АНТИТЕЛА К ЦИКЛИЧЕСКОМУ ЦИТРУЛЛИНИРОВАННОМУ ПЕПТИДУ И АНГИОПОЭТИНОПОДОБНЫЙ БЕЛОК 4-ГО ТИПА КАК МАРКЕРЫ ИММУННОГО ВОСПАЛЕНИЯ И ОСТЕОПОРОТИЧЕСКИХ ПРОЦЕССОВ У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

Османова Г.Я.[1, 2], Александров В.А.[1, 2], Александров А.В.[1, 2], Шилова Л.Н.[1], Черкесова Е.Г.[1], Александрова Н.В.[2], Зборовская И.А.[2]

[1] ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ, г. Волгоград, Россия
[2] ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия

Резюме. Низкоэнергетические переломы при ревматоидном артрите (РА) чаще встречаются у пациентов с высокой активностью и большой длительностью заболевания, а также с высокими титрами антицитруллинированных антител (АЦЦП). При воспалительных артритах также отмечено повышение экспрессии ангиопоэтиноподобного белка 4-го типа (ANGPTL4) в костной ткани. Целью исследования был анализ влияния АЦЦП и ANGPTL4 на системную минеральную плотность кости у пациентов с установленным РА. Антитела к АЦЦП и содержание ANGPTL4 были протестированы в сыворотке крови 96 больных РА (женщин 91,7%) с помощью иммуноферментного метода. Минеральную плотность поясничных позвонков ($BMD_{L1–L4}$), шейки бедра и бедренной кости в целом (BMD_{total}) измеряли методом двухэнергетической рентгеновской абсорбциометрии (DXA). В исследуемой группе АЦЦП и ANGPTL4 были положительными у 61,5% и 41,7% пациентов соответственно. АЦЦП отрицательно коррелировал с BMD_{total}, а ANGPTL4 – с BMD_{L1-L4} ($p < 0,05$). Разделение пациентов на группы с низкой ($n = 34$) и высокой ($n = 62$) активностью по DAS28 продемонстрировало значимое повышение АЦЦП с ростом активности РА ($p = 0,042$). Показатели АЦЦП и ANGPTL4 также были значительно выше в группе больных РА с остеопорозом (ОП) ($n = 45$) по сравнению с таковыми в группе РА без ОП ($n = 51$) ($p = 0,002$ и $p = 0,028$ соответственно). В общей группе больных РА возраст, ин-

Адрес для переписки:
Александров Владислав Андреевич
ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского»
400138, Россия, г. Волгоград, ул. им. Землячки, 76.
Тел.: 8 (8442) 78-90-98, (905) 061-12-23.
E-mail: imlab@mail.ru

Address for correspondence:
Vladislav A. Aleksandrov
A. Zborovsky Research Institute of Clinical and Experimental Rheumatology
76 Zemlyachka St
Volgograd
400138 Russian Federation
Phone: +7 (8442) 78-90-98, (905) 061-12-23.
E-mail: imlab@mail.ru

Образец цитирования:
Г.Я. Османова, В.А. Александров, А.В. Александров, Л.Н. Шилова, Е.Г. Черкесова, Н.В. Александрова, И.А. Зборовская «Антитела к циклическому цитруллинированному пептиду и ангиопоэтиноподобный белок 4-го типа как маркеры иммунного воспаления и остеопоротических процессов у больных ревматоидным артритом» // Медицинская иммунология, 2024. Т. 26, № 2. С. 393-400. doi: 10.15789/1563-0625-ATC-2862

For citation:
G.Ya. Osmanova, V.A. Aleksandrov, A.V. Aleksandrov, L.N. Shilova, E.G. Cherkesova, N.V. Aleksandrova, I.A. Zborovskaya "Antibodies to cyclic citrullinated peptide and angiopoietin-like protein type 4 as markers of immune inflammation and osteoporotic processes in rheumatoid arthritis patients", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2024, Vol. 26, no. 2, pp. 393-400. doi: 10.15789/1563-0625-ATC-2862

