ORIGINAL INVESTIGATIONS

Osteoporosis and sarcopenia in women with rheumatoid arthritis

Dobrovolskaya O.V., Feklistov A.Yu., Efremova A.O., Toroptsova N.V., Nikitinskaya O.A., Demin N.V.
V.A. Nasonova Research Institute of Rheumatology, Moscow
34A, Kashirskoe Shosse, Moscow 115522, Russia

Objective: *to assess bone mineral density (BMD) and the incidence of osteoporosis (OP) and sarcopenia (SP) in women suffering from rheumatoid arthritis (RA).*
Patients and methods. *Eighty-one women (mean age, 59.0Ĭ}8.1 years) with a reliable diagnosis of RA were examined. The women underwent the following studies: a survey using a special questionnaire; tests to measure the functional status of muscles, including those to determine their strength; as well as dual-energy X-ray absorptiometry of the axial skeleton and whole body.*
Results and discussion. *According to the EWGSOP2 criteria, 20 (24.7%) female patients were diagnosed with SP, 24 (29.6%) had OP, and 39 (48.2%) had osteopenia. OP in female patients with and without SP occurred in 35.0 and 27.9% of cases, respectively (p>0.05). BMD in the femoral neck and in the proximal femur as a whole was significantly lower in the presence of SP than in its absence (p=0.0006 and p=0.0061, respectively). The frequency of falls was significantly higher in the female patients with SP than in those without SP (p=0.028). The major osteoporotic and hip fracture probabilities calculated according to the FRAXR algorithm was higher in the patients with SP than in those without SP (p=0.041 and p=0.033, respectively). There were positive correlations of BMD with body mass index, appendicular muscle mass, appendicular muscle index, hand strength, shoulder circumference, and the serum levels of calcium, creatinine and uric acid, as well as negative correlations with age, postmenopausal length, and RA duration.*
Conclusion. *OP and SP are common RA complications that increase the risk of falls and fractures.*

Keywords: *rheumatoid arthritis; sarcopenia; osteoporosis; BMD; FRAXR.*
Contact: *Natalia Vladimirovna Toroptsova;* ***torop@irram.ru***
For reference: *Dobrovolskaya OV, Feklistov AYu, Efremova AO, et al. Osteoporosis and sarcopenia in women with rheumatoid arthritis. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2020;14(2):84–89. DOI: 10.14412/1996-7012-2020-2-84-89*

RA is an autoimmune rheumatic disease of unknown etiology, characterized by chronic erosive arthritis and systemic damage to internal organs, which leads to early disability and shorter life expectancy [1]. Persons suffering from RA may develop complications – conditions pathogenetically associated with the underlying disease. These conditions aggravate the course of RA and require treatment correction. In addition, it is known that RA often occurs against the background of a number of concomitant diseases, which are defined as nosological forms that are not etiologically and pathogenetically related to the underlying disease or its complications. Thus, a comorbid background of RA is formed (from lat. – «co» – together + «morbus» – disease, ailment), that is a condition when two or more diseases, connected by a single pathogenetic mechanism or coinciding in time coexist in one patient. At the same time, there are syndromes that fail to be accurately defined as a complication or concomitant disease, since they can play different roles in RA. These conditions include OP and SP. Both OP and SP can be either concomitant diseases, or secondary syndromes, representing complications of RA.

OP in patients with RA has been studied for many years. It is known that chronic inflammation in RA and prolonged use of glucocorticoids (GCs) in its therapy lead to a decrease in BMD. Studies have proved the significant role of RA in increasing the risk of osteoporotic fractures, and it was included as an independent risk factor in the FRAX® (Fracture Risk Assessment Tool). Despite the long record of studying this issue, the scope of data on the frequency of OP in patients with RA is very large and ranges from 11% to 59% [2,3], which may be due to the heterogeneity of groups by age, gender composition, and even some methodological inaccuracies, for example, evaluation of BMD in young people according to the T-score.

Compared with OP, SP is a younger problem; the concept of SP was introduced into clinical practice only in the late 90s of the last century [4]. According to various authors, the incidence of SP among patients with RA varies from 13.9% to 39.8% [5, 6, 7]. Until 2019, the criteria proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) were used to diagnose SP in white people [8]. These criteria were revised, and in 2018 their second edition (EWGSOP2) [9], which is currently in clinical practice, was presented. A decrease in muscle strength suggests that the patient might have sarcopenia, and SP can be reliably diagnosed only if muscle mass decrease is confirmed with the help of medical instruments. Most often it is done with bioimpedance analysis and dual-energy X-ray absorptiometry (DXA). In the latter case, it is possible to simultaneously diagnose OP. The relationship between SP and OP with their simultaneous presence in RA patients has been actively studied recently.

Objective: to assess the BMD status and determine the frequency of OP and SP in women with RA.

