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Osteoprotegerin gene polymorphisms in postmenopausal women with knee osteoarthritis

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Abstract

Aim – to investigate the associations of rs3134069, rs4355801 and rs3102735 polymorphisms in the *TNFRSF11B* gene with knee osteoarthritis in postmenopausal women.

Material and methods. 483 postmenopausal women were examined, including 157 patients with knee osteoarthritis. The remaining 326 women had no signs of joint disease and formed the control group. All examined women were tested using real-time polymerase chain reaction for single nucleotide polymorphisms rs3134069, rs4355801 and rs3102735 in the *TNFRSF11B* gene.

Results. It was found that genotypes distribution of polymorphisms rs3134069, rs4355801 and rs3102735 in the *TNFRSF11B* gene in the total group of examined women (n = 483) corresponded to the Hardy – Weinberg law (p > 0.05). The analysis of the polymorphic variants' frequency in the *TNFRSF11B* gene revealed an increased frequency of AC or CC genotypes of rs3134069 polymorphism in patients with knee osteoarthritis (OR = 1.91; 95% CI: 1.10–3.32; p = 0.030). Also, the allele C frequency of the above-mentioned polymorphism was increased among patients with osteoarthritis (OR = 1.78; 95% CI: 1.06–2.99; p = 0.040). No association with knee osteoarthritis was found for two other studied polymorphisms in the *TNFRSF11B* gene – rs4355801 and rs3102735 (p > 0.05).

Conclusion. The increased frequency of genotypes AC or CC registration, as well as allele C of rs3134069 polymorphism in the *TNFRSF11B* gene in postmenopausal women with knee osteoarthritis indicates the important role of *TNFRSF11B* gene mutations in the osteoarthritis development and progression. Further research in this area is of great interest both for a deeper understanding of the disease pathogenesis and for the development of personalized approach in the prevention and treatment of knee osteoarthritis in postmenopausal women.

Keywords: women, postmenopause, osteoarthritis, polymorphisms, osteoprotegerin gene.

Conflict of interest: nothing to disclose.

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Полиморфизмы гена остеопротегерина при остеоартрите коленных суставов у женщин в постменопаузе

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Аннотация

Цель – исследовать ассоциации полиморфизмов rs3134069, rs4355801 и rs3102735 гена *TNFRSF11B* с остеоартритом коленных суставов у женщин постменопаузального возраста.

Материал и методы. Обследовано 483 женщины постменопаузального возраста. Из них 157 пациентов имели остеоартрит коленных суставов. Остальные 326 женщин не имели признаков заболевания суставов и составили контрольную группу. Все обследованные женщины при помощи метода полимеразной цепной реакции в режиме реального времени были обследованы на однонуклеотидные полиморфизмы rs3134069, rs4355801 и rs3102735 гена *TNFRSF11B*.

Результаты. Установлено, что распределение генотипов полиморфизмов rs3134069, rs4355801 и rs3102735 гена *TNFRSF11B* в общей группе обследованных женщин (n=483) соответствовало закону Hardy – Weinberg (p>0,05). Анализ частоты полиморфных вариантов гена *TNFRSF11B* позволил выявить повышенную частоту генотипов AC или CC полиморфизма rs3134069 у больных с остеоартритом коленных суставов (OR=1,91; 95% CI: 1,10–3,32; p=0,030). Также среди больных ОА была увеличена частота регистрации аллеля С вышеуказанного полиморфизма (OR=1,78; 95% CI: 1,06–2,99; p=0,040). Для двух других исследованных полиморфизмов гена *TNFRSF11B* (rs4355801 и rs3102735) связи с остеоартритом коленных суставов обнаружено не было (p>0,05).

Заключение. Повышенная частота регистрации генотипов AC или CC, а также аллеля С полиморфизма rs3134069 гена *TNFRSF11B* при остеоартрите коленных суставов у женщин постменопаузального возраста свидетельствует о важной роли мутаций в гене *TNFRSF11B* в развитии и прогрессировании остеоартрита. Дальнейшие исследования в этом направлении представляют большой интерес как для более глубокого понимания патогенеза заболевания, так и для разработки критериев персонифицированного похода в профилактике и лечении остеоартрита коленных суставов у женщин постменопаузального возраста.