DOI: 10.15789/1563-0625-ATC-2862

декс массы тела (ИМТ), длительность и активность заболевания не оказывали значимого влияние на АСРА. Но в группе больных РА с ОП зависимость между АСРА и DAS28 стала достоверной (β = 0,31, p = 0,039). Для ANGPTL4 в общей группе больных РА из всех представленных переменных значимой была только длительность заболевания (β = 0,31, p = 0,039). В регрессионной модели показатель BMD_{total} в равной степени зависел от возраста пациентов (β = -0,28), ИМТ (β = 0,25) и уровня АСРА (β = -0,26). Поиск связи BMD_{L1-L4} с различными характеристиками РА продемонстрировал сильное влияние только ANGPTL4 (β = -0,74; R^2 = 0,57). Обнаруженная зависимость ANGPTL4 и снижения BMD именно в губчатом слое кости позволяет выделить группу пациентов РА с высоким содержанием ANGPTL4 в качестве группы риска именно по переломам позвоночника, и рассмотреть ANGPTL4 в качестве потенциальной мишени для лечения остеопоротических нарушений.

Ключевые слова: ревматоидный артрит, ангиопоэтин-подобный белок 4-го типа, антитела против циклического цитруллинового пептида, минеральная плотность кости, остеопороз, низкотравматичные переломы

ANTIBODIES TO CYCLIC CITRULLINATED PEPTIDE AND ANGIOPOIETIN-LIKE PROTEIN TYPE 4 AS MARKERS OF IMMUNE INFLAMMATION AND OSTEOPOROTIC PROCESSES IN RHEUMATOID ARTHRITIS PATIENTS

Osmanova G.Ya.[a, b], Aleksandrov V.A.[a, b], Aleksandrov A.V.[a, b], Shilova L.N.[a], Cherkesova E.G.[a], Aleksandrova N.V.[b], Zborovskaya I.A.[b]

[a] *Volgograd State Medical University, Volgograd, Russian Federation*
[b] *A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Abstract. Low-energy fractures in rheumatoid arthritis (RA) are more common in patients with high activity and long duration of disease, and with high titers of anti-citrullinated antibodies (ACPA). Increased expression of angiopoietin-like protein type 4 (ANGPTL4) in bone tissue has also been noted in inflammatory arthritis. The purpose of the present study was to analyze the effect of ACPA and ANGPTL4 on systemic bone mineral density in RA patients. Antibodies to ACPA and ANGPTL4 content were detected in blood serum of 96 RA patients (women, 91.7%) by enzyme immunoassay. Mineral density of the lumbar vertebrae (BMD_{L1-L4}), hip neck, and entire femur (BMD_{total}) was measured by dual-energy X-ray absorptiometry (DXA). In study group, the ACPA and ANGPTL4 tests were positive in 61.5% and 41.7% of patients, respectively. Negative correlations were shown between ACPA and BMD_{total}, and of ANGPTL4 with BMD_{L1-L4} ($p < 0.05$). Separation of the patients into groups with low (n = 34) and high (n = 62) DAS28 activity demonstrated a significant increase in ACPA with increasing RA activity (p = 0.042). ACPA and ANGPTL4 scores were also significantly higher in the group of 45 RA patients with osteoporosis (OP) compared to the RA group without OP (n = 51) showing significant difference at p = 0.002 and p = 0.028, respectively. Patients' age, body mass index (BMI), duration and activity of the disease had no significant effect on ACPA in the general group of RA patients. However, the correlation between ACPA and DAS28 proved to be significant in the group of RA patients with OP (β = 0.31, p = 0.039). Among all presented variables, the disease duration was the only significant factor for ANGPTL4 in the total group of RA patients (β = 0.31, p = 0.039). In the regression model, BMD_{total} showed similar correlations with patients' age (β = -0.28), BMI (β = 0.25), and ACPA level (β = -0.26). A search for association between BMD_{L1-L4} and various RA characteristics demonstrated a strong correlation with ANGPTL4 only (β = -0.74; R^2 = 0.57). The revealed correlation between ANGPTL4 and decreased BMD specifically in the spongy layer of bone allows us to identify the RA patients with high ANGPTL4 levels as a risk group specifically for spinal fractures thus considering ANGPTL4 as a potential target for treatment of osteoporotic disorders.

