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Pathophysiological and molecular aspects of the development of osteoporosis in postmenopausal women

Patofizjologiczne i molekularne aspekty rozwoju osteoporozy u kobiet po menopauzie

Radosław Karaś, Agata Gondek, Karolina Kowalczyk, Paweł Madej

Department and Clinic of Gynecological Endocrinology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice

Abstract

Postmenopausal osteoporosis affects every third woman in Poland. The disease results in frequent fractures of the proximal radius - Colles fracture, vertebral compression fractures and life-threatening fractures of the proximal femur. 17β-estradiol has a protective and anti-resorptive effect on bone tissue metabolism. This is done through a number of genomic (via ERα and ERβ receptors) and non-genomic (via GPER1 receptor) mechanisms. Reduced estrogen concentration stimulates peripheral blood mononuclear cells to produce TNFα. This pro-inflammatory cytokine stimulates synthesis of RANKL, a ligand that promotes osteoclast maturation. After menopause, the activation of the wnt/β-catenin signaling pathway slowes down, which is responsible for e.g. for proliferation and maturation of osteoblast progenitor cells and reduced expression of the gene for osteoprotegerin. Estrogens affect the metabolism of bone tissue also by modulating the production of parathyroid hormone and IGF-1, oxygen free radicals (ROS), hypxia-inducible factor (HIF1α), long non-coding RNA (IncRNA), TGFβ cytokine and sclerostin protein. Adipose tissue plays a crucial role in the pathophysiology of postmenopausal osteoporosis. It is also postulated that the influence of genetic predisposition is possible. (Gerontol Pol 2023; 31; 94-102) doi: 10.53139/GP.20233114

Keywords: *osteoporosis, postmenopausal osteoporosis, pathophysiology of osteoporosis, estrogens*

Streszczenie

Osteoporoza pomenopauzalna dotyka co trzecią kobietę w Polsce. W wyniku choroby dochodzi do częstych złamań bliższego odcinka kości promieniowej typu Collesa, złamań kompresyjnych kręgów oraz zagrażających życiu złamań bliższego końca kości udowej. 17β-estradiol ma protekcyjny i przeciwresorpcyjny wpływ na metabolizm tkanki kostnej. Odbywa się to za pośrednictwem licznych mechanizmów genomowych (receptorów ERα i ERβ) i pozagenomowych (receptora GPER1). Zmniejszone stężenie estrogenów pobudza jednojądrzaste komórki krwi obwodowej do produkcji TNFα. Ta prozapalna cytokina pobudza syntezę RANKL, czyli ligandu, który pobudza dojrzewanie osteoklastów. Po menopauzie obserwuje się ponadto obniżoną aktywację szlaku sygnalizacji wnt/β-katenina, który jest odpowiedzialny m.in. za proliferację i dojrzewanie komórek progenitorowych osteoblastów oraz obniżoną ekspresję genu dla osteoprotegeryny. Estrogeny wpływają na metabolizm tkanki kostnej również modulując wytwarzanie hormonów: parathormonu oraz IGF-1, wolnych rodników tlenowych (ROS), czynnika indukowanego hipksją (HIF1α), długiego niekodującego RNA (IncRNA), cytokiny TGFβ oraz białka sklerostyny. W patofizjologii osteoporozy pomenopauzalnej dużą rolę odgrywa tkanka tłuszczowa. Postuluje się także możliwy wpływ czynników i predyspozycji genetycznych. (Gerontol Pol 2023; 31; 94-102) doi: 10.53139/GP.20233114

Słowa kluczowe*: osteoporoza, osteoporoza pomenopauzalna, patofizjologia osteoporozy, estrogeny*

Introduction

Menopause is a specific time when the function of the ovaries is significantly changed, which has consequences for the functioning not only of the reproductive system, but of the entire woman's body [1]. In Poland, natural menopause occurs between the ages of 45 and 56, with a median age of 51.25 [2]. The early symptoms of

