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Pathogenetic mechanisms of postmenopausal osteoporosis formation and their relationship with cardiovascular pathology

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ABSTRACT

Involutional hormonal processes characteristic of the postmenopause are accompanied by disorders that deteriorate the quality of life in the female population and lead to an increased risk of developing metabolic diseases of the bones and cardiovascular system. In modern medicine, it is extremely important to understand the pathogenesis of postmenopausal osteoporosis (PMO) in association with cardiovascular diseases, which are the main causes of mortality in the population.

This review is devoted to determining the key aspects of the pathogenesis of PMO and identifying their relationships with cardiovascular pathology. Epidemiological data are assessed, the main mechanisms of PMO and vascular pathology development are considered, the fundamental role of hormone deficiency, immune dysregulation disorders, and disorders of macrophage polarization is described, and data on the association between the pathogenesis links of the studied pathological processes are analyzed.

The obtained data will form a unified approach to reducing the growing prevalence of cardiovascular diseases and complications of PMO and contribute to the development of new research areas in disease prevention.

Keywords: osteoporosis, postmenopause, cardiovascular diseases, atherosclerosis, estrogen, macrophages

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Патогенетические механизмы формирования постклимактерического остеопороза и их взаимосвязь с кардиоваскулярной патологией

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РЕЗЮМЕ

Инволюционные гормональные процессы, характерные для постклимактерического периода, сопровождаются расстройствами, ухудшающими качество жизни женской половины населения и приводящими к повышению риска развития метаболических заболеваний скелета и сердечно-сосудистой системы. С позиции современной медицины крайне важным является понимание патогенеза постклимактерического остеопороза (ПКО) в ассоциации с кардиоваскулярными заболеваниями, занимающими лидирующие позиции в структуре смертности населения.

Данный обзор посвящен определению ключевых аспектов патогенеза формирования ПКО и выявлению их взаимосвязей с кардиоваскулярной патологией. Проведена оценка эпидемиологических данных, с разных позиций рассмотрены основные механизмы развития ПКО и сосудистой патологии, описана основополагающая роль гормонального дефицита, дисрегуляторных расстройств иммунной системы, нарушений поляризации макрофагов, проанализированы данные, доказывающие сопряженность звеньев патогенеза изучаемых патологических процессов.

Собранные в обзоре сведения позволят сформировать единый подход к снижению растущей распространенности сердечно-сосудистых заболеваний и осложнений остеопороза среди женщин постклимактерического периода и будут способствовать разработке новых научных направлений в профилактике заболеваний.

Ключевые слова: остеопороз, постменопауза, сердечно-сосудистые заболевания, атеросклероз, эстроген, макрофаги

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Currently, the observed trend toward increased life expectancy in developed countries leads to an increase in the number of postmenopausal women and a rise in the incidence of related diseases. Osteoporosis and cardiovascular diseases are among the most common postmenopausal complications [1, 2].

Postmenopausal osteoporosis (PMO) is understood as a widespread systemic metabolic bone disease, characterized by progressive loss of bone tissue following the onset of natural or induced menopause [3,4].

PMO belongs to type I primary osteoporosis and accounts for 85% of all forms of this group of diseases [1]. The social significance of this disease is determined by its consequences – fractures of the vertebrae and tubular bones, which is one of the main causes of disability in the elderly population [5]. While the majority of premenopausal women have normal bone mineral density (BMD) parameters, by the age of 70, 27–60% of patients are diagnosed with osteopenia, while 70% of women develop osteoporotic changes in hip and lumbar spine [6]. According to statistics, almost half of women are unable to work as a result of fractures, and about 20% of them become disabled [7].

The most commonly occurring hip fracture is a serious complication of osteoporosis, and the associated high mortality rates vary from 12 to 40% during the first year after the fracture. The risk of fatal outcomes also increases due to high probability of a vertebral compression fracture, since it is the trabecular bone tissue that is the most susceptible to damage [3, 8]. The analysis of fracture frequency dynamics revealed a statistically significant increase in rates in recent years. According to the prognosis, the number of osteoporotic femoral neck fractures is expected to double by 2050 [9].

