diseases and drugs take throughout the lifetime interfere the bone condition and contribute to osteoporosis. Activation of osteoclastic bone resorption has a major role in pathogenesis of bone loss and fractures (19). In elderly patients, frequent deficiency

Tab. 2. Diseases, the development of which involves the OPG/RANKL/RANK pathway

OPG/RANKL/RANK-mediated disease	Major mechanism(s)
Postmenopausal osteoporosis	↑ Bone marrow stromal cell expression of RANKL
Primary hyperparathyroidism	↑ RANKL expression, ↓ OPG expression by osteoblasts
Sporadic Paget's disease	↑ Stromal cell expression of RANKL
Rheumatoid arthritis	↑ RANKL expression by synoviocytes and T cells
Periodontal bone loss	↑ RANKL expression by activated T cells
Myeloma bone disease	↑ RANKL expression by myeloma cells
Osteolytic bone metastases	RANKL expression by tumor cells
Humoral hypercalcemia of malignancy	↑ RANKL expression, ↓ OPG expression by osteoblasts influenced by PTHrP
Familial expansile osteolysis	Activating mutations of the RANK gene
Idiopathic hyperphosphatasia (Juvenile Paget's disease)	Inactivating mutations of the OPG gene

of vitamin D impairs absorption of calcium and induces secondary hyperparathyroidism.

Progress in the area of genetics and molecular biology has contributed to recognition of the genetic mechanisms underlying numerous conditions, including osteoporosis. In this way it allowed for better understanding of etiology and risk factors of the disease. Recognition of genotypes underlying osteoporosis is likely to enable a targeted therapy for a given patient, ensuring efficient and active prevention.

Osteoporosis is known to be conditioned by a number of polymorphisms, the so-called "candidate genes" for its development. The studies of the condition evaluate variability of such genes across populations, based on identification of polymorphisms of a single nucleotide (SNP). The polymorphisms may influence variability of such traits, e.g. bone mineral density. In order to recognize the genetic mechanisms underlying osteoporosis, it may be necessary to investigate carefully the polymorphisms SNP of osteoprotegerin genes, RANK receptor and RANKL ligand as well as other factors which have an indirect role in physiology of the human skeleton.

The clinical and personal parameters evaluated in the context of investigations of polymorphisms associated with osteoporosis are: body mass, growth, BMI, date of menarche and last menstruation, number of pregnancies, years from menopause, birth weight and other. Those very parameters have been selected for evaluation as they are suggested to be associated with BMD scores and the risk of osteoporosis (21, 22). The

studies pointed to a statistically significant relation between higher bone mass and BMI as well as elevated BMD and lower risk of osteoporosis (23).

It is claimed that the birth weight has an important role in reaching the peak body mass as well as BMD scores in adults. Investigations carried out in a group of Caucasian females aged over 70, showed that the birth weight was associated with BMD values (21). Also studies performed in the group of monozygotic and dizygotic twins at reproductive age showed the birth weight significantly related to BMD scores in adults (22).

The studies carried out so far have not showed explicitly the role of *OPG* gene polymorphism in susceptibility to osteoporosis. The studies (23, 24) indicated that in case of polymorphism T-950C of *OPG* gene, the genotype CC could be a factor of higher risk of faster bone mass lost and the onset of osteoporosis in Polish postmenopausal women. It was also observed that homozygotic genotypes of polymorphism G1181C and A-163G of *OPG* gene may have a role in the birth weight of females and in the elevated risk of osteoporosis.

It has been known that the results of studies differ across populations. So far there have been scarce evaluations of that type carried out among Polish population. In case of the mentioned polymorphism A-163G of *OPG* gene, it was observed that the birth weight among the evaluated population of healthy postmenopausal women was significantly lower than in females with genotype AA of polymorphism A-163G of *OPG* gene, as compared to the birth weight of women with genotype GG. In this group it was also shown that patients with genotype GG reached the last menstruation age much later than females with genotype AA. Evaluation of the parameter BMD L2-L4 AM (%) revealed also the scores for healthy postmenopausal women with genotype AG lower than for genotype GG.