Ключевые слова: женщины, постменопауза, остеоартрит, полиморфизмы, ген остеопротегерина.

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Список сокращений
OA – остеоартрит; IL – интерлейкин; OPG – остеопротегерин; OR и 95% CI – отношения шансов и 95% доверительный интервал; RANK и RANKL – активатор рецептора ядерного фактора κB и его лиганд соответственно; *TNFRSF11B* – ген, кодирующий остеопротегерин.

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INTRODUCTION

Osteoarthritis (OA) is one of the more common diseases of the musculoskeletal system. The chronic pathological process in OA may involve various joints. Most often, the disease affects the knee joints. Gonarthritis is a progressive disease with degenerative changes of all tissues of the knee joint: meniscus, cartilage, subchondral bone tissue, ligaments and muscles associated with them, and subcutaneous fat.

The incidence of OA grows significantly with age. Conducted epidemiological studies indicate the highest prevalence of pathology in middle age and especially in advanced and old age. Thus, in 33.2% of cases OA is found in people of retirement age, and, according to some data, among people over 60 years of age it even reaches 50% or more [1–4]. It should be noted that 10% of people over 55 years of age has damage to the knee joints, which is accompanied by severe functional impairments in a quarter of cases.

The damage to the knee joints in OA comes with pain, swelling, reduced range of motion and increasing loss of the joint function. The majority of patients demonstrates sleep disorders, reduced ability of performing exercise, lifting heavy objects and walking. Gradually, the capability to perform and to lead an independent life are decreasing. OA inevitably leads to the disability of the patient. As a result, due to the patient's loss of ability to work, the costs of diagnosing and treating the pathology, paying for sick leave and disability pensions, knee joint disease places a huge burden not only on the family budget, but also on the budget of the entire healthcare system and society as a whole.

Recent achievements in the studies of pathogenesis of OA show new opportunities in the treatment of the disease and unlock promising mechanisms and targets for new therapeutic agents. It is to be noted, however, that now there are no methods of therapy to effectively stop the pathological process and further damage to the tissues of the joint or to eliminate any of the structural damage to the cartilage tissue that might have developed [5]. Total joint replacement in OA might involve adverse consequences, specifically, it may be accompanied with infectious complications and fibrosis [6]. Besides, despite the success in the development of artificial joints, the surgery is a high-risk and costly alternative to conservative therapy, and the service life of prosthetic devices is limited.

The very high incidence of OA and the lack of therapy to ensure the structural and functional restoration of the joints indicate the necessity of development of up-to-date methods of early diagnosis and prevention of the disease. One of the measures to prevent the development of OA should be the identification of high-risk groups for the development of joint pathology for the timely administration of appropriate preventive programs to patients. To do that, the medical practitioners should have distinct criteria for early identification of people at high risk of OA and justify the need to prescribe preventive and therapeutic measures for them.

The development of prognostic criteria affecting the risk of developing the disease should be based on a deep understanding of its etiopathogenesis. It must be considered that OA is a polygenic, multifactorial pathology. Osteoarthritis is the result of combined action of several factors on the human organism that might conventionally be divided into two groups, genetic and non-genetic. The non-genetic risk factors of OA include excessive weight and obesity, metabolic syndrome, physical inactivity, trauma, advanced and old age, alcohol consumption, smoking, history of joint diseases (Reiter disease, gouty arthritis, etc.) [6]. One of the main predisposing factors to the disease is female gender, and postmenopausal women are most susceptible to the disease.