Keywords: rheumatoid arthritis, angiopoietin-like protein type 4, anti-citrullinated protein antibodies, bone mineral density, osteoporosis, fragility fractures

Introduction

Rheumatoid arthritis (RA) is the most common joint disease of inflammatory genesis and it is characterized by a symmetrical pattern of arthritis and the appearance of systemic symptoms. Osteoporosis (OP) is a frequent concomitant pathological condition in RA characterized by low bone mass and disruption of bone microarchitectonics [7]. It leads to an increased risk of spontaneous fractures resulting from minimal or even no trauma.

Bone remodeling disorders in RA lead to an imbalance between bone formation and bone resorption, partially due to the effects of chronic inflammation. With the years, osteopenia can progress to OP with increased bone fragility, increased risk of fracture, decreased quality of life, and a poor prognosis, especially in patients on long-term glucocorticoids. It was noted that low-traumatic fractures in RA are more common in patients with high pathological process activity and long duration of the disease, as well as with high titers of anti-citrullinated protein antibodies (ACPA).

Numerous cells, cytokines, molecules and signaling pathways (RANK/RANKL/OPG – receptor activator of nuclear factor (NF)-kB/and its ligand/osteoprotegerin; Wnt/DKK1/Scl – Wnt, drosophila segment polarity gene wingless and integrated or int-1 of the vertebrate homolog/Dickkopf-1/Sclerostin) are involved in the disbalanced bone remodeling process in RA and directly depend on the interaction between inflammatory and immune systems. Inflammatory cytokines (such as TNFα, IL-6, IL-1) stimulate osteoclastogenesis while disrupting osteoblastogenesis [5]. Autoantibodies are also involved in the pathogenesis of bone resorption in RA. ACPA can have a direct and independent effect on osteoclasts, becoming a significant factor in the loss of bone mass. Vimentin protein is an important target in the pathogenesis of RA, and antibodies to citrullinated vimentin are probably capable of playing an initial role in the progression of systemic osteoporosis [9].

ACPA, rheumatoid factor (RF), and C-reactive protein (CRP) ≥ 0.3 mg/dL predict progression of bone erosion and cartilage destruction in RA [1]. A recent study showed that seropositivity for RF and/or ACPA influences systemic bone loss in patients with RA, with different effects of ACPA and/or RF on osteoclastogenesis in cortical and cancellous bone regions [14]. However, longitudinal assessments of changes in bone mineral density (BMD) in RA patients are inconsistent and involve multiple factors (inflammation, disease activity, use of glucocorticoids, etc.).

The existing methods of determining markers of bone synthesis and resorption are not sufficiently informative to determine the correlation between immune inflammation and osteoporotic processes in bone in RA. A number of cytokines (IL-6, IL-8, IL-11, IL-15, RANKL) and adipokines (chimerin, nesfatin, angiopoietin-like proteins) have been proposed as potential markers of bone and articular cartilage destruction. Angiopoietin-like protein 4 (ANGPTL4) belongs to the family of circulating angiopoietin-like proteins that are active in various body cells and are thought to be involved in repairing and remodeling damaged tissue. The C-terminal fibrinogen-like domain of ANGPTL4 is able to interact with extracellular matrix receptors through the N-linked glycan chain, selectively preventing the activation of the cytokine cascade in endothelial cells and inhibiting the process of neovascularization. ANGPTL4 supports cartilage matrix degradation through increased secretion of inflammatory factors and matrix metalloproteinase [8]. Increased ANGPTL4 expression in bone tissue (in both osteoclasts and osteoblasts) has been noted in inflammatory arthritis, especially in hypoxia [10]. Our earlier preliminary study of the role of ANGPTL4 in increasing bone resorption and the development of osteopenia in patients with RA showed a negative correlation between ANGPTL4 and bone mineral density in the spine [3].

The purpose of this study was to analyze the effect of ACPA and ANGPTL4 on systemic bone mineral density in patients with established RA.