Patients and methods

the study included 81 women aged 40 to 75 years with definite RA in accordance with ACR / EULAR 2010 criteria [10]. The patients with a 3–4 functional class of the RA, bone avascular necrosis, severe concomitant somatic diseases, mental and cognitive impairment were not included. The study was con-

ducted within the framework of the research program № AAAA-A19-119021190150-6 «Development of complex therapy methods of the musculoskeletal diseases». The local ethical committee of the V. A. Nasonova Research Institute of Rheumatology approved the procedure, and informed written consent was obtained from all individual participants before they were included in the study.

Patients were interviewed according to the original questionnaire, which included questions on socio-demographic data, a gynecological history, concomitant diseases and the therapy carried out for them. Functional abnormalities were assessed by the Disability Index Health Assessment Questionnaire (HAQ). RA activity was determined by the DAS 28 index (Disease Activity Score) using erythrocyte sedimentation rate (ESR) with a ranking of high (DAS 28>5.1), moderate (3.1⩽DAS 28⩽5.1) and low (2.6⩽DAS 28 <3.1). Remission of the disease was established in the case of DAS 28 less than 2.6 [10]. Also, the level of C-reactive protein (CRP) and routine serum biochemical parameters were determined for all patients.

Body composition and BMD were evaluated by DXA (Discovery A, Hologic, USA). In the course of body composition study, appendicular muscle mass (AMM) was calculated – the sum of the muscle mass of the arms and legs, and appendicular muscle index (AMI) – the ratio of AMM to the value of height squared (kg / m^2). Handheld dynamometry and the chair stand test were performed to evaluate muscle strength. The functional state of the muscles was assessed using the Short Physical Performance Battery, «Up and go» test and 4-m gait speed test. SP was diagnosed in accordance with the EWGSOP2 criteria [9]. Further analysis was carried out depending on the presence or absence of SP (groups SP + and SP-).

BMD in postmenopausal women in accordance with WHO criteria was evaluated by the T-score (the number of standard deviations (SD) from the average value of the peak bone mass in young adults) in the lumbar spine (LS), the femoral neck (FN) and the total hip (TH): normal > -1 SD, osteopenia – from -1 to -2.5 SD, OP ⩽ -2.5 SD. We used the Z-score to evaluate premenopausal women, which corresponds to the number of SD from the average value of bone mass for a given age. OP was diagnosed with a value of Z-score less than -2.0 SD. A 10-year probability of the major osteoporotic fracture and hip fracture was calculated by FRAX® [11].

Statistical analysis was performed with the help of the software package Statistica for Windows, version 12.0 (StatSoft Inc., USA). Data were analyzed for compliance with normal distribution using the Shapiro-Wilk test. The descriptive statistics of the outcome measures are presented as the mean and standard deviation (M ± SD) or median and interquartile range (Me [25; 75 percentile]). The Mann–Whitney U test was used to compare the quantitative indicators of two independent groups. Quality indicators were compared using the Fisher test. A Spearman correlation analysis was performed. The result was considered statistically significant with $p < 0.05$.

Table 1 *Descriptive characteristics of patients with RA (n=81)*

Variables	Value
Age, M±SD (years)	59,0 ±8,1
Postmenopausal women, n (%)	71 (87,7)
Years since menopause, Me [25; 75 percentile]	10 [6; 17]
RA duration, Me [25; 75 percentile] (years)	7 [3; 11]
Smokers, n (%)	8 (9,9)
HAQ, M±SD	1,48±0,69
DAS 28-ESR, M±SD	4,8±1,3
ESR, Me [25; 75 percentile] (mm / h)	17 [13; 26]
CRP, Me [25; 75 percentile] (g / l)	12,1 [3,0; 17,1]
Oral GCs > 3-months, n (%)	40 (49,4)
GCs cumulative dose, Me [25; 75 percentile] (mg) in terms of prednisone	8125 [3650; 16420]
Treatment with bDMARDs, n (%)	13 (16,1)

Results

The general characteristics of the group are presented in table 1. It should be noted that more than half of the women (51.9%) were under the age of 60. Disease activity was high in 43% and moderate in 47% of the examined individuals. Only 10% of the women had the DAS 28 index corresponding to remission or low RA activity. 40 (49.4%) patients took oral GC more than 3 months. 13 (16.1%) received biologic disease-modifying antirheumatic drugs (bDMARDs), including 8 – rituximab, 3 – etanercept, 1 – adalimumab, 1 – tofacitinib.

According to muscle strength tests, 73 (90%) patients with RA met the criteria of probable sarcopenia. The whole body DXA data showed that the mean AMM was 17.8±3.0 kg and the mean AMI was 6.9±1.2 kg / m^2, with 20 (24.7%) people having an AMI value corresponding to the EWGSOP2 SP criteria. All patients with low AMI had low muscle strength, which allowed us to diagnose a confirmed SP. Patients with SP did not differ from women without SP in mean age, however the duration of RA was longer in the group of individuals with SP. BMI was significantly lower in patients with SP, among whom there were more people with a BMI of 18–25 kg / m2 ($p = 0.0002$). Calcium intake with food did not differ in both groups ($p > 0.05$). 70% of patients with SP took oral GCs, which was significantly more than among people without SP ($p = 0.03$), while the cumulative dose of GCs did not differ. There were no differences between the groups in terms of inflammatory activity (DAS 28, ESR, CRP), while the group with SP had a significantly higher serum creatinine level. The frequency of low-energy fractures in women with and without SP did not differ, but the number of falls during the year preceding the survey was greater in individuals with SP (Table 2).