Evaluation of polymorphism G1181C showed slightly higher frequency of genotype CC in women with normal T-score, compared to osteoporotic/osteopenic women taken together as well as in comparison to the osteoporotic group alone. Moreover, polymorphism of *OPG* gene is associated with the preserved bone mass in the lumbar spine in homozygotic 1181CC individuals while the homozygotic genotype 1181GG and the heterozygotic 1181GC were more frequent in patients diagnosed with osteoporosis (25). However, a few authors observed no significant relation between genotype *OPG* G1181C and BMD (26, 27). Unfortunately, the mechanism underlying the effect of polymorphism G1181C of *OPG* gene on BMD is not known, however conversion of the third *OPG* aminoacid from the basic lysine into asparagine may influence the kinetics of *OPG* secretion (28).

Vidal et al. (27) observed the tendency for more frequent homozygotic genotypes of wild GG type in polymorphism G1181C in women with reduce BMD scores, as compared to the controls. Similar results were obtained by Langdah et al. (25) who evaluated

osteoporotic females. They found statistical differences between BMD for genotypes GC and CC of polymorphism G1181C. The maximum BMD scores were revealed for CC homozygotes, while in females with genotype GG the values of BMD L2-L4 were lower.

The activator of the receptor of the nuclear factor κ B (RANK) is expressed in osteoclasts and their precursors. Interaction between RANK and its ligand (RANKL) has been identified as the ultimate common regulation route for bone resorption (29). Binding with RANK receptor on osteoclast precursors, RANKL controls differentiation, proliferation and survival of osteoclasts. As indicated above, osteoprotegerin is the natural inhibitor of RANKL, it is not surprising then that the relation of OPG and RANKL are disturbed upon deficiency of estrogens, hyperparathyroidism as well as other conditions stimulating bone resorption (30-32). RANKL is expressed also in synovial lymphocytes and fibroblasts and may have an indirect role in bone loss during inflammatory conditions (33, 34). As the major role of RANKL is to regulate bone metabolism through the control of development of osteoclasts, most of the studies of polymorphism of *RANKL* gene focus in the relation between the genetic variance of *RANKL* and bone diseases, such as osteoporosis.

The results obtained by (35) indicate the lack of statistical relation between genotypes of the evaluated polymorphism 575C/T of *RANK* gene and the onset of osteoporosis and such bone parameters as T-score, Z-score, BMD L2-L4 YA% or BMD L2-L4 AM%. It was only in the osteoporotic group that statistically lower T-score was noted for genotype CC.

In case of polymorphism *RANKL* C-643T, statistical relations between particular genotypes and the body weight and the BMI were observed in osteoporotic women. In females with genotype TT, lower birth weight was observed (36). More frequent genotype TT and lower frequency of genotype CT were observed in women with osteoporosis, as compared to healthy postmenopausal females as well as when osteopenic and osteoporotic women were taken together with normal T-score group. Evaluation of frequency of allele showed that allele T was more frequent in both, women with osteoporosis and in general, in patients with T-score < -1, as compared to individuals with normal scores.

Relation has also been shown between *RANK* and *RANKL* genes and the age of menarche and the age of natural menopause (37).

It is estimated that one billion people worldwide, mainly the elderly inhabitants of cities in Europe and the USA, show deficiency of vitamin D (38-40). The question of vitamin D deficiency concerns also young people, as proved by epidemiological studies carried out by American universities. As shown, about 50% of youth show calcidiol concentrations not exceeding 50 nmol/L (41, 42). Low calcidiol (below 50 nmol/L) was observed in 30-50% of inhabitants of high insolation regions, such as United Arab Emirates, Turkey or

India (43). Inhabitants of those regions usually cover their bodies, reducing therefore synthesis of vitamin D. Biologically active double-hydroxylated form of vitamin D, calcitriol, as well as its analogues, effect upon the target cells via VDR receptor.

The role of *VDR* gene polymorphism in autoimmune diseases is now intensively studied.

Relation between bone mineral density and the variant of *VDR* gene, coding the protein receptor for vitamin D, has also been shown. The physiological mechanism underlying the effect of the genotype polymorphism of the receptor for vitamin D on bone mineral density has not been recognized yet. It is likely to be associated with impaired intestinal absorption of calcium. It is claimed that in some conditions a numerous group of patients shows excessive or insufficient presence of particular variants of *VDR* gene. This was confirmed by studies by Springer et al. (44), who observed relation between the genotype of vitamin D receptor and the development of hepatic osteodystrophy. Patient with allele T of *VDR* gene showed 2-3-fold higher risk of spinal fracture.