Adres do korespondencji / Correspondence address: Radosław Karaś, Department and Clinic of Gynecological Endocrinology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, ul. Medykow 14, 40-752 Katowice (+48 32) 789 40 00 adam.bednorz@emc-sa.pl
ORCID: Radosław Karaś: 0009-0006-2243-8099, Agata Gondek:0009-0006-9014-8800, Karolina Kowalczyk: 0000-0003-1406-5211, Paweł Madej: 0000-0002-6447-1667

menopause include hot flushes, drenching sweats, heart palpitations, headaches and dizziness, sleep problems, mood swings, difficulties in concentrating and remembering, and depression that may develop into depression [3, 4]. Also, the risk of developing metabolic syndrome rises [5]. With the passage of time, the postmenopausal period may be associated with the development of osteoporosis [3].This article presents an overview of the current state of knowledge on the pathophysiological processes and molecular factors in the development of postmenopausal osteoporosis.

Hormonal changes after menopause

Estrogens are a group of steroid hormones that include: estrone, estradiol (17β-estradiol), estriol (16-hydroxyestradiol) and estetrol (15α-hydroxyestriol). Each of them has 4 rings in its structure and is made of 18 carbon atoms. Commonly, the term "estrogen" refers to estradiol because its physiological function is dominant. Estriol and estetrol are more specific to pregnancy, with estetrol being only present during this period. It is produced by the fetal liver and enters the mother's blood through the placenta [6].

The starting substrate for estrogen synthesis is cholesterol, which is mainly derived from low-density lipoproteins (LDL). The site of estrogen synthesis is mainly the granular layer of the ovarian follicle, but also the adrenal cortex and adipose tissue. Estrogens are involved in the regulation of the menstrual cycle, bone density, brain function, cholesterol metabolism, inflammation, and development of breast tissues and female reproductive organs [6].

After the last menstrual cycle of a woman, there is a significant reduction in the concentration of estradiol in the blood plasma, and the ovaries cease to take part in its regulation. The peripheral conversion of androstenedione to estrone and estrone to estradiol with the participation of the 17-hydroxysteroid dehydrogenase enzyme becomes more important. 5% of the estrone undergoes this conversion. The concentration of progesterone is also drastically reduced, because corpus luteum is no longer responsible for its synthesis and this role is assigned only to the adrenal cortex [7]. As a consequence of the described functional changes in the postmenopausal period, the levels of sex hormones: 17b-estradiol, testosterone, androstenedione and dehydroepiandrosthenedione (DHEA) decrease and follicle stimulating hormone (FSH) levels increases above 25 IU.

Postmenopausal osteoporosis

Postmenopausal osteoporosis is a disease of the skeletal system that is characterized by changes in the structure of bone tissue and reduced density. This results in greater susceptibility to injuries and fractures, which develops after menopause.

Within a decade after the onset of menopause, there is a loss of between 20 to 30% of spongy substance and 5-10% of compact bone tissue [8]. Fractures of the proximal radius of the Colles type and vertebral compression fractures (usually Th4-L5 vertebrae) are characteristic for postmenopausal osteoporosis. Up to 60% of vertebral fractures are asymptomatic. Over time, excessive kyphosis of the spine (the so-called widow's hump) and a decrease in height of 2-4 cm may develop. Particularly dangerous for health and life are fractures of the proximal end of the femur, which may lead to cardiovascular, thromboembolic and infectious complications, which may result in the patient's death [9].

In Poland, every 3rd woman is affected by osteoporosis (and every 5th man) [10]. The knowledge of Polish women aged 60-70 about osteoporosis and its prevention was assessed as follows: insufficient in 17%, sufficient in 43%, good in 29%, while only 11% had very good knowledge [11].

