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Pathogenetic Role of Bone Tissue in the Formation of Metabolic and Inflammatory Disorders in Postmenopausal Women

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Introduction

Postmenopausal osteoporosis has long been viewed primarily as a direct consequence of age-related decline in ovarian function [11]. According to classical concepts, a decrease in estrogen levels naturally leads to loss of bone mass, disruption of skeletal microarchitecture, and, as a result, an increased risk of fractures [2]. Bone tissue acts mainly as an object of hormonal regulation, and osteoporosis itself is a local manifestation of endocrine deficiency [3]. However, over the past two decades this understanding has expanded significantly [1-4]. Data have accumulated indicating that bone tissue is not a passive object of hormonal regulation [9]. It itself actively secretes signaling molecules, interacts with cells of the immune system, and participates in the regulation of energy metabolism [9,10]. This fundamentally changes the view of the pathogenesis of postmenopausal osteoporosis: it is not only a local process in the skeleton, but a systemic disease affecting several physiological axes [1-22].

The field that studies the interaction between the bone and immune systems is called osteoimmunology [1-4]. Within this field, it has been shown that estrogen deficiency triggers a cascade of reactions in which bone resorption, chronic inflammation, and metabolic disorders are closely intertwined [4-15].

Bone Tissue as an Endocrine-Immune Organ

For a long time, bone was perceived exclusively as a supporting and protective structure [14-16]. However, modern studies have shown that it also performs endocrine functions [9-18]. Osteoblasts and osteocytes secrete osteocalcin, a protein that participates not only in the mineralization of the bone matrix, but also in the regulation of energy metabolism, tissue sensitivity to insulin, and adipocyte function [18,19]. Osteocytes produce fibroblast growth factor, which regulates phosphate-calcium metabolism and kidney function [9-18]. Osteoblasts express the ligand of the receptor activator of nuclear factor kappa-B, RANKL, a key molecule that not only triggers osteoclast differentiation, but also interacts with immune cells carrying the corresponding receptor [14-21].

Thus, bone tissue is simultaneously included in two regulatory systems [9-17]. On the one hand, it participates in the endocrine regulation of metabolism [9-19]. On the other hand, it is part of the

immune system, since its cells produce cytokines, chemokines, and factors that influence the activity of lymphocytes and macrophages [1-4]. In estrogen deficiency, both of these functions are disrupted, and bone becomes a source of pathological signals that spread far beyond the skeleton [2-22].

Direct Effect of Estrogen Deficiency on Bone Cells

Normally, estrogen maintains the balance of bone remodeling, limiting resorption and stimulating bone formation [13-23]. The mechanism of this action is multifaceted [10-24]. Estrogen suppresses the production of RANKL by osteoblasts and simultaneously stimulates the production of osteoprotegerin, a soluble decoy that binds RANKL and prevents it from activating the receptor on the surface of osteoclasts [14-24]. Estrogen supports the differentiation of mesenchymal stem cells toward osteoblasts rather than adipocytes [20-27]. It also protects osteoblasts and osteocytes from apoptosis, prolonging their functional life [21-28].

With the onset of menopause, this regulatory function is lost [1-3]. The ratio of RANKL to osteoprotegerin shifts sharply toward RANKL [17-24]. This leads to hyperactivation of osteoclasts, deepening of resorption cavities, and accelerated loss of bone mass [5-22]. In the first years after menopause, loss of trabecular bone can be especially rapid, which explains the high frequency of vertebral fractures precisely during this period [2-5]. In parallel, calcium absorption in the intestine decreases and the level of active vitamin D falls [17-20]. In response, parathyroid hormone secretion increases, which additionally stimulates osteoclasts [21,22]. Secondary hyperparathyroidism develops, enhancing resorption [3-22]. Clinically, this explains why in some women bone mass falls precipitously, while in others slowly, and why vitamin D and calcium deficiency aggravates the course of osteoporosis [3-22].

Immune Component of Estrogen Deficiency

Fundamentally important for understanding the systemic nature of postmenopausal osteoporosis is that estrogen regulates not only bone but also immune cells [4-22]. It suppresses the production of proinflammatory cytokines (interleukin-1 β , interleukin-6, tumor necrosis factor α) and stimulates the production of anti-inflammatory ones (interleukin-4 and interleukin-10) [4-15].

In estrogen deficiency, this balance is disrupted, and the body transitions to a state of chronic subclinical inflammation [8-15].

Clinical data confirm this position [10-15]. In postmenopausal women, levels of interleukin-1 β , interleukin-6, and tumor necrosis factor α in blood plasma are elevated [4-12]. Moreover, interleukin-1 levels correlate with bone resorption activity, and estrogen treatment reduces these parameters [4-15]. This means that estrogen deficiency is the driving force behind increased cytokine expression, and not merely a background [4-22]. In addition, in postmenopausal women the number and functional activity of immune cells change: the number of CD19⁺ B lymphocytes decreases, the cytokine production profile of T cells changes, and the number of circulating monocytes and neutrophils increases [4-7]. A phenotype is formed that can be designated as «inflammatory aging» of the immune system [12-15].