The multifactorial nature of the disease, complex pathogenetic mechanisms with underlying hormonal deficiency, and the impact on other body systems allow to consider osteoporosis as a multidisciplinary problem. In addition to pronounced osteoporotic changes and related fractures, it is characteristic of postmenopausal women to have progression of cardiovascular diseases (CVDs). A number of authors [7, 10–12] have proven that the frequency of CVDs significantly increases in people suffering from osteoporosis. Globally, the prevalence of CVDs in postmenopausal women exceeds the prevalence of CVDs in premenopausal women and men of the same age [13].

One of the known causes of this phenomenon is osteolysis, which leads to an increase in the level of calcium ions in the vascular bed and their further deposition on the inner wall of the vessels. Calcification of the vascular wall ultimately leads to the development of ischemic heart disease, acute cerebrovascular accident, and other CVDs [12].

However, these risk factors do not fully reflect a more severe course of cardiovascular pathologies in this group [14]. Therefore, from the standpoint of modern medicine, comprehensive understanding of the pathophysiological mechanisms of the relationship between postmenopausal osteoporosis and CVDs is certainly an important task, since it might not only improve the diagnosis of serious pathologies and affect further progression of diseases with the formation of common risk groups, but also become an incentive to discover new directions in their treatment.

Pathogenetic role of immune dysregulation in the development of PMO

PMO is considered to be a multifactorial disease. At the same time, most of the studies indicate the fundamental role of hypoestrogenism in the process of bone loss in postmenopausal women. The effect of estrogens in this case is described either as direct, due to the influence on specific estrogen receptors by regulating the transcription of target genes, or as indirect, through a change in the production of stimulants and blockers of bone remodeling [15]. Moreover, in comparison with the reproductive period, when adequate estrogen secretion maintains mineral homeostasis and ensures the formation of a peak in bone mass and maintenance of BMD in the future, the onset of menopause is characterized by significant shifts in the hormonal regulation of bone metabolism [3, 15].

Of course, the mechanisms that underlie the loss of bone mass associated with estrogen deficiency are much more complex and are not limited to the model of direct regulatory effects of these hormones on bone tissue [15]. Recent studies of osteoimmunology have proven the role of immune dysregulation in the initiation of various inflammatory diseases of bone tissue, including osteoporosis. Cells of immune and bone systems have many common molecules, such as transcription factors, signaling molecules, cytokines or chemokines, and the osteoclast at the cellular level can be considered as a prototype of an osteoimmune cell [16]. Therefore, the so-called immunoporosis was clearly revealed from the standpoint of the effect of T helper 1 (Th1), T helper 2 (Th2), and T helper 17 (Th17) cells, as well as regulatory T cells and other cells of the immune system [17].

It was also found that postmenopausal women with osteoporosis have certain immune status disorders compared with healthy women of the same age, and their T cell activity parameters exceed normal values. Now this is associated with the absence of an estrogen blocking effect on the production of pro-osteoclastogenic cytokines (tumor necrosis factor alpha, interleukin-1 beta (IL-1β), interleukin-6 (IL-6) [18]. Thus, the presence of PMO in women is combined with an increase in the concentrations of IL-1β, IL-6, IL-8, IL-17A, and receptor activator of nuclear factor kappa-B ligand (RANKL) and a decrease in the levels of IL-4 and IL-10 [15]. Moreover, under normal conditions, suppression of pro-osteoclastogenic cytokine secretion by hormones is implemented both due to a direct effect on T cells and an indirect effect by inhibiting IL-7 and stimulating transforming growth factor-beta (TGF-β) [18]. Estrogens are able to directly induce apoptosis of bone-resorbing osteoclasts, while the pool size of preosteoclasts not involved in bone resorption is also reduced by estrogens [19].