Estrogenic effects on bone tissue metabolism

The antiresorptive effect of estrogens on bone tissue is related to the genomic and extragenomic effects on the bone marrow and bone tissue cells. The consequence of this is reduced production of osteoclasts, earlier apoptosis, and reduced resorption capacity of these cells [12]. There are two types of nuclear receptors for estrogens: ERα receptor (product of ESR1 gene on chromosome 6) and ERβ receptor (product of ESR2 gene on chromosome 14) [6]. Both types of receptors are found in osteoblasts, osteocytes and osteoclasts. ERα are dominant in the substantia compacta, and ERβ in the substantia spongiosa [13]. There is also a G protein-coupled estrogen receptor (GPER1) [6]. Activation of this membrane receptor is responsible for the extragenomic effects of estrogens. Ligand binding causes increased phosphorylation of ERK1 and ERK2 kinases and inhibition of JNK kinase [6, 13].

The protective effect of estrogens on bone tissue is highly complex. It involves, among others, the activation of the ERα of osteoblasts by 17β-estradiol, and consequently the stimulation of the expression and synthesis of the Fas ligand (FasL). FasL acting in bone tissue paracrinely stimulates the death of osteoclasts. After ligand bin-

ding, the Fas receptor oligomerizes and activates caspase 8 and the Fas-associated death domain-containing protein. FasL exists in both membrane and soluble forms. The soluble form is formed with the participation of metalloproteinase-3, whose expression is also stimulated by 17β-estradiol. Metalloproteinase-3 may be a potential new therapeutic target in the treatment of postmenopausal osteoporosis [14].

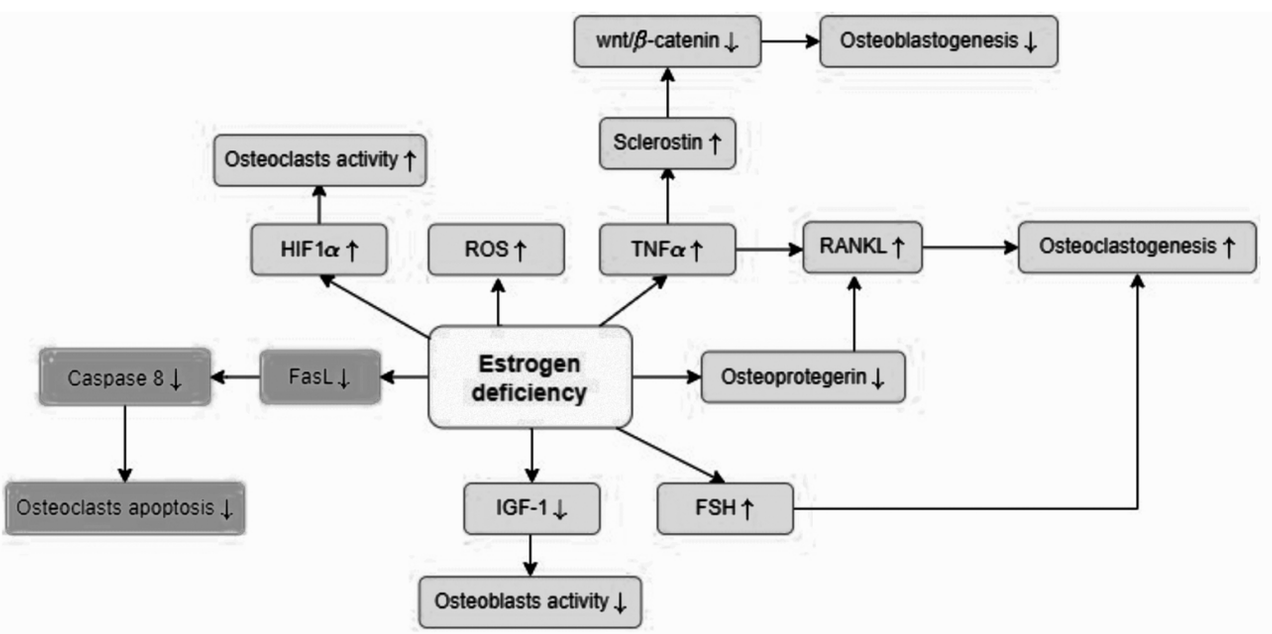
Osteoclasts are bone-destroying cells formed from monocytes in response to osteoclastogenic factors such as RANKL, M-CSF and other inflammatory cytokines. The most important of them is TNFα secreted probably by T lymphocytes. This is suggested by the results of studies conducted on mice, which showed that mice with a deficiency of T lymphocytes are protected against bone loss after ovariectomy [15]. Reduced estrogen concentration stimulates peripheral blood mononuclear cells to produce TNFα. This in turn stimulates bone marrow stromal cells, osteoblasts and T lymphocytes to produce RANKL and M-CSF. TNFα levels in postmenopausal women are higher than in premenopausal women. TNFα not only stimulates bone resorption but also inhibits its reconstruction [13, 15]. The anabolic effects of osteoblasts are inhibited because TNFα is an antagonist of the bone morphogenetic protein (BMP) pathways and of the Wnt pathway. In the BMP pathway, osteoblast maturation is stimulated by BMP proteins 2, 4 and 7, but BMP3 does the opposite. Moreover, the expression of BMP3 in osteoblasts is stimulated by TNFα [15].