Materials and methods

All patients included in the study met the criteria of the 2010 ACR/EULAR diagnostic classification of RA. Exclusion criteria were: the presence of other autoimmune diseases, hyperthyroidism, diabetes mellitus and malignant neoplasm of any localization; severe liver and kidney dysfunction; long-term use of drugs that affect bone metabolism; pregnant or lactating women; the presence of signs of acute bacterial and viral infection at the time of the study.

A total of 96 patients with RA (91.7% women and 8.3% men) aged 29 to 75 years old were examined. Clinical and laboratory characteristics of RA patients are presented in Table 1.

Physical examination of patients included anthropometry with determination of body mass index (BMI), collection of medical history, and assessment of disease activity according to DAS index28. Blood samples were collected in the morning after an overnight fast (at least 12 hours) in order to minimize daily

TABLE 1. CLINICAL AND LABORATORY CHARACTERISTICS OF RA PATIENTS

Studied indicator	Value	%
Age, years	55.4±10.7	
Patients under the age of 50		33.3
Duration of RA, years	9.0 (3.0-15.5)	
Patients with RA duration < 5 years		30.2
RA activity by DAS28-ESR, points	3.48±1.12	
Patients with moderate RA activity (3.2 < DAS28 ≤ 5.1)		57.3
Seropositivity for RF and/or ACPA		76.0
Presence of erosions		77.1
Body mass index, points	28.50±6.07	
Smoked at the time of the study		7.29
Treatment with biological anti-rheumatic drugs		4.17
Treatment with glucocorticoids > 3 months		61.5

Note. Values are presented as mean ± standard deviation (M±SD) for parametric variables, median and quartiles 1 and 3 (Me ($Q_{0.25}$-$Q_{0.75}$) for nonparametric continuous variables; as percentage of total sample (%) for categorical variables.

fluctuations in the determined values, and were stored at -80 °C until analysis. Erythrocyte sedimentation rate (ESR, mm/h) by Westergren method, C-reactive protein (mg/L) and rheumatoid factor (IU/mL) were evaluated by standard laboratory procedures. Serum analysis included required tests for antibodies to cyclic citrullinated peptide (Anti-CCP hs; Orgentec Diagnostika, Germany) and angiopoietin-like protein type 4 (RayBio Human ANGPTL4 ELISA Kit, RayBiotech, USA), which were quantified by ELISA according to kit manufacturer instructions.

The mineral density of the lumbar vertebrae at the level of L1-L4 (BMD_{L1-L4}), femoral neck, and femur (BMD_{total}) in general was measured by dual-energy X-ray absorptiometry (DXA) on a Lunar Prodigy (GE, USA). Each patient's BMD was compared with the average BMD of healthy young adults of the same sex. The default diagnostic threshold for OP was T-criterion: T points ≥ -1 were considered normal bone density, T points between < -1 and > -2.5 as osteopenia, and T points ≤ -2.5 as OP.

Statistical analysis was performed using STATISTICA 10.0 software (StatSoft Inc., USA) and Microsoft Office Excel (Microsoft Corp., USA). The studied indicators were preliminarily checked for normal distribution. The data are presented as mean ± standard deviation (M±SD) or median (Quartile 1, Quartile 3) (Me ($Q_{0.25}$-$Q_{0.75}$), as appropriate. Data for categorical variables were expressed as absolute numbers and percentages. Spearman's correlation coefficient (r) was used to determine the correlations between the variables. The comparison of proportions between the study groups was analyzed using the chi-square test (χ^2). Mann–Whitney U test (U test) and Kruskal–Wallis ANOVA test (H test) were used to compare data groups. We used univariate analysis followed by multivariate logistic regression analysis of variables with $p < 0.1$ to analyze influencing factors. The data with a probability value less than 0.05 ($p < 0.05$) were considered statistically significant.

Results and Discussion

The average serum ACPA concentration of RA patients was 64.7 (8.4-778) ng/mL, ANGPTL4 was 1.82 (0.56-10.7) ng/mL. In the studied group of RA patients ACPA and RF-IgM were positive in 61.5% and 69.8% of patients, respectively. The upper limit of normal (M+3SD) equal to 3.17 ng/mL was established after determination of ANGPTL4 in serum of 48 practically healthy persons comparable by sex and age with the studied group of RA patients. 41.7% of RA patients were found positive for ANGPTL4.