In total, the processes of osteoclast differentiation in PMO are stimulated by two regulatory factors:

The cytokine ligand – receptor system RANKL / RANK / OPG. It is known that in a state characteristic of PMO, there is an increased production of RANKL, which is necessary for further connection with RANK and its activation. A subsequent increase in the expression of nuclear factor kappa-B (NF-κB) activates the nuclear factor of activated T cells 1 (NFATc1), which, in turn, is the protein initiator of bone resorption and contributes to progressive bone destruction [20, 21].

The macrophage colony-stimulating factor (M-CSF) produced by osteoblasts. It stimulates intracellular tyrosine kinase, resulting in the subsequent proliferation and differentiation of osteoclast progen-

itor cells – monocytes, macrophages, preosteoclasts [21].

Macrophages are of particular interest among progenitor cells, since it is a heterogeneous population of cells that exhibit unique plasticity under changing environmental conditions [20, 22, 23]. Over the past decades, a lot of research was dedicated to the functional features of various macrophage phenotypes, and nowadays there are reliable data proving the role of these cells in the pathogenesis of osteoporosis [4, 17].

Thus, it is known that for women who have reached the age of postmenopause and have a low level of estrogens, there is an imbalance between the proinflammatory M1 and anti-inflammatory M2 phenotype, leading to a change in the polarization of macrophages. The shift in the ratio of macrophage phenotypes and the resulting discrepancy between the number of osteoclasts and their precursors negatively affect the state of bone tissue and contribute to the development and progression of osteoporosis [4, 19, 23].

It is estrogens that coordinate the balance between macrophages and osteoclasts, determining the course of PMO [21], as evidenced by a number of studies. Thus, in a model of experimental osteoporosis after ovariectomy in mice, bone marrow macrophages were isolated from the femur, followed by induced polarization of M1 macrophages by lipopolysaccharide (LPS) / interferon gamma (IFNγ) and M2 macrophages – by IL-4 / IL-13, respectively. After stimulation of the M1 and M2 RANKL phenotypes, it was found that it was the M2 phenotype that mainly differentiated into a functional osteoclast, and not M1, which led to a change in the M1 / M2 ratio [19]. Conducting a similar study, but under conditions of a normalized hormonal background using 17β-estradiol (E2), it was showed that restoring the level of estrogens prevented osteoclastogenesis from M2 macrophages, and the ratio of phenotypes remained normal. The effect of the endocrine profile on the balance between macrophages and osteoclasts is shown in Figure 1.