A group of BMP proteins was formerly collectively referred to as osteogenin. Particularly noteworthy is the BMP2 protein belonging to the group of TGFβ proteins. BMP2 stimulates the development of the cartilage plate and strongly stimulates osteogenesis [16].

ERα activation is also dependent on the wnt/β-catenin signaling pathway, which is important in response to mechanical stress on osteocytes [13]. The enhancing effect of estrogens on the wnt/β-catenin signaling pathway also leads to the proliferation and maturation of osteoblast progenitor cells [17]. The wnt family contains 19 different glycoproteins. Their attachment to the receptors results in signal transduction to the cell nucleus. There are two types of wnt receptors in the cell membrane: Frizzled and LRP. Their connection with wnt forms a trimeric complex. Then, Dvl proteins are attached to Frizzled, and axin to LRP. This activates β-catenin. β-catenin goes to the cell nucleus, where it stimulates transcription factors TCF/LEF, which initiate osteogenesis [18]. The overall effect of estrogen deficiency on bone tissue metabolism is shown in figure 1.

Immunology of postmenopausal osteoporosis

Estrogen deficiency leads to an increase in the concentration of IL-6, IL-1β and IL-7. IL-6 stimulates osteoblasts to synthesize RANKL, IL-1β directly stimulates osteoblasts to resorption and indirectly activates them as



Rycina 1. Wpływ niedoboru estrogenów na metabolizm tkanki kostnej. FasL – ligand Fas, HIF1α - czynnik indukowany hipoksją, ROS – wolne rodniki tlenowe, TNFα – czynnik martwicy nowotworów, RANKL - ligand aktywatora receptora jądrowego czynnika κ B, FSH – hormon folikulotropowy, IGF-1 – insulinopodobny czynnik wzrostu 1.

Figure 1. The effect of estrogen deficiency on bone tissue metabolism. FasL – Fas ligand, HIF1α - hypxia-inducible factor, ROS – oxygen free radicals, TNFα – tumor necrosis factor, RANKL - Receptor Activator for Nuclear Factor κ B Ligand, FSH – Follicle-stimulating hormone, IGF-1 – Insulin-like growth factor 1