Undoubtedly, the most important contributor to the OA etiopathogenesis is the genetic component. The analysis of results of molecular and genetic studies of OA allowed identification of several hundred genes, whose polymorphisms may affect the risk of development of joint disease [7]. It is to be noted that among these candidate genes a group of genes are identified as coding the immune factors. Particularly, such genes as IL-11, TLR-4, TGFB1, TNFSF11 are mentioned. They participate in the development of the immune response and inflammation. There are some studies focusing on research of the role of polymorphisms of the gene *TNFRSF11B* in the development of the joint damage. This gene codes the osteoprotegerin (OPG), a cytokine from the family of tumor necrosis factor. In particular, a study was carried out on the role of genetic mutations in the said gene on the development of knee OA among the population of Great Britain and China [8–11]. No similar studies have been conducted in Russia.

AIM

Study the associations of the polymorphisms of rs3134069, rs4355801 and rs3102735 in the *TNFRSF11B* gene with knee osteoarthritis in postmenopausal women.

MATERIAL AND METHODS

The study was performed within a complex joint research of the Federal State Funded Educational Institution of Higher Education Donetsk State Medical University of the Ministry of Health of the Russian Federation and the S.I. Georgievsky Medical Academy of the Federal State Autonomous Educational Institution of Higher Education "Crimean

Federal University named after V.E. Vernadsky." The study is approved by the Ethics Committee of the FSFEI HE DSMU of the Ministry of Health of the Russian federation (Protocol No. 27/5-1 dated 14.04.2021.) The analysis included results of diagnostic findings of 483 postmenopausal women. The median and interquartile range of age of the examined women were 61 [55; 67] years, duration of the menopause, 12 [6; 20] years. The height, weight and body mass index values were 162 [157; 166] cm, 72 [64; 82] kg, and 27.6 [24.2; 31.3], respectively.

The design of the work involved a case-control study. 157 patients with clinical and instrumental confirmed osteoarthritis of the knee joint were included in the main group, and the control group consisted of the remaining 326 women without signs of joint disease.

Inclusion criteria in the main group: female gender, postmenopause, osteoarthritis of the knee joints, written voluntary informed consent.

Inclusion criteria in the control group: female gender, postmenopause, absence of joint diseases, written voluntary informed consent.

Exclusion criteria: male gender, joint injuries, diseases of the endocrine and immune systems, rheumatic, mental, oncological and hematological pathologies, chronic inflammatory diseases.

The parameters of the women from the main and the control groups are given in **Table 1**. The results show a correlation between the representatives of the two groups in age (p=0.798) and duration of postmenopause (p=0.545).

To perform molecular genetic studies, peripheral blood of the patients was used that was sampled following an overnight fast into plastic vacuum blood tubes with EDTA as anticoagulant. Isolation of DNA from blood leukocytes was carried out using a set of reagents "PROBA-RAPID-GENETIKA" (Scientific Production Company "DNK-Technologia," Russia). The isolated DNA sample was used to identify three polymorphisms of the gene *TNFRSF11B* – rs3134069 (245 A>C), rs4355801 (A>G), and rs3102735 (163 (160) T>C).

To detect the above polymorphisms, the real time polymerase chain reaction method was used. Commercially available sets of reagents manufactured by Scientific Production Company "DNK-Technologia" LLC, (Russia). The method was implemented with the use of the following laboratory equipment: detecting amplifier DT-96 (Scientific Production Company "DNK-Technologia," Russia,) high-speed laboratory centrifuge Micro-120 (Hettich Zentrifugen, Germany), solid-state thermostats 24-15 and microcentrifuges/shakers ("Biokom," Russia), compartment BAVp-01-"Laminar-S"-1,2 ("Laminarnie Sistemy," Russia), medical laboratory dispensers of various volumes (Brand, Germany.)