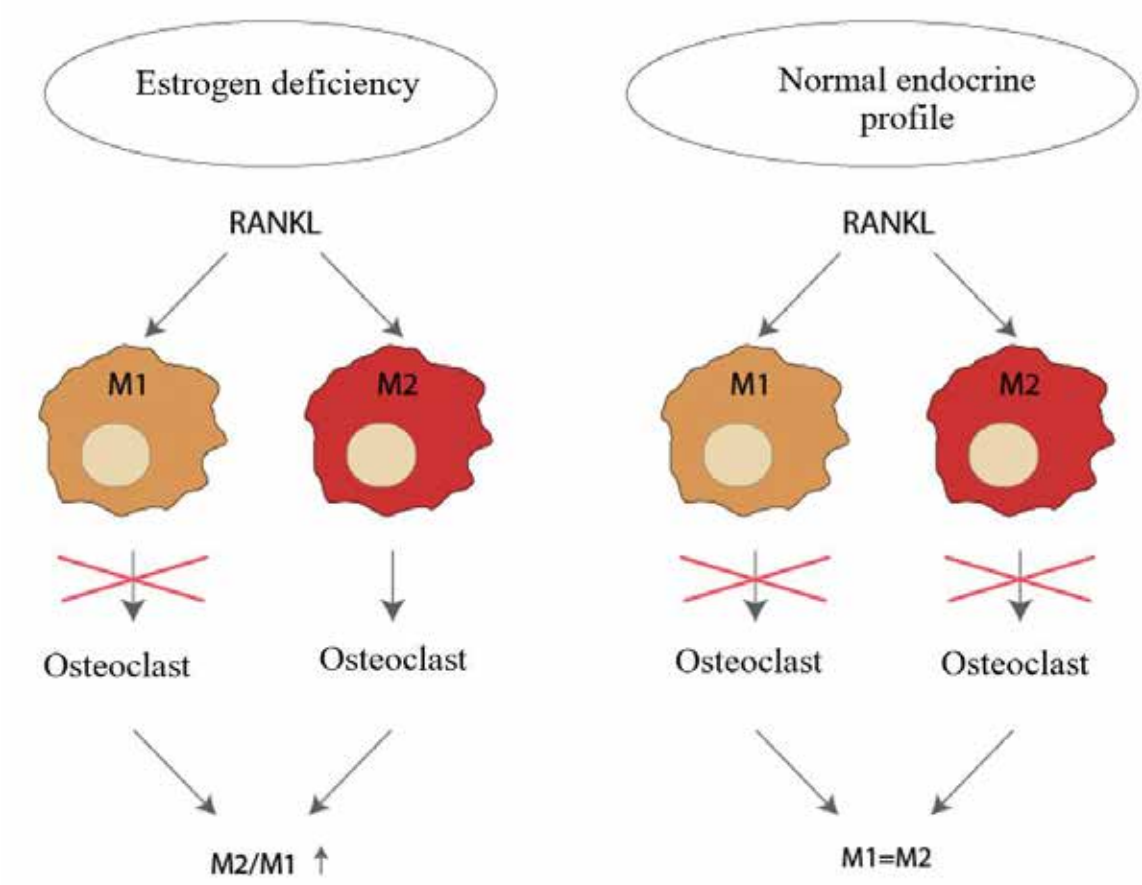

Fig. 1. Effect of endocrine profile on the balance between macrophages and osteoclasts: M1, M2 – macrophage phenotypes; M2 / M1 – a shift in the ratio of macrophages toward the M2 phenotype

These phenomena are explained by the fact that estrogen protects the M2 macrophage from RANKL stimulation due to selective action through the α-estrogen receptor (ERa) and subsequent blocking of the nuclear translocation of NF-kB p65 [19, 20]. A selective α-estrogen receptor agonist PPT (4, 4′, 4″ -(4-propyl-[1H]-pyrazole-1, 3, 5-triyl) trisphenol) can reproduce a similar therapeutic effect in treatment of osteoporosis in ovariectomized mice.

Therefore, against the background of estrogen deficiency, osteoclastogenesis of macrophages of the M2 phenotype leads to a shift in the M1 / M2 ratio and contributes to the progression of PMO.

MECHANISMS OF THE RELATIONSHIP BETWEEN PMO AND CARDIOVASCULAR DISEASES

The postmenopausal period is dangerous not only due to progressive loss of bone mass, but also due to an increased likelihood of CVD. Unfortunately, quite often, these processes mutually aggravate each other, worsening the quality of patients' lives and causing the development of serious complications [7, 10]. Currently, there are data from a number of authors confirming the relationship between vascular diseases and bone tissue, which can be traced both in the presence of similar pathogenesis links and in observations conducted during experimental and clinical studies [24, 25].

In particular, estrogen deficiency underlying PMO, is also a risk factor for CVDs in women after their reproductive function has declined. Moreover, the effect of sex hormones on CVD is diverse: they regulate the mechanisms of vasodilation, the relationship between hypoxia and angiogenesis, and the formation and development of left ventricular diastolic dysfunction. They are also crucial in the regulation of calcium homeostasis and participate in the coordination of the contraction and relaxation of cardiomyocytes [2, 13].

17β-estradiol (E2) mentioned earlier as a factor that prevents osteoclastogenesis from M2 macrophages and normalizes the ratio of phenotypes in osteoporosis is also involved in vasodilation processes. This occurs mainly due to the regulation of nitric oxide synthesis by binding to estrogen receptors that are present in endothelial cells [21, 26].