a mediator of TNFα-dependent activation. In turn, IL-7 activates T lymphocytes [12, 15, 19, 20]. There are presumptions that cytokines secreted by T lymphocytes in the postmenopausal period are the main factor stimulating bone resorption and leading to the development of osteoporosis [12, 15]. Stimulated T cells secrete not only TNFα, but also interferon γ (IFN-γ). It activates major histocompatibility complex class II (MHC II) molecules on the surface of APCs: macrophages and dendritic cells, which leads to further activation of T lymphocytes [19]. Among the types of T lymphocytes, a special pro-osteoporotic role is attributed to Th17 lymphocytes. Estrogens have an inhibitory effect on the thymus, therefore, when their concentration is reduced after menopause, during 5-7 years, the thymus begins to function more efficiently, taking part in the production of Th17 lymphocytes [13]. At the same time, the activity of regulatory T lymphocytes (Tregs) is curbed. The lower concentration of estrogens slows the expression of the gene for osteoprotegerin (OPG), which inhibits RANKL [15]. OPG is a 401 amino acid protein whose gene is located on the long arm of chromosome 8. Its concentration rises under the influence of vitamin D3, estradiol, TGF-β, TNF-α and IL-1, and diminishes in response to PTH, glucocorticoids, prostaglandin E2. OPG is a "decoy receptor" for RANKL [21], which inhibits osteoclast differentiation, blocks their activity and induces osteoclast apoptosis [22].

Naive CD4+ T cells stimulated by IL-1β, IL-6 and TGFβ-3 to induce expression of the transcription factor RORγt become Th17 cells. Continuous stimulation by IL-23 is required to keep them alive. Th17 lymphocytes produce IL-17, which directly stimulates the synthesis of RANKL by osteoblasts [15]. The gene for IL-17 is located on chromosome 6 (6p12). There are six isoforms of this pro-inflammatory cytokine (IL-17A-F) that interact with five types of receptors (IL-17RA-E). IL-17 stimulates the secretion of M-CSF and RANKL by osteoblasts and mesenchymal stem cells, and consequently increases the formation of osteoclasts [23].

A study by DeSelm et al. showed that deletion of the gene for the major IL-17 receptor (IL-17RA) protects mice from bone resorption after ovariectomy. Lowered estrogen concentration causes intensified expression of the Act1 protein, which interacts with IL-17RA and is a signaling mediator. IL-17RA mRNA expression is unaffected. The lack of Act1 in osteoblasts also inhibits osteoclastogenesis [24]. Moreover, IL-17 restrains the anabolic role of osteoblasts [15].

Patients suffering from rheumatoid arthritis (RA) are particularly at risk of developing osteoporosis in the postmenopausal age. It is suggested that pro-inflammatory factors produced in the affected joints - mainly TNFα, IL-17 and RANKL is the penetrate into the systemic circulation of [15]. Therapy directed against TNFα causes a decrease in the level of chemerin in the serum of patients suffering from RA, which is associated with lower secretion of IL-6 as well as the macrophage migration inhibitory factor [25].

Estrogen Deficiency and Reactive Oxygen Species (ROS)

Reactive Oxygen Species are also involved in the osteoporotic process after menopause. Glutathione peroxidase is the dominant antioxidant enzyme in osteoclasts. The function of this enzyme is to break down intracellular hydrogen peroxide. Overexpression of this enzyme in osteoclasts suppresses their formation [13]. Estrogens also have an indirect antioxidant effect. This feature results from the stimulation of gene expression for glutathione peroxidase and the mitochondrial superoxide dismutase isoenzyme [26]. 17β-estradiol also restrains the release of cytochrome c from the inner membrane of the mitochondrion, which in turn inhibits cell apoptosis and enhances the efficiency of the electron transport chain [27]. It means that estrogen deficiency leads to an increase in the concentration of ROS in, among others, the bone marrow. As a result, the CD80 molecules on bone marrow dendritic cells are upregulated. These molecules interact with the CD28 molecule on the surface of T cells to promote their production of TNF α. Ovariectomy in mice improves the ability to present antigens by dendritic cells 5 times, and by macrophages 2 times [19].