T Lymphocytes

T cells are key participants in osteoimmunological interactions [1-4]. Among them, T helper type 17 cells, which secrete interleukin-17, and regulatory T cells, which suppress inflammatory reactions, are of particular importance [4-6]. In estrogen deficiency, the number of Th17 cells increases, while the number of regulatory T cells decreases [5-6]. Interleukin-17 stimulates the production of RANKL by osteoblasts and enhances osteoclastogenesis [4-6]. In addition, Th17 cells promote the migration of inflammatory monocytes into the bone marrow, where they become osteoclast precursors [5-13].

The imbalance between Th17 and regulatory T cells is considered one of the central mechanisms of bone loss in postmenopausal osteoporosis [12-16]. Clinically, this is manifested by elevated levels of tumor necrosis factor α and interleukin-6 in the blood, which additionally stimulate RANKL [4-12].

B Lymphocytes

Under physiological conditions, B cells produce a significant portion of all osteoprotegerin in the bone marrow and thereby suppress osteoclastogenesis [8]. In estrogen deficiency, the situation changes [7,8]. Activated B cells begin to secrete RANKL rather than osteoprotegerin, and the production of granulocyte-macrophage colony-stimulating factor increases, which stimulates the differentiation of neutrophils and osteoclast precursors [7-22]. In addition, B cells can suppress osteoblast differentiation through signaling pathways and tumor necrosis factor [7,8]. Thus, in postmenopausal osteoporosis, B cells turn from defenders of bone tissue into its destroyers, which once again emphasizes the systemic nature of the pathological process [7,8].

Macrophages

Macrophages are precursors of osteoclasts and at the same time key regulators of inflammation [3-22]. Two main phenotypes are distinguished [14-22]. M1 is proinflammatory, which secretes interleukin-1, interleukin-6, tumor necrosis factor α , and reactive oxygen species [4-15]. M2 is anti-inflammatory, which secretes interleukin-10, transforming growth factor β , and bone morphogenetic protein 2, promoting osteogenesis [4-22].

In estrogen deficiency, macrophage polarization shifts toward M1 [4-15]. Moreover, M2 macrophages can differentiate into mature osteoclasts in the presence of RANKL only in the absence of estrogen [9-14]. This means that estrogen directly restrains the transformation of macrophages into bone-destroying cells [4-22]. During menopause, this restraining factor disappears, and macrophages become a source of both proinflammatory

cytokines and osteoclasts [8-15]. Paracrine factors released by M1 macrophages suppress the osteogenic differentiation of mesenchymal stem cells and reduce the expression of osteoprotegerin, which additionally shifts the balance toward resorption [18].

Neutrophils

In women with postmenopausal osteoporosis, an increase in the neutrophil-to-lymphocyte ratio in peripheral blood is detected, associated with a decrease in bone mineral density [4-12]. They form neutrophil extracellular traps, express RANKL, and secrete interleukin-6 and interferon γ [12-15]. Activated neutrophils are able to attach directly to osteoblasts and stimulate resorption of the osteoblast matrix [4-22]. Interestingly, in patients with chronic neutropenia, bone mineral density is also reduced [22]. This means that neutrophils are necessary for normal bone homeostasis, but their hyperactivation leads to bone loss [4-12]. Thus, the balance between deficiency and excess of neutrophils proves critical for the state of the skeleton [12-22].

Mast Cells

Mast cells in the bone marrow in estrogen deficiency increase in number and are located in close proximity to osteoclasts [4-22]. Their mediators - histamine, interleukin-6, tumor necrosis factor α , RANKL - stimulate osteoclastogenesis [4-14]. Mice with mast cell deficiency are protected from bone loss after ovariectomy, which indicates a direct role of these cells in pathogenesis [17-22]. Blockade of the histamine H1 receptor in postmenopausal women improved bone tissue condition compared with placebo, which confirms the clinical significance of this mechanism [4-12]. In addition to influencing osteoclasts, mast cell mediators can also affect osteoblasts, although this aspect has been studied less [4-22].

Oxidative Stress as a Connecting Link

In estrogen deficiency, the activity of sirtuins - SIRT1, SIRT3, SIRT6 - decreases [10,11]. These are NAD⁺-dependent deacetylases that support osteoblast function, protect mitochondria, suppress NF- κ B and inflammation, and regulate antioxidant enzymes [10-17]. When SIRT1, SIRT3, and SIRT6 are suppressed, reactive oxygen species accumulate [17]. They activate NF- κ B, which increases RANKL and decreases osteoprotegerin [10-14]. They suppress the Wnt/ β -catenin signaling pathway, which inhibits osteoblasts [11]. They cause apoptosis of osteoblasts and osteocytes and stimulate the differentiation of mesenchymal stem cells into adipocytes instead of osteoblasts [10-18].