The cytokine system RANKL / RANK / OPG, which affects both the stages of bone remodeling and the development of arterial calcification, is one of the common factors involved in the regulation of bone tissue and vascular mineralization [27]. In this case, special attention should be paid to osteoprotegerin (OPG), an important secreted protein of the tumor necrosis factor family, which regulates bone density by inhibiting osteoclast differentiation and activation and affects the development of arterial calcification. By binding to its ligand (OPGL), it suppresses the interaction between RANK and OPGL on osteoclasts and their precursors, acting as a secreted inhibitor of the RANK signaling pathway [11]. Studies on mice involving targeted deletion of the osteoprotegerin gene showed a significant decrease in total bone density and high incidence of fractures, as well as a decrease in the incidence of calcification in the aorta and renal arteries. Statistical data confirm the relationship between a high degree of aortic calcification and a pronounced decrease in BMD. Besides, they confirm that the risk of carotid artery calcification for women with osteoporosis is approximately 4 times higher than that in women with a normal BMD index in the femoral neck [24, 27].

One of the significant pathogenetic factors affecting the development of CVD is disturbance of macrophage polarization. Currently, a lot of data have been obtained on the role of macrophage phenotypes in the development of atherosclerotic lesions [11, 13, 22]. As in the case of osteoclastogenesis regulation, the effect of M1 and M2 phenotypes is opposite, contributing to a shift in the overall ratio of macrophages and progression of the lesion or, conversely, restoration of the vascular tissue.

However, in this case, activation of each phenotype is closely related to the change in the metabolic processes occurring in atherosclerosis. Thus, proinflammatory M1 macrophages are characterized by an anabolic type of metabolism, so they mainly regulate glycolysis or the pentose phosphate pathway. The anti-inflammatory M2 phenotype, in turn, is associated with oxidative phosphorylation and fatty acid oxidation. Therefore, such factors as hyperlipidemia, hypoxia, and hyperglycemia can change polarization of macrophages toward the glycolytic M1 phenotype and shift the initial equilibrium, contributing to the progression of atherosclerosis [22].

The localization of phenotypes also confirms the dual role of macrophages. For example, staining of M1 phenotype markers is mainly limited to one of the most unstable areas inside the plaque, while M2 phenotype markers are more often present in the vascular adventitia or areas of stable plaques. M1 macrophages are also more common in the foci of infarction than

M2 macrophages [11]. These data confirm that the M1 phenotype, which, according to many authors, is proatherogenic, characterizes progressive lesions, while regressing plaques are enriched with the antiatherogenic M2 phenotype, which promotes restoration of vascular wall tissues (Fig. 2).