Estrogens and hypoxia-inducible factor α (HIF1α)

The intraosseous zone of the bone marrow cavity and the epiphyseal growth plates are the areas of reduced oxygenation. The function of chondrocytes and osteoblasts in these areas is regulated by hypoxia-inducible factor. This is a transcription factor consisting of two subunits: HIF1α and HIF1β. The HIF1α subunit undergoes post-translational processing catalyzed by proline hydroxylase, which requires oxygen and the Fe2+ ion to perform its function. HIF1α plays a role in tumor growth by participating in vasculogenesis by stimulating endothelial growth factor (VEGF). In terms of the progression of postmenopausal osteoporosis, more important is the fact that estrogens inhibit HIF1α in a mechanism independent of the degree of oxygenation of the tissue area. In the case of estrogen deficiency, there is an amplified activity

of this factor in osteoclasts, which stimulates their activation and resorption of bone tissue [28].

Long non-coding RNA (IncRNA) in postmenopausal osteoporosis

Postmenopausal osteoporosis is also accompanied by changes in the expression of long (>200 nucleotides) non-coding RNAs. An example of an IncRNA is SNHG1. Its oncogenic role is well known. SNHG1 is downregulated in women with postmenopausal osteoporosis, but is not altered in postmenopausal women without osteoporosis. Thus, it seems that SNHG1 is involved in the osteoporotic process, although the molecular mechanism remains unclear. Huang et al. suggest that plasma SNHG1 can be used as a predictive biomarker of postmenopausal osteoporosis [29].

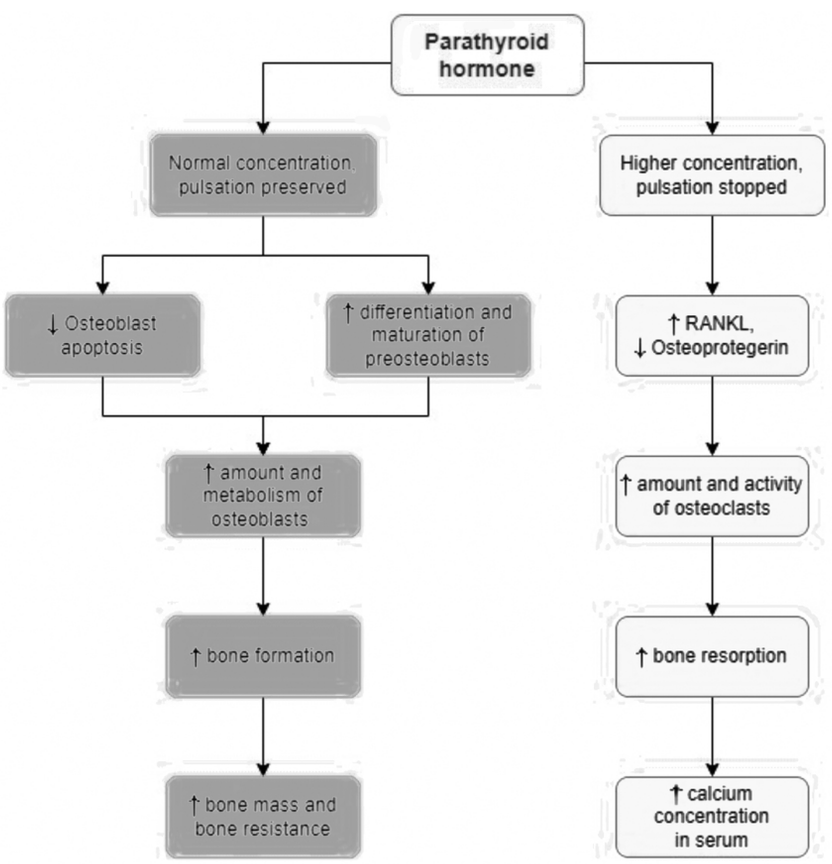
The role of the parathyroid glands in postmenopausal osteoporosis

Parathyroid function in postmenopausal women seems to be divided into two types. In the early postmenopausal period, the skeletal effects of estrogen deficiency predominate. Intensified bone resorption leads to increased release of calcium into the plasma, which results in reduced formation of parathyroid hormone (PTH) [30].

