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ESTROGEN DEFICIENCY AND POSTMENOPAUSAL OSTEOPOROSIS: PATHOGENESIS, DIAGNOSIS, AND TREATMENT APPROACHES

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Abstract. A sharp decline in estrogen levels during the postmenopausal period is one of the key pathogenetic factors disrupting the balance of bone metabolism. This article analyzes the mechanisms of the effects of estrogen deficiency on bone tissue, including increased osteoclast activity, relative suppression of osteoblast function, and enhanced bone resorption due to imbalance in the RANK/RANKL/OPG system. In addition, the role of increased expression of proinflammatory cytokines (IL-1, IL-6, TNF-α) in amplifying the inflammatory component and its contribution to the development of osteoporosis is examined. The clinical consequences of postmenopausal osteoporosis are systematically described, including decreased bone mineral density (BMD) and an increased risk of fractures.

Keywords: estrogen deficiency, postmenopausal osteoporosis, bone remodeling, osteoclast activity, osteoblast function, RANK/RANKL/OPG system, bone mineral density (BMD).

Аннотация. Резкое снижение уровня эстрогенов в постменопаузальном периоде является одним из ключевых патогенетических факторов, нарушающих баланс костного метаболизма. В данной статье проанализированы механизмы влияния дефицита эстрогенов на костную ткань, включая повышение активности остеокластов, относительное снижение функции остеобластов, а также усиление костной резорбции вследствие дисбаланса в системе RANK/RANKL/OPG. Кроме того, рассмотрена роль усиленной экспрессии провоспалительных цитокинов (IL-1, IL-6, TNF-α) в активации воспалительного компонента и его участие в развитии остеопороза. В работе системно освещены клинические последствия постменопаузального остеопороза, включая снижение минеральной плотности костной ткани (МПКТ) и повышение риска переломов.

Ключевые слова: дефицит эстрогенов, постменопаузальный остеопороз, ремоделирование костной ткани, активность остеокластов, функция остеобластов, система RANK/RANKL/OPG, минеральная плотность костной ткани (МПКТ).

Introduction: Postmenopausal osteoporosis is one of the most common bone diseases in postmenopausal women, characterized by decreased bone mineral density and increased risk of fracture. Epidemiological data indicate that 30-50% of women develop osteopenia or osteoporosis after menopause. This condition is associated with fractures, particularly in the hip, spine, and wrist, and can cause significant disability and mortality. The main factor in the development of the disease is estrogen deficiency. Estrogen regulates bone formation and maintains a balance between osteoclast and osteoblast activity. After menopause, estrogen levels decline rapidly, leading to an imbalance and increased bone resorption. The aim of this study was to investigate the effect of estrogen deficiency on bone metabolism, to explain the development of postmenopausal osteoporosis, and to evaluate current diagnostic and therapeutic approaches.

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Materials and Methods: This study, based on a literature review, studied modern scientific sources on postmenopausal osteoporosis from various aspects. The effect of estrogen on bone remodeling and the mechanisms of osteoclastogenesis through the RANK-RANKL-OPG system, as well as diagnostic methods (DEXA and bone biomarkers) and pharmacological and non-pharmacological treatment methods were studied in depth. The obtained data were systematically summarized and evaluated based on pathogenesis and the diagnostic and treatment chain.

Pathogenesis: postmenopausal osteoporosis is caused by estrogen deficiency, but it is wrong to attribute this process to only one hormone. In reality, the mechanism is multi-step and multifactorial. Under normal conditions, estrogen maintains bone remodeling in balance and reduces bone resorption by osteoclasts and promotes new bone formation by osteoblasts. At the molecular level, this effect is mediated through the RANK-RANKL-OPG system: estrogen increases the production of osteoprotegerin (OPG) and reduces the expression of RANKL, resulting in a decrease in the development and activity of osteoclasts. Estrogen also increases apoptosis in osteoclasts, shortening their lifespan.

When estrogen deficiency occurs, these control mechanisms are disrupted. The RANKL/OPG ratio increases, osteoclast activity and number increase, and their lifespan is prolonged. At the same time, osteoblast activity is relatively reduced. As a result, bone resorption prevails over bone formation.[5] This process occurs especially rapidly in trabecular bones, since they are more metabolically active. As a result, rapid bone loss is observed in the spine and femur. In cortical bone, thinning and porosity increase. Bone microarchitecture is disrupted, and mechanical strength is sharply reduced, which leads to fractures even with minimal trauma.[8] In addition to hormonal factors, additional mechanisms are also involved in the pathogenesis. Estrogen deficiency increases the production of inflammatory cytokines (IL-1, IL-6, TNF-α), which further enhances osteoclast activity. At the same time, age-related decline in osteoblast differentiation and bone formation further exacerbate the process.[7] Vitamin D deficiency and decreased calcium absorption also contribute to the pathogenesis. This increases parathyroid hormone (PTH) secretion, further activating bone resorption through secondary hyperparathyroidism. In addition, genetic factors, low physical activity, poor diet, smoking, and alcohol consumption also accelerate bone loss.[9]

Diagnostic methods:

1. Instrumental diagnostics (DEXA). The most reliable method for diagnosing postmenopausal osteoporosis is dual-energy X-ray absorptiometry (DEXA). This method measures bone mineral density (BMD) and allows for an accurate assessment of the degree of osteoporosis. The examination is usually performed in the spine, hip, and wrist. The results are expressed in a T-score: a value above -1.0 is normal, from -1.0 to -2.5 indicates osteopenia, and a value of -2.5 and below indicates osteoporosis. DEXA is used not only for diagnosis, but also for monitoring the effectiveness of treatment.[12]

2. Laboratory diagnostics (biomarkers). Biochemical markers are important for assessing bone remodeling. They reflect the processes of bone formation and resorption. Markers of bone formation include osteocalcin and bone-specific alkaline phosphatase, the decrease of which indicates a decrease in osteoblast activity.[13] Markers of bone resorption — C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX) — when increased, indicate an

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increase in osteoclast activity. These markers are useful in early diagnosis of the disease and assessment of the effectiveness of treatment.