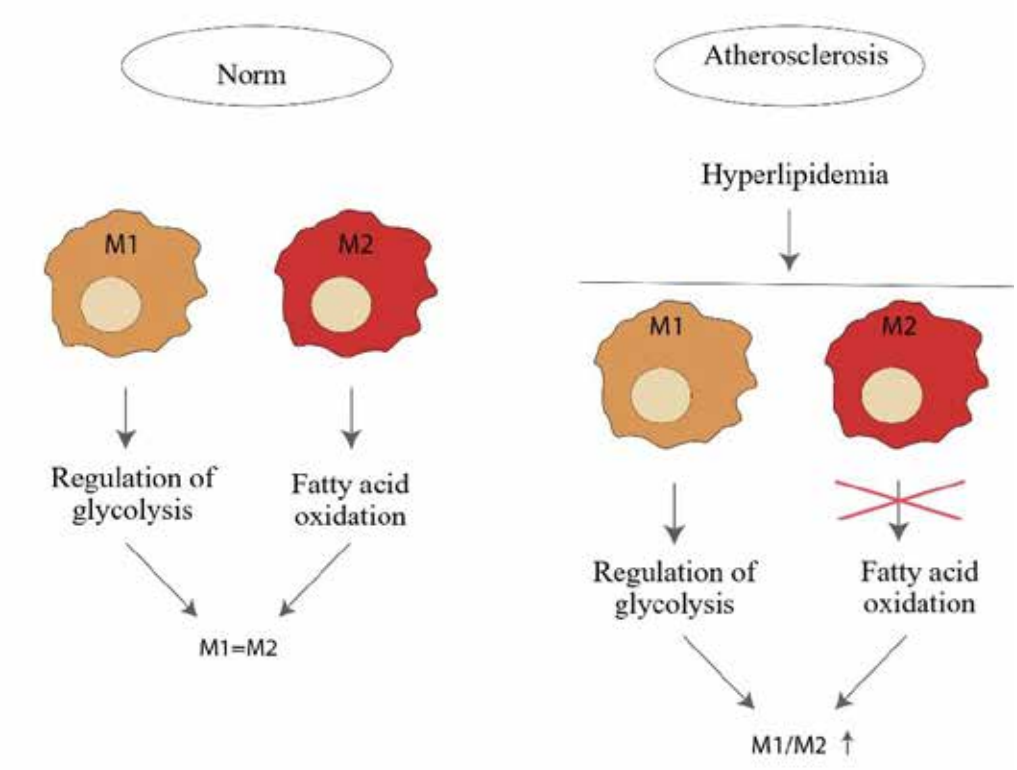

Fig. 2. The role of macrophage phenotypes in the development of atherosclerotic lesions. FA – fatty acids; M1 / M2 – shift in the ratio of macrophages toward the M1 phenotype

In addition to the common links in the pathogenesis of vascular lesion formation and bone tissue reduction, these pathological conditions are reciprocal in relation to corrective therapy. The results of some studies indicate that bisphosphonates, which are used in treatment of osteoporosis as bone resorption inhibitors, have a positive effect on the vascular wall and even reduce the degree of vascular calcification [11]. In order to prevent or reduce progression of subclinical atherosclerosis and vascular calcification, other groups of drugs used in the treatment of osteoporosis were also studied, which included antiresorptive agents (monoclonal antibodies targeting RANKL, selective estrogen receptor modulators) and anabolic bone therapy (teriparatide). However, currently, such studies are few, which is an incentive for the development and introduction into clinical practice of new pathogenetically substantiated methods for treatment of comorbid diseases under consideration [25].

CONCLUSION

The mechanisms of PMO formation following the impact of hormonal imbalance on bone tissue are extremely complex. Hypoestrogenism is the main trigger in the imbalance of bone remodeling which can directly or indirectly induce bone resorption processes. Metabolic disorders and dysregulated immune disorders perform a particular function in maintaining degenerative processes and disease progression. The change in the immune status is largely due to the lack of a blocking effect of estrogens on the regulatory factors of the RANKL / RANK / OPG system, which affects activation of NFATc1 and M-CSF and is responsible for proliferation and differentiation of osteoclast progenitors.

Impairment of macrophage polarization in conditions of estrogen deficiency is associated with the absence of a blocking effect of the hormone on estrogen receptors. In such an environment, activation of M2

phenotype osteoclastogenesis leads to increased bone resorption, which underlies osteoporotic changes. In addition, the analysis made it possible to establish the presence of a close correlation between PMO and cardiovascular pathology from the standpoint of the hormone factor, bone proteins, cytokines, and macrophage polarization. Thus, osteoprotegerin, acting as a secreted inhibitor of the RANKL signaling pathway, is responsible for changing the overall bone density, as well as for the development of large vessel calcification, and its effects on the relationship between a decrease in BMD and an increase in the risk of calcification have been confirmed by statistical data.

It is also shown that due to the disruption of polarization processes, macrophages undergo structural changes during the development of both PMO and cardiovascular pathologies. Only in atherosclerosis, macrophage phenotypes are described according to metabolic shifts, as pro-atherogenic M1 and anti-atherogenic M2, while in osteoporosis, they are classified as proinflammatory M1 and anti-inflammatory M2 phenotypes. At the same time, during the analysis of the collected data, it was found out that in case of PMO, the M1 / M2 ratio is characterized by a shift toward the M2 phenotype, and in case of atherosclerosis, the shift is mainly toward the M1 phenotype. However, the observed pattern in the relationship between cardiovascular pathology and osteoporosis has not been studied enough.