Parameter	Control group (n=326)	Main group (n=157)	P
Age, years	61,0 [55,0; 67,0]	61,0 [55,0; 67,0]	0,798
Duration of postmenopause, age	12,5 [6,0; 20,0]	12,0 [6,0; 19,0]	0,545

Table 1. *Age and postmenopause duration in the examined postmenopausal women*

Таблица 1. *Возраст и длительность постменопаузы у обследованных женщин постменопаузального возраст*

The results were processed using the Medstat statistical software package. Age and duration of postmenopause were assessed using median and interquartile range indicators (Me [Q1; Q3]). The frequency of identification of polymorphous variants of the gene *TNFRSF11B* in the samples was represented both in absolute values and percentages. To determine whether the distribution of the studied genotypes corresponded to the Hardy–Weinberg law, as well as to analyze the frequency of genetic markers in groups, the Chi-square test was used. In assessing the associations of the genotypes and the alleles with the disease, the odds ratio (OR) was calculated as well as the 95% confidence interval (95% CI).

RESULTS

The studies revealed that the distribution of the genotypes of the polymorphisms rs3134069, rs4355801 and rs3102735 of the gene *TNFRSF11B* among the studied women in the postmenopausal age corresponded to the Hardy–Weinberg law without showing significant difference from the expected occurrence (p>0.05). The genotypes of the polymorphism rs3134069 AA, AC and CC were registered respectively in 424 (87.8%), 56 (11.6%) and 3 (0.6%) cases. The analysis of gene variants based on the rs4355801 polymorphism showed, that 99 women (20.5%) were homozygous for the A allele (AA), 141 women (29.2%) were homozygous for the G allele (GG), and 243 examined individuals (50.3%) were heterozygous (AG). The TT and CC genotypes of the rs3102735 polymorphism were found in 370 (76.6%) and 5 (1.0%) of women, respectively, and the TC genotype in 108 individuals (22.4%).

The occurrence of genotypes and alleles of the rs3134069 polymorphism of the *TNFRSF11B* gene among patients with osteoarthritis of the knee joint follows in **Table 2**. Due to the small number of women with the CC genotype (1 in the main group, 2 in the control group), they were combined with carriers of the AC genotype. The data obtained indicate an increased frequency of the AC or CC genotype in patients with joint pathology (OR=1.91; 95% CI: 1.10–3.32; p=0.030). There was also an increased incidence rate of the C allele of the said polymorphism (OR=1.78; 95% CI: 1.06–2.99; p=0.040) in the group of patients with osteoarthritis.

The results of testing for polymorphisms rs4355801 and rs3102735 of the TNFRSF11B gene showed the lack of their association with osteoarthritis of the knee joint in postmenopausal women (**Tables 3, 4**).

Genotypes and alleles	Control group (n = 326)		Main group (n = 157)		P
	N	%	N	%	
AA	294	90,2	130	82,8	0,030
AC+CC	32	9,8	27	17,2	
A	618	94,8	286	91,1	0,040
C	34	5,2	28	8,9	

Table 2. *Genotypes and alleles frequency of rs3134069 polymorphism in the TNFRSF11B gene in postmenopausal women with knee osteoarthritis*

Таблица 2. *Частота регистрации генотипов и аллелей полиморфизма rs3134069 гена TNFRSF11B среди женщин постменопаузального возраста с остеоартритом коленных суставов*

Genotypes and alleles	Control group (n = 326)		Main group (n = 157)		P
	N	%	N	%	
AA	67	20,5	32	20,4	0,541
GA	159	48,8	84	53,5	
GG	100	30,7	41	26,1	
A	293	44,9	148	47,1	0,568
G	359	55,1	166	52,9	

Table 3. *Genotypes and alleles frequency of rs4355801 polymorphism in the TNFRSF11B gene in postmenopausal women with knee osteoarthritis*

Таблица 3. *Частота регистрации генотипов и аллелей полиморфизма rs4355801 гена TNFRSF11B у женщин постменопаузального возраста с остеоартритом коленных суставов*

Genotypes and alleles	Control group (n = 326)		Main group (n = 157)		P
	N	%	N	%	
CC	4	1,2	1	0,6	0,569
TC	69	21,2	39	24,9	
TT	253	77,6	117	74,5	
C	77	11,8	41	13,1	0,654
T	575	88,2	273	86,9	