Parathyroid hormone is an 84-amino acid peptide secreted by the parathyroid glands. Its N-terminal fragment plays the main biological role. The regulation of plasma PTH concentration is regulated by a negative feedback mechanism against calcium. This is enabled by the CaR calcium receptor present in the membrane of parathyroid cells [31].

Lower estrogen concentration enhances the sensitivity of osteoblasts to the action of PTH, which, when activated, stimulates osteoclasts. The effects of PTH, such as indirect stimulation of osteoclasts, are compensated by the stimulation of renal excretion of calcium released from bone tissue and the inhibition of intestinal calcium absorption. This is to prevent hypercalcemia. Later on, when the extraskeletal effects of estrogen deficiency dominate, the concentration of PTH increases [8]. This is confirmed by a study by Oluboyo et al., which also indicated a significant increase in the concentration of phosphates in the blood of postmenopausal women [30].

The effect of PTH on bone metabolism is extremely complex and it depends both on the concentration of the hormone and the pulsation of its secretion (figure 2).



Rycina 2. Wpływ parathormonu na metabolizm tkanki kostnej. RANKL - ligand aktywatora receptora jądrowego czynnika κ B
Figure 2. Effect of parathyroid hormone on bone tissue metabolism. RANKL - Receptor Activator for Nuclear Factor κ B Ligand

The receptor for PTH type I in bone tissue is found only on the surface of osteoblasts. It is a heptahelical membrane receptor associated with G protein. The physiological concentration of PTH and its pulsatile release leads to an anabolic effect on bone tissue. Hormone binding to the receptor causes the activation of kinases: A, C and MAP, as well as phospholipases A and D. This leads to the inhibition of osteoblast apoptosis, and the increase in IGF-1 synthesis. Sclerostin expression is also slowed down. This causes the Wnt/β-catenin pathway leading to the increase in the number and activity of osteoblasts to work more effectively. However, the high concentration of PTH in plasma and the lack of pulsations lead to enhanced expression of the RANKL gene and inhibition of OPG synthesis, which activates osteoclastogenesis [31].

Estrogens regulate the absorption of calcium from the intestines and the inhibition of its removal by the kidneys, because they participate in the metabolism of vitamin D, making the concentration of total 1,25-dihydroxycholecalciferol higher [8]. The vitamin D receptor is expressed both in osteocytes and osteoblasts, which leads to the suppression of bone resorption [17]. Estrogens together with vitamin D also reduce the risk of developing the metabolic syndrome [5].

TGFβ, IGF-1 and estrogen deficiency

Increased bone resorption after menopause is not accompanied by a parallel growth in bone formation. Bone formation is stimulated by TGFβ and IGF-1. In in vitro studies, estrogens stimulate the secretion of these factors [8]. The IGF-1 receptor (IGFR1) activates the PI3 kinase. Further signal transduction using the Ras GTPase, AKT kinase enhances cell proliferation and survival by regulating multiple pathways. ERα is able to bind the regulatory part of PI3 kinase, and 17β-estradiol enhances this binding, leading to activation of AKT kinase. This is because 17β-estradiol stimulates the interaction between ERα and IGFR-1, and this improves the ability to activate the PI3 kinase pathway [32]. This means that postmenopausal estrogen deficiency inhibits the reconstruction of bone tissue as a result of insufficient stimulation of osteoblasts to synthesize the above-mentioned growth factors [8, 19].

Sclerostin and collagen in postmenopausal osteoporosis

Post-menopausal women have higher levels of circulating sclerostin because its secretion is less inhibited by estrogens. Sclerostin is a protein encoded by the SOST gene and produced by osteocytes. Its synthesis is stimulated by myocyte enhancer factor 2 (MEF2), whose activity is in turn increased by TNFα [33]. Sclerostin has an antagonistic effect on the wnt pathway, which decelerates the production of bone matrix by osteoblasts [13].

Estrogens stimulate fibroblasts to synthesize collagen. It accounts for 90% of the proteins produced by osteoblasts. Therefore, it is highly probable that also in the mechanism of insufficient stimulation of osteoblasts by estrogens, there is a reduced synthesis of collagen by these cells [8].