No correlation between ACPA and ANGPTL4 was observed neither in the general group of RA patients ($p > 0.1$), nor in individual patient groups depending on sex, age (< and > 50 years), duration of disease, presence of erosions, and RF-IgM

TABLE 2. ACPA AND ANGPTL4 LEVELS IN RA PATIENTS DEPENDING ON THE PRESENCE OF SECONDARY OSTEOPOROSIS

Indicator	Group I	Group II
ACPA, units/mL	15.5 (7.05-139.00)	252 (25.8-1028.0)**
ANGPTL4, ng/mL	0.98 (0.46-3.47)	3.53 (0.68-12.10)*

Note. ACPA, antibodies against cyclic citrullinated peptide; ANGPTL4, angiopoietin-like protein type 4; intergroup differences: *, $p < 0.05$; **, $p < 0.01$.

seropositivity ($p > 0.05$). ACPA was positively correlated with RF ($r = 0.3$), DAS28 ($r = 0.22$) and negatively with BMD_{total} ($r = -0.26$); for all measures $p < 0.05$. ANGPTL4 was positively correlated with RF ($p = 0.32$), disease duration ($p = 0.23$) and negatively with BMD_{L1-L4} ($r = -0.69$); for all measures $p < 0.05$.

When comparing groups of patients with different RA activity no significant differences in ACPA content (H test = 6.1, $p = 0.11$) and ANGPTL4 (H test = 2.9, $p = 0.41$) were obtained. This is probably associated with significant prevalence of patients with moderate disease activity. The separation of patients into groups with low (DAS28 ≤ 3.2, $n = 34$) and high (DAS28 > 3.2, $n = 62$) RA activity demonstrated a significant increase in ACPA with increasing activity of the pathological process (U test = 2.03, $p = 0.042$). No significant changes were found for ANGPTL4 (U test = 1.68, $p = 0.093$).

Patients were divided into two groups according to BMD of the lumbar or bilateral hip joint and the presence of a history of low-energy fractures: group I – RA without OP (RA/OP^-; $n = 51$); group II – RA with OP (RA/OP^+; $n = 45$). Patients did not differ by gender ($p = 0.11$), DAS28 index ($p = 0.39$), BMI ($p = 0.07$), presence of erosions ($p = 0.88$) and seropositivity for RF ($p = 0.35$), but the second group included older patients ($p = 0.018$), with greater duration of disease ($p = 0.03$) and inflammatory indices (CRP and ESR, $p < 0.05$). ACPA and ANGPTL4 scores were significantly higher in the RA/OP^+ group compared with those in the RA/OP^- group (U test: $Z = 3.08$, $p = 0.002$ and $Z = 2.2$, $p = 0.028$, respectively) (Table 2).

ACPA-positivity can be considered as a specific risk factor for systemic bone mass loss, and potentiation of ACPA effects on osteoclastogenesis is observed in the presence of RF [4]. This probably results from the generation of immune complexes with ACPA and the resulting stimulation of osteoclast activation and cytokine production in macrophages. Osteoclast-mediated bone destruction in RA is regulated by immune cells and their cytokines as well as ACPA [6] and possibly ANGPTL.

Next, a regression analysis was performed using the new characteristics of the studied factors (the linear character of the correlation between the variables was ensured). Factors influencing ACPA and ANGPTL4 with $p < 0.1$ were included in a multivariate logistic regression analysis.

In the general group of RA patients, age, BMI, duration and activity of the disease had no significant effect on ACPA. But in the RA/OP^+ group, the correlation between ACPA and DAS28 became significant ($\beta = 0.31$, $p = 0.039$).Of all the variables presented, only disease duration was significant for ANGPTL4 content in the overall group of RA patients ($\beta = 0.31$, $p = 0.039$). The effect of this factor on ANGPTL4 was more pronounced in the RA/OP^- group ($\beta = 0.35$, $p = 0.012$), but not in the RA/OP^+ group ($p = 0.79$).