Table 4. *Genotypes and alleles frequency of rs3102735 polymorphism in the TNFRSF11B gene in postmenopausal women with knee osteoarthritis*

Таблица 4. *Частота регистрации генотипов и аллелей полиморфизма rs3102735 гена TNFRSF11B у женщин постменопаузального возраста с остеоартритом коленных суставов*

DISCUSSION

The pathophysiology of OA is associated with numerous factors, which include metabolic disorders, oxidative stress, apoptosis, cellular aging, and mitochondrial dysfunction [6]. Among the sophisticated complex of pathogenic mechanisms of the disease, one of the key contributors is the immune [6, 12]. Numerous studies indicate that the decisive trigger in the development of the disease is intra-articular inflammation. The persistence of the inflammatory component causes the process to become chronic, and its severity reflects the degree of progression of OA. Undoubtedly, the cause of inflammation is the overexpression of proinflammatory cytokines in plasma and synovial fluid, which leads to the death of chondrocytes, catabolism of cartilage tissue, synovitis, and damage to the subchondral bone.

Important cellular elements involved in the inflammatory response are chondrocytes, synoviocytes, macrophages; among cytokines, interleukins (IL)-6, IL-1β, IL-8, IL-17 are considered key mediators in joint tissue damage, as well as tumor necrosis factor alpha (TNF-α), which are respectively referred to as prodegenerative factors [13]. An increase in the secretion of the above prodegenerative proinflammatory cytokines is associated with an increase in the expression of catabolic markers (matrix metalloproteinases -3, -13, aggrecanases ADAMTS-4 and ADAMTS-5, and others), involved in the breakdown of collagens and proteoglycans. These cytokines are counteracted by pro-anabolic factors, which include insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF-β), IL-4, IL-10, and others. It should be noted that an imbalance in cytokine regulation towards the predominance of the function of prodegenerative cytokines underlies the degradation of the extracellular matrix of cartilage and the development of OA.

Cytokine dysfunction developing in OA leads to damage to joint tissues through various mechanisms. Degradation of cartilage tissue is mediated by signaling pathways such as MAPKs, Wnt/β-catenin, Notch. One of the major pathways is the NF-κB (nuclear factor-κB), and the most important mediators are representatives of the RANKL/RANK/OPG cytokine system (RANK and RANKL are activators of the receptor of the nuclear factor κB and its ligands, respectively). The system is the key in the activation of the NF-κB-signaling pathway, in the regulation of osteoclastogenesis and remodeling of the bone tissue in the normal and in the pathologic condition. The disorders of this system, among other things, are leading in the pathogenesis of osteoporosis [14, 15]. The receptor activator of the nuclear factor κB ligand (RANKL) ensures maturation, differentiation and activation of osteoclasts through its specific receptor RANK. Osteoprotegerin, the main producing cells of which are osteoblasts, as an important component of the RANKL/RANK/OPG cytokine system, has the opposite effect. OPG inhibits the activity of osteoclasts and thereby provides a protective role against bone resorption, being a soluble “trap receptor” for RANKL.

In OA, there is a close correlation between dysfunction of the OPG/RANK/RANKL regulatory system and histological changes in the subchondral bone with the appearance of a proinflammatory osteoblast phenotype [16]. It was established, however, that OPG and RANKL affect more than just the subchondral bone. Both cytokines are also expressed in the cartilage damaged in the course of OA [17]. The increased production of RANKL results in the degradation of the cartilage tissue, because the increased RANKL/OPG ratio is related to the high synthesis of matrix metalloproteinases -3, -9, -13 and increase of catabolic processes, whereas the induction with OPG bay be a protective and compensatory phenomenon [16]. Administration of the drug osteoprotegerin leads to a decrease in the intensity of pain, inhibits the formation of osteophytes and improves the structural characteristics of the affected joint in OA [18]. Experimental models in mice also show the beneficial effect of systemic administration of OPG on the state of bone and cartilage tissue in OA [19].