Therefore, it is necessary to further study these and other links in the pathogenesis of the considered diseases, both individually and in relation to each other. Clear understanding of the described and possible new mechanisms can not only make a great contribution to the development of strategies to reduce the growing prevalence of cardiovascular pathologies and complications of osteoporosis among postmenopausal women, but will also help to form a unified approach to the prevention of these diseases.

REFERENCES

1. Gabdrakhmanova I.V., Zubova O.Yu. Osteoporosis in postmenopausal women. *Bulletin of the RSMU.* 2014;2:31 (in Russ.).
2. Serezina E.K., Obrezan A.G. The effect of sex and age hormonal changes on the development of heart failure. *Russian Journal of Cardiology.* 2020;25(6):161–168 (in Russ.). DOI: 10.15829/1560-4071-2020-3710.
3. Postnikova S.L. Features of postmenopausal osteoporosis. *General Medicine.* 2004;4:41–45 (in Russ.).
4. Yang D.H., Yang M.Y. the role of macrophage in the pathogenesis of osteoporosis. *Int. J. Mol. Sci.* 2019;20(9):2093. DOI: 10.3390/ijms20092093.
5. Sinyachenko O.V., Klimovitsky F.V., Morozyuk D.M., Ermolaeva M.V., Liventsova E.V. Clinical and pathogenetic features of reduced bone mass in postmenopausal women. *Pain. Joints. Spine.* 2020;10(2):101–105 (in Russ.). DOI: 10.22141/2224-1507.10.2.2020.206946.
6. Mazurenko E.S., Malyutina S.K., Shcherbakova L.V., Ragino Yu.I., Rymar O.D. Risk factors of osteoporotic distal forearm fractures in postmenopausal women in Novosibirsk. *Practical Medicine.* 2018;9:174–179 (in Russ.). DOI: 10.32000/2072-1757-2018-9-174-179.
7. Skripnikova I.A., Kolchina M.A., Kosmatova O.V., Myagkova M.A., Drapkina O.M. Association of cardiovascular and fracture risks in women without clinical manifestations of atherosclerosis. *Cardiovascular Therapy and Prevention.* 2020;19(6):43–48 (in Russ.). DOI: 10.15829/1728-8800-2020-2724.
8. Isaikin A.I., Isaikina O.Yu., Shadyzheva T.I., Shor Yu.M., Kachanovsky M.S. Back pain and osteoporosis. *Neurology, neuropsychiatry, psychosomatics*. 2019;11(3):63–68. (in Russ.). DOI: 10.14412/2074-2711-2019-3-63-68.
9. Bairamov A.A., Maevsky E.I., Zelener A.O., Karonova T.L., Shabanov P.D., Glushchenko V.V. Bone remodeling processes at the stages of correction of experimentally induced osteoporosis. *Bulletin of NovSU.* 2020;1(117):23–29 (in Russ.). DOI: 10.34680/2076-8052.2020.1(117).23-29.
10. Kolchina M.A., Kosmatova O.V., Novikov V.E., Skripnikova I.A. Early markers of athrosclerotic cardiovascular diseases and osteoporotic fractures in a postmenopausal woman (clinical case). *The Clinician.*2019;3–4:53–58 (in Russ.). DOI: 10.17650/1818-8338-2019-13-3-4-53-58.
11. Xu H., Jiang J., Chen W., Li W., Chen Z. Vascular macrophages in atherosclerosis. *J. Immunol. Res.* 2019;2019:4354786. DOI: 10.1155/2019/4354786.
12. Hu X., Ma S., Yang C., Wang W., Chen L. Relationship between senile osteoporosis and cardiovascular and cerebrovascular diseases. *Exp. Ther. Med.* 2019;17(6):4417–4420. DOI: 10.3892/etm.2019.7518.
13. Jiao L., Machuki J.O., Wu Q., Shi M., Fu L., Adekunle A.O. et al. Estrogen and calcium handling proteins: new discoveries and mechanisms in cardiovascular diseases. *Am. J. Physiol. Heart Circ. Physiol.* 2020;318(4):H820–829. DOI: 10.1152/ajpheart.00734.2019.
14. Evans M.A., Sano S., Walsh K. Cardiovascular disease, aging, and clonal hematopoiesis. *Annu. Rev. Pathol.* 2020;15:419–438. DOI: 10.1146/annurev-pathmechdis-012419-032544.
15. Mailyan E.A., Reznichenko N.A., Ignatenko G.A. Cytokines serum levels in postmenopausal osteoporosis. *Crimean Journal of Experimental and Clinical Medicine.* 2018;8(1):36–42 (in Russ.).
16. Föger-Samwald U., Dovjak P., Azizi-Semrad U., Kerschan-Schindl K., Pietschmann P. Osteoporosis: pathophysiology and therapeutic options. *EXCLI J.* 2020;19:1017–1037. DOI: 10.17179/excli2020-2591.
17. Srivastava R.K., Dar H.Y., Mishra P.K. immunoporosis: immunology of osteoporosis-role of T cells. *Front Immunol.* 2018;9:657. DOI: 10.3389/fimmu.2018.00657.
18. Povoroznyuk V.V., Reznichenko N.A., Maylyan E.A. Immunological aspects of postmenopausal osteoporosis. *Bulletin of Siberian Medicine*. 2013;3(11):21–26 (in Russ.).