ACPA is known as a risk factor not only for joint destruction in patients with RA, but also for bone mass loss, especially in the proximal femur [12]. This relationship was also confirmed in our study. In the regression model, femoral BMD was almost equally dependent on patient age ($\beta = -0.28$), BMI ($\beta = 0.25$), and ACPA level ($\beta = -0.26$). The square of the multiple correlation coefficient (R^2) in this model was 0.22. The search for associations between BMD_{L1-L4} and other RA characteristics (age, disease duration and activity, BMI, RF level, CRP, ANGPTL4 and ACPA) showed a strong influence only of ANGPTL4 ($\beta = -0.74$), with an R^2 value for the whole model equal to 0.57.

In a review by D'Onofrio B. et al. the main specific risk factors for osteoporotic fractures in RA are activity and duration of the disease, presence of disability and use of glucocorticoids, but not the presence of any autoantibodies [4]. Reduced BMD correlated with the presence of autoantibodies is only one possible link in the multifactorial process of osteoporotic fracture and cannot fully explain the relationship between autoantibodies and low-energy vertebral fractures in RA [13].

ANGPTL4 actively promotes lipid metabolism by inhibiting lipoprotein lipase and hepatic lipase activity, in addition to regulating inflammation and

TABLE 3. CORRELATION COEFFICIENTS BETWEEN ACPA, ANGPTL4 AND BMD VALUES IN DIFFERENT BONE SECTIONS

Indicator	ACPA		ANGPTL4	
	Coefficient	p	Coefficient	p
BMD_{total}	a = 0.9365 b = -0.015	< 0.001 0.048	a = 0.8858 b = -0.012	< 0.001 0.234
BMD_{L1-L4}	a = 1.0223 b = -0.003	< 0.001 0.729	a = 1.0596 b = -0.076	< 0.001 < 0.001

Note. ACPA, antibodies against cyclic citrullinated peptide; ANGPTL4, angiopoietin-like protein type 4; BMD_{total}, femoral bone mineral density; BMD_{L1-L4}, spinal bone mineral density at L1-L4 level; a, b, nonlinear relationship equation factors.

participating in metabolic processes. Whole-genome association studies have shown an association of ANGPTL4 with triglyceride, triglyceride-rich lipoprotein cholesterol, and low-density lipoprotein cholesterol levels. Plasma ANGPTL4 is negatively correlated with high-density lipoprotein cholesterol (HDL-C) [11]. In addition, HDL-C, after adjusting for sex, age, and BMI, was a predictor of the development of OP in RA patients [15]. A detailed evaluation of the potential importance of ANGPTL4 for the prevention and treatment of patients with spinal OP remains to be performed.

At the final stage of the study, we evaluated the coefficients of nonlinear dependence equations of immune inflammation markers and osteoporotic processes (Table 3).

Both coefficients were highly significant in describing the power equation ($y = ax^b$) for the relationship between BMD_{total} and ACPA, as well as for BMD_{L1-L4} and ANGPTL4. ACPA levels can reliably predict BMD_{total}: $BMD_{total} = 0{,}936x[ACPA]^{-0{,}015}$, and serum ANGPTL4 levels predict – BMD_{L1-L4}: $BMD_{L1-L4} = 1{,}06x[ANGPTL4]^{-0{,}076}$.

Along with the opinion that RA patients are particularly prone to cortical bone layer OP (especially the femoral neck) and that they have a greater predisposition to periarticular bone loss having elevated levels of ACPA [2], many studies present conflicting results (depending on the patient groups analyzed, fracture rates vary from 8 to 49%) in reducing BMD and vertebral fracture rates [4]. The dependence of ANGPTL4 and reduction of BMD in the cancellous bone layer allow us to identify a group of RA patients with high ANGPTL4 content as a risk group specifically for spinal fractures, and to consider ANGPTL4 as a potential target for the treatment of osteoporotic disorders.

Biomarkers remain powerful tools to predict BMD changes, targeting each skeletal anatomical region individually to help prevent low-energy fractures in patients with RA. However, the detection of the dependence of various biomarkers and quantitative indicators of bone tissue (mass or bone density) does not allow us to judge with the same confidence the changes in qualitative characteristics of bone (such as bone strength), which the new technologies are aimed at assessing.