Thus, based on the evidence obtained to date, OPG is believed to play an important role in the pathogenesis of knee OA. It has been shown that OPG together with RANKL demonstrates an association with the severity of OA, especially in the early stages of the disease. It is assumed, therefore, that an increase in OPG concentration can be considered as an early marker of the disease, and the level of cytokine expression as a sign of the degree of its progression [20, 21]. Considering the foregoing, it is possible to suggest that the mutations of the gene *TNFRSF11B* coding the OPG molecules, may influence the etiopathogenesis of OA. This can be explained from the pathogenic perspective, since single-nucleotide genetic polymorphisms can cause quantitative or structural-functional changes in the encoded protein, which, in turn, can affect the pathogenesis of OA, either promoting or preventing the development of the disease.

In our work, we found an association with knee OA in postmenopausal women for one of the three gene

polymorphisms studied (rs3134069) of the *TNFRSF11B*. It should be noted that the currently available works devoted to the study of the role of genetic polymorphisms of the TNFRSF11B gene in the development of knee OA are few and do not provide a clear understanding of the significance of polymorphic variants of the above gene in the etiopathogenesis of the disease. In a study conducted in China that included 132 men and 261 women with knee OA, associations of single nucleotide polymorphisms of the *TNFRSF11B* gene with the disease were also established [9]. The rs1485286, rs1905786 and rs1032128 polymorphisms were associated with joint pathology. It is noteworthy that the sampling used in the study, as differentiated from our research, included not only women, but men as well; besides, the polymorphism rs3134069 used in our work was not tested by the Chinese authors. The latter polymorphism was not studied by the English researchers [8], who found an association of the alleles in the VNTR (rs71569778) area of the gene *TNFRSF11B* only in women with OA of the knee joint, but not in men. In another study, whose authors included in their research results of inspection of 749 women aged 43–67 with OA of the knee joint, the association of the polymorphism rs1564858 of the gene *TNFRSF11B* with the progression of the disease and the formation of osteophytes was shown [10]. The same team of authors identified a connection of haplotypes of the two polymorphisms s1564858 and rs2073618 of the gene *TNFRSF11B* with the risk of development of OA of the knee joints in a mixed group of patients that included 298 men and 305 women aged [11].

Thus, in our study, as well as in other studies, connections were established between polymorphic variants of the *TNFRSF11B* gene and OA of the knee joints, including in postmenopausal women. Despite the fact that different groups of authors studied various polymorphisms of the above gene, the results obtained, at a minimum, may indicate the important role of mutations in the *TNFRSF11B* gene in the development and progression of osteoarthritis. Further studies aimed at studying the role of osteoprotegerin in OA, including at the genetic level, are of great interest both for a deeper understanding of the pathogenesis of the disease and for the development of criteria for a personalized approach in the prevention and treatment of a highly common disease of the musculoskeletal system.

CONCLUSION

A molecular genetic examination of 157 postmenopausal women with osteoarthritis of the knee joints and 326 women without signs of joint damage showed an association of the rs3134069 polymorphism of the *TNFRSF11B* gene with the disease. In patients with OA, an increased incidence of he genotype AC or CC ($p=0.030$) as well as allele C ($p=0.040$) of the said polymorphism was seen. For the two other studied polymorphisms of the gene *TNFRSF11B* (rs4355801 and rs3102735), no connection with the OA of the knee joints was found ($p>0.05$).