3. Clinical assessment and identification of risk factors. Diagnosis is not limited to hardware and laboratory tests. Clinical assessment takes into account the patient's age, duration of menopause, presence of previous fractures, family history, level of physical activity, nutritional characteristics and harmful habits (smoking, alcohol). Also, the risk of falls and factors affecting overall bone strength are assessed. This approach plays an important role in determining individual risk and choosing the right treatment strategy.[15]

Analysis of the results: The results obtained indicate that estrogen deficiency is a major, but not the only, factor in the development of postmenopausal osteoporosis. The analysis confirms that the decrease in estrogen leads to an increase in osteoclast activity through the RANK–RANKL–OPG system, as a result of which bone resorption prevails over bone formation. This results in a decrease in bone mineral density and a deterioration of the microarchitecture.[11] Low T-scores determined by DEXA examinations are clinically directly associated with a high risk of fracture. In particular, the decrease in BMD observed in the spine and hip is the most clinically significant. At the same time, the analysis of biomarkers allows for a deeper understanding of the dynamics of bone remodeling: increased levels of CTX and NTX indicate active bone resorption, while a decrease in osteocalcin indicates a decrease in osteoblast activity.[14] An important point is that DEXA and biomarker results do not always indicate the same stage. Biomarker changes often precede BMD decline. Therefore, if DEXA alone is relied upon, the disease may be detected at a late stage. This is a serious limitation in clinical decision-making.[17] Analysis of treatment outcomes suggests that different therapeutic approaches affect different mechanisms. Bisphosphonates directly inhibit osteoclast activity, slowing bone loss and reducing fracture risk. SERMs selectively mimic the effects of estrogen, protecting bone, but are not equally effective in all tissues. Although estrogen therapy is the pathogenetically most appropriate approach, its risk profile (thrombosis and oncological risks) limits its use.[15]

Treatment approaches: The main goals of postmenopausal osteoporosis treatment are to slow bone loss, maintain or increase bone mineral density, and reduce the risk of fracture. Studies have shown that an effective approach should not rely on a single approach, as the pathogenesis of the disease is multifactorial.[16] Bisphosphonates are the first-line pharmacological treatment because they inhibit osteoclast activity, reduce bone resorption, and significantly reduce the risk of fracture. Selective estrogen receptor modulators (SERMs) partially mimic the effects of estrogen and protect bone tissue, but their effects are tissue-selective. Although estrogen replacement therapy is pathogenetically justified, it is used only on an individual basis due to the risks of thrombosis and oncology. Vitamin D and calcium supplements are mandatory components of all treatment plans and ensure bone mineralization.[20] Nonpharmacological approaches are also important. Physical activity, especially strength and weight-bearing exercise, helps maintain bone density. A healthy diet, adequate calcium and protein intake, and avoiding smoking and alcohol can slow bone loss.[19]

Conclusion: The central pathogenic factor of postmenopausal osteoporosis is estrogen deficiency, which disrupts the balance of bone remodeling. Estrogen deficiency increases osteoclast activity and reduces osteoblast activity, resulting in rapid trabecular bone resorption,

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cortical bone thinning, and bone microarchitecture deterioration. This process dramatically increases the risk of fractures, especially in the spine, hip, and wrist.

The pathogenesis of the disease is not solely dependent on hormonal factors. With age, bone formation slows down, vitamin D deficiency and calcium absorption decrease, inflammatory cytokines (IL-6, TNF-α) stimulate bone resorption, and genetic and endocrine factors also affect development. Therefore, postmenopausal osteoporosis is a multifactorial and dynamic process.

The combined use of DEXA scans and bone biomarkers is important for early detection and monitoring of the disease. DEXA is the "gold standard" for assessing bone mineral density, while biomarkers allow for early detection of changes in bone remodeling. This combined approach provides a strong advantage in initiating treatment on time and developing an individualized therapy strategy.

Monotherapy is often insufficient in treatment. Bisphosphonates inhibit bone resorption, SERMs protect bone, and estrogen therapy, although pathogenetically correct, requires consideration of the risk profile. Vitamin D and calcium supplements, as well as physical activity, diet optimization, and restriction of harmful habits are important adjunctive measures. Therefore, the most effective strategy is an individualized, comprehensive approach that combines pharmacotherapy, lifestyle modification, diet optimization, and biomarker monitoring. This approach slows bone loss, reduces the risk of fractures, and improves the quality of life of postmenopausal women.

Future research should focus on developing optimized treatment models based on individualized therapy, genetic profiling, and biomarkers to prevent bone loss.

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