Despite a number of limitations of this study (single-center cross-sectional study; no data on the postmenopausal status of patients; no consideration of the effects of the drugs used on immune cells and bone metabolism), gaining new knowledge about any possible mechanisms of secondary osteoporosis in RA will help make decisions about intervention early in the primary disease and prevent serious complications associated with osteoporotic fractures.

Conclusion

Apparently, in order to track systemic bone loss in RA even before the clinical debut of the disease, initial OP screening using DXA and calculation of the estimated 10-year risk of osteoporotic fractures by FRAX should be performed with special attention not only in ACPA-positive patients [2], but also in RA patients with high serum ANGPTL4 values. To prevent loss of systemic bone mass (especially in the femur) in ACPA-positive patients the focus should be on reducing disease activity, and in ANGPTL4-positive patients on timely prescription of anti-osteoporotic medications.

Acknowledgments

The authors are grateful to the staff of the Volgograd Center for Diagnostics and Treatment of Osteoporosis (chief Polyakova Yu.V.) for their help in collecting clinical materials, as well as to the staff of the Department of Clinical Laboratory Diagnostics of Volgograd Medical University (chief Zavodovsky B.V.) for methodical assistance in conducting laboratory tests.

References

1. Abdelhafiz D., Baker T., Glascow D.A., Abdelhafiz A. Biomarkers for the diagnosis and treatment of rheumatoid arthritis – a systematic review. *Postgrad. Med., 2023, Vol. 135, no. 3, pp. 214-223.*

2. Adami G., Saag K.G. Osteoporosis pathophysiology, epidemiology, and screening in rheumatoid arthritis. *Curr. Rheumatol. Rep., 2019, Vol. 21, no. 7, 34.* doi: 10.1007/s11926-019-0836-7.

3. Aleksandrov V.A., Shilova L.N., Aleksandrov A.V., Osmanova G.Y., Aleksandrova N.V., Zborovskaya I.A. The decrease in bone mineral density depends on the concentrations of angiopoietin-like protein type 4 in patients with rheumatoid arthritis. *Ann. Rheum. Dis., 2021, Vol. 80, no. S1, 225.* doi: 10.1136/annrheumdis-2021-eular.2266.

4. D'Onofrio B., di Lernia M., de Stefano L., Bugatti S., Montecucco C., Bogliolo L. Personalized therapeutic strategies in the management of osteoporosis in patients with autoantibody-positive rheumatoid arthritis. *J. Clin. Med., 2022, Vol. 11, no. 9, 2341.* doi: 10.3390/jcm11092341

5. Fang Q., Zhou C., Nandakumar K.S. Molecular and cellular pathways contributing to joint damage in rheumatoid arthritis. *Mediators Inflamm., 2020, Vol. 2020, 3830212.* doi: 10.1155/2020/3830212.

6. Jung Y.K., Kang Y.M., Han S. Osteoclasts in the inflammatory arthritis: implications for pathologic osteolysis. *Immune Netw., 2019, Vol. 19, no. 1, e2.* doi: 10.4110/in.2019.19.e2.

7. Klose-Jensen R., Tse J.J., Keller K.K., Barnabe C., Burghardt A.J., Finzel S., Tam L.S., Hauge E.M., Stok K.S., Manske S.L. High-resolution peripheral quantitative computed tomography for bone evaluation in inflammatory rheumatic disease. *Front. Med., 2020, Vol. 7, 337.* doi: 10.3389/fmed.2020.00337.

8. Liu F.J., Xie L.Y., Li H.Z., Cao S.N., Chen Y.Z., Bin-Shi, Wang D.D. Expression of ANGPTL4 in nucleus pulposus tissues is associated with intervertebral disc degeneration. *Dis. Markers, 2021, Vol. 2021, 3532716.* doi: 10.1155/2021/3532716.

9. Llorente I., García-Castañeda N., Valero C., González-Álvaro I., Castañeda S. Osteoporosis in rheumatoid arthritis: dangerous liaisons. *Front. Med. (Lausanne), 2020, Vol. 7, 601618.* doi: 10.3389/fmed.2020.601618.