The results obtained indicate the need for a further study of the role of osteoprotegerin, a cytokine of the tumor necrosis factor superfamily, in the etiopathogenesis of knee OA at both the molecular and genetic levels.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Compliance with ethical standards. The study was approved by the Ethics Committee of THE Donetsk State Medical University named after M. Gorky (protocol No. 27/5-1 dated April 14, 2021).	***Соблюдение этических норм.*** Выполнение исследования одобрено этическим комитетом ФГБОУ ВО «Донецкий государственный медицинский университет имени М. Горького» (протокол № 27/5-1 от 14.04.2021 г.).
Study funding. This research received no external funding.	***Источник финансирования.*** Исследование проводилось без спонсорской поддержки.
Conflict of Interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. G.A. Ignatenko – was responsible for research planning, development of the study concept and design, literature review, approval of the manuscript for publication. N.A. Reznichenko – participated in the development of the study design, literature review, approval of the manuscript for publication. P.N. Fedulichev – provided literature review, data collection, statistical processing, analysis and interpretation of the obtained data, wrote the first draft of the manuscript. E.A. Mailyan – verified the critical intellectual content and conclusions, provided statistical data processing, detailed text editing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Г.А. Игнатенко – планирование исследования, разработка концепции и дизайна исследования, обзор литературы, утверждение рукописи к публикации. Н.А. Резниченко – участие в разработке дизайна исследования, обзор литературы, утверждение рукописи к публикации. П.Н. Федуличев – обзор литературы, сбор данных, статистическая обработка, анализ и интерпретация полученных данных, подготовка текста, редактирование. Э.А. Майлян – проверка критически важного интеллектуального содержания, статистическая обработка, подготовка текста, формулирование выводов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

REFERENCES / ЛИТЕРАТУРА

1. Aleshkevich AI, Martusevich NA, Bondar TV. Risk factors and features of clinical manifestations of early radiological stages of osteoarthritis of the knee joint. *Medical Journal*. 2022;2:41-44. (In Russ.). [Алешкевич А.И., Мартусевич Н.А., Бондарь Т.В. Факторы риска и особенности клинических проявлений ранних рентгенологических стадий остеоартроза коленного сустава. *Медицинский журнал*. 2022;2:41-44]. https://doi.org/10.51922/1818-426X.2022.2.41

2. Zborovskaya IA, Mozgovaya EE, Bedina SA, et al. Osteoarthritis – a modern view of treatment. *Lekarstvennyj vestnik*. 2019;13(4):7-15. (In Russ.). [Зборовская И.А., Мозговая Е.Э., Бедина С.А., и др. Остеоартроз – современный взгляд на лечение. *Лекарственный вестник*. 2019;13(4):7-15].

3. Kabalyk MA. Prevalence of osteoarthritis in Russia: regional aspects of trends in statistical parameters over 2011-2016. *Rheumatology Science and Practice*. 2018;56(4):416-422. (In Russ.). [Кабалык М.А. Распространенность остеоартрита в России: региональные аспекты динамики статистических показателей за 2011–2016 гг. *Научно-практическая ревматология*. 2018;56(4):416-422]. https://doi.org/10.14412/1995-4484-2018-416-422

4. Apostu D, Lucaciu O, Mester A, et al. Systemic drugs with impact on osteoarthritis. *Drug Metab Rev*. 2019;51(4):498-523. https://doi.org/10.1080/03602532.2019.1687511

5. Grässel S, Zaucke F, Madry H. Osteoarthritis: Novel Molecular Mechanisms Increase Our Understanding of the Disease Pathology. *J Clin Med*. 2021;10(9):1938. https://doi.org/10.3390/jcm10091938

6. Jiang W, Chen H, Lin Y, et al. Mechanical stress abnormalities promote chondrocyte senescence – The pathogenesis of knee osteoarthritis. *Biomed Pharmacother*. 2023;167:115552. https://doi.org/10.1016/j.biopha.2023.115552

7. Boer CG, Hatzikotoulas K, Southam L, et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell*. 2021;184(18):4784-4818.e17. https://doi.org/10.1016/j.cell.2021.07.038

8. Hulin-Curtis SL, Bidwell JL, Perry MJ. Tumour necrosis factor receptor superfamily member 11B polymorphisms and association with knee osteoarthritis in women. *Int J Immunogenet*. 2012;39(3):207-9. https://doi.org/10.1111/j.1744-313X.2012.01083.x

9. Qi Y, An F, Wang J, et al. Association of OPG gene polymorphisms with the risk of knee osteoarthritis among Chinese people. *Mol Genet Genomic Med*. 2019;7(6):e662. https://doi.org/10.1002/mgg3.662