A vicious circle is formed: estrogen deficiency leads to a decrease in sirtuins, accumulation of reactive oxygen species, activation of NF- κ B, inflammation, and resorption, which in turn further enhance oxidative stress [10,11]. This circle closes not only at the level of bone tissue, but of the entire organism, since reactive oxygen species and proinflammatory cytokines circulate in the blood and affect other organs and tissues [10-13].

Clinical Manifestations of the Systemic Process

On the part of the bone system, accelerated loss of trabecular bone in the first years of postmenopause, low-trauma fractures of vertebrae, femoral neck, and radius, decreased height, kyphotic deformity, and chronic pain syndrome in compression vertebral fractures are observed [2-5]. Fractures in osteoporosis are often accompanied by implant failure, delayed healing, and increased mortality [3-22].

On the part of metabolism, insulin resistance associated with undercarboxylated osteocalcin, visceral obesity, dyslipidemia,

and sarcopenia develop [18-19]. Visceral fat itself is a source of proinflammatory cytokines, which closes another vicious circle [15-18]. Sarcopenia, in turn, increases the risk of falls, which, combined with bone fragility, sharply increases the probability of fracture [19-22].

On the part of inflammation, elevated levels of C-reactive protein, interleukin-6, and tumor necrosis factor α in plasma, an increase in the total number of leukocytes, lymphocytes, and monocytes, an increased neutrophil-to-lymphocyte ratio, as well as signs of immune aging - accumulation of exhausted and senescent CD4⁺ T cells - are detected [4-12]. These changes are found both in peripheral blood and directly in bone tissue [4-15].

Women with postmenopausal osteoporosis more often have metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, and chronic subclinical inflammation [15-18]. This is not a coincidence - these are common pathogenetic links [15-22]. Bone and metabolism mutually enhance pathology: osteoporosis contributes to metabolic disorders through the secretion of osteocalcin and cytokines, and metabolic disorders aggravate bone resorption through inflammation and oxidative stress [10-18].

Clinical Phenotypes

Based on the combination of bone, metabolic, and inflammatory disorders, several phenotypes of patients can be distinguished [3-22].

The first is «classical» postmenopausal osteoporosis [2,3]. These are lean women with early menopause, in whom loss of trabecular bone predominates [5-22]. They have moderately elevated proinflammatory cytokines, and metabolic disorders are weakly expressed [4-22]. This phenotype is closest to the traditional understanding of osteoporosis [2,3].

The second is «metabolic» osteoporosis [18,19]. These are women with visceral obesity, insulin resistance, and dyslipidemia [15-18]. Bone mineral density may be normal or even elevated, but loss of cortical bone and disruption of microarchitecture predominate [18,19]. Chronic inflammation is pronounced, and the risk of fractures is high despite normal densitometry [15-22]. This phenotype explains the so-called paradox of obesity and osteoporosis [18,19].

The third is «inflammatory» osteoporosis [4-22]. These are women with autoimmune diseases, chronic infections, or chronic obstructive pulmonary disease [3-22]. They have pronounced Th17 activation, high RANKL levels, rapid bone loss, and poor fracture healing [4-6]. They require a special therapeutic approach, since standard regimens may be insufficiently effective without control of the underlying inflammatory process [3-22].

Conclusion

Postmenopausal osteoporosis is not an isolated disease of the bone system, but a systemic pathological process in which bone tissue acts as an active participant [1-9]. Through the secretion of osteocalcin, RANKL, and other mediators, it influences the immune system and metabolism [14-18]. In response, immune cells - T lymphocytes, B lymphocytes, macrophages, neutrophils, and mast cells - enhance bone resorption and maintain chronic inflammation [4-22].

The key links of pathogenesis form a single chain [4-6]. Estrogen deficiency leads to derepression of RANKL and hyperactivation of

osteoclasts [14-22]. The imbalance between Th17 and regulatory T cells maintains chronic inflammation [5,6]. A decrease in sirtuins enhances oxidative stress and activates NF- κ B [10,11]. A vicious circle arises in which bone, inflammation, and metabolic disorders mutually reinforce each other [10-15].

Clinically, this means that a postmenopausal woman with osteoporosis requires comprehensive assessment - not only densitometry, but also metabolic and inflammatory status [13-22]. Only such an approach allows understanding the individual phenotype of the patient and choosing the optimal treatment strategy [3-20]. Further research should be aimed at developing clinical algorithms that take into account the systemic nature of the disease, and at searching for therapeutic targets acting simultaneously on bone metabolism, inflammation, and oxidative stress [7-21].

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