Follicle-stimulating and luteinizing hormones

Menopause is associated not only with lowered estrogen levels in the blood, but also with increased secretion of FSH by the pituitary gland. FSH receptors are located on the surface of osteoclasts and their activation stimulates osteoclastogenesis [17, 34]. Binding of the ligand to the receptor activates Gi2α, which results in lessened concentration of cellular cAMP [35]. Then, the MEK/Erk, NFκB and Akt pathways are activated [17, 35]. Lutropin receptors are found on the surface of osteoblasts. The role of luteinizing hormone in bone metabolism remains unclear [17].

Adipose tissue and postmenopausal osteoporosis

Hormonal changes after menopause can lead to weight gain. Adipose tissue is very active endocrine gland and secretes many hormones called adipokines, e.g. leptin, adiponectin or resistin, as well as sex steroid hormones. Leptin is a peptide hormone whose secretion rises with the amount of body fat. Leptin receptors are located, among others, on osteoblasts and chondrocytes [36]. The effect of leptin on osteoblasts is a beneficial increase in the concentration of OPG in relation to RANKL [37], an improvement in collagen synthesis and stimulation of proliferation of these cells [36]. The central action of leptin is opposed to its peripheral action. Systemic administration of high doses of leptin may have negative effects on bone tissue, similarly to its central administration. This is due to the fact that high doses of leptin are associated with weight loss and a decrease in serum IGF1 levels. However, the systemic effect of leptin is dominated by its peripheral effect, which is a protective effect on bone tissue [37].

Plasma adiponectin levels are inversely related to body fat mass and BMI [38]. Its receptors (AdipoR1 and AdipoR2) are found on the surface of osteoblasts, stimula-

ting their maturation and proliferation. It also suppresses the differentiation of CD14+ monocytes into osteoclasts [37]. A study by Williams G.A. et al. using mice proved that the influence of adiponectin on bone tissue is dominated by indirect processes that lead to higher bone resorption [39]. In turn, resistin stimulates the proliferation of both osteoblasts and osteoclasts. However, its resultant effect is not clear [37].

Chemerin also seems to have an effect on bone metabolism.. Neutralization of chemerin leads to the inhibition of osteoclastogenesis, the expression of acid phosphatase and metallopeptidase 9 [40]. Chemerin in human chondrocytes activates intracellular MAP and Akt cascades, resulting in intensified TNFα and IL-6 secretion [25].

The study by Engin-Üstün et al. showed that the concentration of chemerin in the serum is significantly lower in women with postmenopausal osteoporosis compared to the control group [41]. However, the results of the study by Saba Tariq et al. are different [42]. The issue of the effect of chemerin on bone metabolism in postmenopausal women requires further research in larger research groups.

Genetic predisposition of postmenopausal osteoporosis

Numerous studies are currently being conducted to determine the relationship between the polymorphism of genes for estrogen receptors (e.g. ESR1 PvuII, ESR1 XbaI, ESR1 G2014A, ESR2 AluI) and the risk of osteoporosis. Although the results of many studies are contradictory, it seems that polymorphisms of these genes do not lead to an elevated risk of developing osteoporosis. However, it turns out that the A allele variant of the ESR2 RsaI polymorphism may play a protective role in the development of osteoporosis [43].

Summary

Lower estrogen levels in postmenopausal women cause intensified bone resorption. There is an increased release of TNFα, RANKL, ROS, HIF1α, sclerostin, FSH and a decreased release of IGF-1, FasL and osteoprotegerin. Hormones of adipose tissue and parathyroid hormone also have a large impact on the state of bone tissue. A detailed understanding of the pathophysiology of postmenopausal osteoporosis is the starting point for research into the search for new medications directed against this disease. Knowledge of pathomechanisms also allows to raise awareness of physicians. Apropriate education of patients is crucial to introduce effective preventive or therapeutic measures.

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Conflict of interest
None

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