10. Valdes AM, Hart DJ, Jones KA, et al. Association study of candidate genes for the prevalence and progression of knee osteoarthritis. *Arthritis & Rheumatism*. 2004;50(8):2497-2507. https://doi.org/10.1002/art.20443

11.Valdes AM, Van OM, Hart DJ, et al. Reproducible genetic associations between candidate genes and clinical knee osteoarthritis in men and women. *Arthritis & Rheumatism*. 2006;54(2):533-539. https://doi.org/10.1002/art.21621

12. Riggs KC, Sankar U. Inflammatory mechanisms in post-traumatic osteoarthritis: a role for CaMKK2. *Immunometabolism (Cobham)*. 2023;5(4):e00031. https://doi.org/10.1097/IN9.0000000000000031

13. Geng R, Li J, Yu C, et al. Knee osteoarthritis: Current status and research progress in treatment (Review). *Exp Ther Med*. 2023;26(4):481. https://doi.org/10.3892/etm.2023.12180

14. Ignatenko GA, Mailyan EA, Nemsadze IG, et al. The role of cytokines in bone tissue remodeling in norm and pathology. *Tavricheskiy mediko-biologicheskiy vestnik*. 2020;1:133-139. (In Russ.). [Игнатенко Г.А., Майлян Э.А., Немсадзе И.Г., и др. Роль цитокинов в ремоделировании костной ткани в норме и патологии. *Таврический медико-биологический вестник*. 2020;1:133-139]. https://doi.org/10.37279/2070-8092-2020-23-1-133-139

15. Ignatenko GA, Nemsadze IG, Mirovich ED, et al. The role of cytokines in bone remodeling and pathogenesis of postmenopausal osteoporosis. *Medical Herald of the South of Russia*. 2020;11(2):6-18. (In Russ.). [Игнатенко Г.А., Немсадзе И.Г., Мирович Е.Д., и др. Роль цитокинов в ремоделировании костной ткани и патогенезе постменопаузального остеопороза. *Медицинский вестник Юга России*. 2020;11(2):6-18]. https://doi.org/10.21886/2219-8075-2020-11-2

16. Kovács B, Vajda E, Nagy EE. Regulatory Effects and Interactions of the Wnt and OPG-RANKL-RANK Signaling at the Bone-Cartilage Interface in Osteoarthritis. *Int J Mol Sci*. 2019;20(18):4653. https://doi.org/10.3390/ijms20184653

17. Kwan Tat S, Amiable N, Pelletier JP, et al. Modulation of OPG, RANK and RANKL by human chondrocytes and their implication during osteoarthritis. *Rheumatology (Oxford)*. 2009;48(12):1482-90. https://doi.org/10.1093/rheumatology/kep300

18. Sagar DR, Ashraf S, Xu L, et al. Osteoprotegerin reduces the development of pain behaviour and joint pathology in a model of osteoarthritis. *Ann Rheum Dis*. 2014;73(8):1558-65. https://doi.org/10.1136/annrheumdis-2013-203260

19. Kadri A, Ea HK, Bazille C, et al. Osteoprotegerin inhibits cartilage degradation through an effect on trabecular bone in murine experimental osteoarthritis. *Arthritis Rheum*. 2008;58(8):2379-86. https://doi.org/10.1002/art.23638

20. Naik S, Sahu S, Bandyopadhyay D, Tripathy S. Serum levels of osteoprotegerin, RANK-L & vitamin D in different stages of osteoarthritis of the knee. *Indian J Med Res*. 2021;154(3):491-496. https://doi.org/10.4103/ijmr.IJMR_873_19

21. Rodríguez Ruiz A, Tuerlings M, Das A, et al. The role of TNFRSF11B in development of osteoarthritic cartilage. *Rheumatology (Oxford)*. 2022;61(2):856-864. https://doi.org/10.1093/rheumatology/keab440