10. Masuko K. Angiopoietin-like 4: A molecular link between insulin resistance and rheumatoid arthritis. *J. Orthop. Res., 2017, Vol. 35, no. 5, pp. 939-943.*

11. Olshan D.S., Rader D.J. Angiopoietin-like protein 4: A therapeutic target for triglycerides and coronary disease? *J. Clin. Lipidol., 2018, Vol. 12, no. 3, pp. 583-587.*

12. Tomizawa T., Ito H., Murata K., Hashimoto M., Tanaka M., Murakami K., Nishitani K., Azukizawa M., Okahata A., Doi K., Saito M., Furu M., Hamaguchi M., Mimori T., Matsuda S. Distinct biomarkers for different bones in osteoporosis with rheumatoid arthritis. *Arthritis Res. Ther., 2019, Vol. 21, no. 1, 174.* doi: 10.1186/s13075-019-1956-1.

13. Wysham K.D., Baker J.F., Shoback D.M. Osteoporosis and fractures in rheumatoid arthritis. *Curr. Opin. Rheumatol., 2021, Vol. 33, pp. 270-276.*

14. Yu S.F., Chen J.F., Chen Y.C., Wang Y.W., Hsu C.Y., Lai H.M., He H.R., Ko C.H., Chiu W.C., Cheng T.T. The impact of seropositivity on systemic bone loss in rheumatoid arthritis-a 3-year interim analysis of a longitudinal observational cohort study. *Front. Med. (Lausanne), 2022, Vol. 9, 885801.* doi: 10.3389/fmed.2022.885801.

15. Zeng T., Tan L., Yu J., Wu Y. High density lipoprotein in rheumatoid arthritis: emerging role in predicting inflammation level and osteoporosis occurrence. *Scand. J. Clin. Lab. Invest., 2020, Vol. 80, no. 5, pp. 375-380.*

Авторы:

Османова Г.Я. *– ассистент кафедры госпитальной терапии ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ; младший научный сотрудник, ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия*

Александров В.А. *– ассистент кафедры госпитальной терапии ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ; младший научный сотрудник, ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия*

Authors:

Osmanova G. Ya., *Assistant Professor, Department of Hospital Therapy, Volgograd State Medical University; Junior Research Associate, A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Aleksandrov V.A., *Assistant Professor, Department of Hospital Therapy, Volgograd State Medical University; Junior Research Associate, A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Александров А.В. *— д.м.н., доцент, профессор кафедры клинической лабораторной диагностики ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ; заведующий лабораторией функциональных методов исследования, ультразвуковой диагностики и восстановительной терапии ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия*

Aleksandrov A.V., *PhD, MD (Medicine), Professor, Department of Clinical Laboratory Diagnostics, Volgograd State Medical University; Head, Laboratory of Functional Research Methods, Ultrasound Diagnostics and Rehabilitation Therapy, A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Шилова Л.Н. *— д.м.н., доцент, заведующая кафедрой госпитальной терапии ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ, г. Волгоград, Россия*

Shilova L.N., *PhD, MD (Medicine), Associate Professor, Head, Department of Hospital Therapy, Volgograd State Medical University, Volgograd, Russian Federation*

Черкесова Е.Г. *— к.м.н., доцент кафедры госпитальной терапии ФГБОУ ВО «Волгоградский государственный медицинский университет» Министерства здравоохранения РФ, г. Волгоград, Россия*

Cherkesova E.G., *PhD (Medicine), Associate Professor, Department of Hospital Therapy, Volgograd State Medical University, Volgograd, Russian Federation*

Александрова Н.В. *— к.м.н., старший научный сотрудник, ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия*

Aleksandrova N.V., *PhD (Medicine), Senior Research Associate, A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Зборовская И.А. *— д.м.н., профессор, директор ФГБНУ «Научно-исследовательский институт клинической и экспериментальной ревматологии имени А.Б. Зборовского», г. Волгоград, Россия*

Zborovskaya I.A., *PhD, MD (Medicine), Professor, Director, A. Zborovsky Research Institute of Clinical and Experimental Rheumatology, Volgograd, Russian Federation*

Поступила 24.04.2023
Принята к печати 07.05.2023

Received 24.04.2023
Accepted 07.05.2023