19. Dou C., Ding,N., Zhao C., Hou T., Kang F., Cao Z. et al. Estrogen deficiency – mediated M2 macrophage osteoclastogenesis contributes to M1/M2 ratio alteration in ovariectomized osteoporotic mice. *J. Bone Miner. Res.* 2018;33(5):899–908. DOI: 10.1002/jbmr.3364.
20. Li Z., Zhu X., Xu R., Wang Y., Hu R., Xu W. Deacylcynaropicrin Inhibits RANKL –induced osteoclastogenesis by inhibiting NF-κB and MAPK and promoting M2 polarization of macrophages. *Front Pharmacol.* 2019;10:599. DOI: 10.3389/fphar.2019.00599.
21. Nevzati E., Shafighi M., Bakhtian K.D. et al. Estrogen induces nitric oxide production via nitric oxide synthase activation in endothelial cells. Neurovascular events after subarachnoid hemorrhage. *Acta Neurochirurgica Supplement.* 2015;120:141–145. DOI: 101007/978-3-319-04981-6_24.
22. Dushkin M.I. The macrophage is multifaceted and ubiquitous. *Science First Hand.* 2012;5(47):26–33 (in Russ.).
23. Chen Y., Jiang W., Yong H., He M., Yang Y., Deng Z. et al. Macrophages in osteoarthritis: pathophysiology and therapeutics. *Am. J. Transl. Res.* 2020;12(1):261–268. PMID: 32051751; PMCID: PMC7013211.
24. Aldangarova G.A., Zhaymyrzaeva G.A., Musabekova Zh.B., Abzaliev K.B. Features of the cardiovascular system of a woman during hormonal adjustment. *Bulletin of surgery in Kazakhstan.* 2018;57(4):8–15 (in Russ.).
25. Skripnikova I.A., Kosmatova O.V., Kolchina M.A., Myagkova M.A., Alikhanova N.A. Atherosclerosis and osteoporosis. Common targets for cardiovascular and anti-osteoporotic drugs (Part II). The effect of anti-osteoporotic drugs on the vascular wall state. *Rational Pharmacotherapy in Cardiology.* 2019;15(3):359–367 (in Russ.). DOI: 10.20996/1819-6446-2019-15-3-359-367.
26. Fandino J., Marbacher S., Fathi A.-R. et al. Neurovascular events after subarachnoid hemorrhage. Cham: Springer International Publishing; 2015:141–145. ISBN 978-3-319-04981-6.
27. Bochkareva E.V., Butina E.K., Savin A.S., Drapkina O.M. Breast artery calcification and osteoporosis in postmenopausal woman: a case report and opinion on the problem.*Cardiovascular Therapy and Prevention.* 2020;19(4):94–98 (in Russ.). DOI: 10.15829/1728-8800-2020-2574.

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