So far, most of the contributions have not proved the effect of *VDR* genotype on mineral density of lumbar vertebrae (45, 46). However, the studies by Boroń et al. (47) show a relation between the values of BMD L2-L4 AM with the genotype of polymorphism 283A/G of *VDR* gene. Women with genotype AA and osteoporosis showed significantly lower values of this parameter, as compared to females with genotype GG. Studies of Polish population also showed predominance of allele T of polymorphism *TaqI* of *VDR* gene in osteoporotic patients (48). In this way the authors suggest the relation between *VDR* polymorphism and the risk of osteoporosis.

Studies of female population in the United States pointed to the relation between *VDR* genotype and the risk of osteoporotic bone fractures (49-51). On the other hand, no such relation between bone fractures and polymorphism of *VDR* gene was found among European populations (52).

Among other regulators of the signaling pathways of bone remodeling, the role of cytokines has been emphasized for their capacity to enhance or to inhibit bone resorption. Interleukin IL-17 or TNF- α increase *RANKL* expression, therefore they are regarded as proresorptive factors, stimulating osteoclastogenesis (53). Interleukin 17 is a newly discovered cytokine secreted by numerous cells. The latest studies point to IL-17 situated in the upper part of the inflammatory cascade, stimulating fibroblasts as well as synovial cells and macrophages to increase expression of proinflammatory cytokines. Moreover, IL-17 initiates the loss of proteoglycans and stimulates in chondrocytes the enhanced expression of enzymes, responsible for degradation of collagen. At the same time, metalloproteinases are secreted, which are regulated by IL-17 in the presence of proinflammatory cytokine. IL-17 is thought to stimulate osteoblasts to synthesize prostaglandin E₂ and to ex-

press the gene receptor NF- κ B (RANK), which induces osteoclastogenesis. In this way, also IL-17 has a role in intensive bone resorption, e.g. in rheumatoid arthritis. Comprehensive understanding the mechanism of IL-17 effect on chondrocytes and bones could help implementation of new therapies in skeletal system conditions (54, 55).

Investigations (56) carried out among Polish female population to evaluate polymorphism 197G/A IL-17, no statistically significant changes were observed as associated with the effect of the evaluated polymorphism on development of osteoporosis. However, a clear tendency of this cytokin has been shown to inhibit osteoporosis in individuals with polymorphic homozygotic genotype AA. Interleukin 17 is a cytokine associated with proinflammatory properties (57). Patients suffering from osteo-articular conditions show enhanced osteoclastogenesis and activity of osteoclasts as well as impaired bone remodeling (58).

The major cause of bone resorption is the excess of cytokines (including IL-17), which promote osteoclastogenesis through induction of RANKL, at simultaneous deficiency of cytokines which inhibit such a process (59). Not only does IL-17 enhance expression of osteoclasts, initiated by RANKL, but has also the capacity to induce such a process independently (60).

The osseous tissue is also influenced by adipokines. The fatty tissue produces a variety of adipokines (adiponectin, leptin and visfatin). The adipokines control, among other, the response to insulin and bone metabolism (61, 62). It has been proved that both, mRNA for omentin-1 and their plasma concentrations are inversely correlated with obesity, BMI and resistance to insulin (63). Several adipokines induce proliferation of osteoblasts (63, 65), which is indicative, among other, of close relations between omentin-1 and osteoblasts. Clinical studies have shown that serous omentin-1 is negatively correlated with BMD in girls with anorexia nervosa (66) and in Iranian postmenopausal females (67). Xie et al. (62, 68) observed also that omentin-1 reduces bone loss in mice without ovaries and in OPG mice, stimulates proliferation and inhibits differentiation of osteoblasts in mice.

It is also worth noting that, although omentin-1 levels are lowered in obese people, it has a role in regulation of OPG and RANKL expression. Some preliminary studies of the role of polymorphism 326A/T of omentin gene in the development of osteoporosis in menopausal women show that the carrier state of genotype TT of gene ITLN-1 is associated with lowered T-score and the values of BMD in the lumbar spine, which correlates with the increased risk of fracture (69).

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