Patients with SP demonstrated significantly difference from those without SP in such indicators as the disease duration, BMI, use of GCs, and creatinine level.

OP in at least one measurement area was detected in 22 (29.6%) patients with RA, osteopenia – in 39 (48.2%), and normal BMD – in 18 (22.2%) women. Among people with SP the frequency of OP was not significantly higher than in patients without SP (35.0% and 27.9%, respectively) (Fig. 1).

A comparative analysis of the absolute data of the BMD and the T-score showed that these values in FN and TH were significantly less in the group of patients with SP than in individuals without SP. LS BMD in patients with SP was also lower than in

Table 2 *Comparative characteristic of patients with and without SP*

Показатель	SP+ (n=20)	SP- (n=61)	p
Age, M±SD (years) <60 years, n, %	58,9±6,9 10 (50)	59,1±8,4 32 (53)	>0,05 >0,05
RA duration, Me [25; 75 percentile] (years)	13 [5; 23]	6 [1; 32]	**0,004**
Age of menopause, M±SD (years) Years since menopause, Me [25; 75 percentile]	47,3±4,1 10 [7;18]	48,9±4,8 10 [5; 16]	>0,05 >0,05
BMI, Me [25; 75 percentile] (kg/m^2)	24,5 [22,4; 25,8]	27,7 [25,5; 32,4]	**0,0002**
Daily calcium intake, Me [25; 75 percentile] (mg)	728,2 [475,0; 815,7]	734,1 [549,5; 968,8]	>0,05
Low-energy fractures in the past, n (%)	3 (15)	10 (16)	>0,05
Falls in the previous year, n (%) Repeated falls, n (%)	9 (45) 4 (20)	10 (16) 7 (11)	**0,028** >0,05
Oral GCs, n (%) GCs cumulative dose, Me [25; 75 percentile] (mg) in terms of prednisone	14 (70) 8967,5 [3650; 16106]	26 (43) 8000 [2965; 16420]	**0,030** >0,05
Treatment with bDMARDs, n (%)	4 (20)	9 (15)	>0,05
HAQ, M±SD	1,50±0,82	1,47±0,67	>0,05
DAS 28, M±SD	4,6±1,6	4,8±1,1	>0,05
ESR, Me [25; 75 percentile], (mm / h)	16 [10; 23]	18 [13; 31]	>0,05
CRP, Me [25; 75 percentile] (g / l)	10,5 [4,2; 17,5]	13,2 [1,9; 18,1]	>0,05
Creatinine, M±SD (μmol / l)	67,6±13,4	60,3±13,6	**0,010**

RA patients without SP, however, the differences did not reach the level of statistical significance (Table 3).

The 10-year probability of osteoporotic fracture, determined with the FRAX® tool, was significantly higher for major osteoporotic fracture and for hip fracture in patients with SP (Table 4).

We carried out a correlation analysis between the BMD value of different measurement areas and some factors that showed significant differences in women with and without SP, as well as with body composition parameters and some other indicators which could be associated with a BMD decrease (Table 5).

It was found out that BMD in all measurement areas positively correlated with BMI, serum calcium level, AMM, grip strength of the right hand and negatively correlated with age. The degree of correlation between BMD and age was the lowest of all correlations identified. LS and FN BMD negatively correlated with the duration of postmenopause, and LS and TH BMD had a direct relationship with serum uric acid level. TH and FN BMD positively correlated with AMI, grip strength of the left (non-dominant) hand, and circumference of the right and left shoulders. In addition, an inverse correlation was found between the TH BMD and the duration of RA and the direct correlation with serum creatinine level.

Discussion

In our study the frequency of SP in RA patients was 24.7%, which means that every fourth patient had this pathology. Even although we used updated criteria of SP, our data are consistent with the research of M. Barone et al. [12] and Giles JT et al. [13], in which SP was detected in 21.0% and 25.9% of patients, respectively. At the same time, in other studies, the frequency of SP was significantly higher and amounted to 37.1% [14] and 39.8% [6]. Such a scatter of data is due to the fact that previous studies used previously developed criteria for SP or various devices for muscle mass determining. Also these studies included patients of different ages, and people of both sexes [7].

We did not find any connection between SP and the age of the patients — it occurred with the same frequency in people of middle (up to 60 years) and elderly (60 years and older) age, however, other studies demonstrated a correlation between SP and the age of RA patients [6,7, 14]. We also didn't find any correlation between the duration of postmenopause and the presence of SP. At the same time patients with SP had a significantly lower BMI than women without SP, which is consistent with data given by other authors [6, 13].

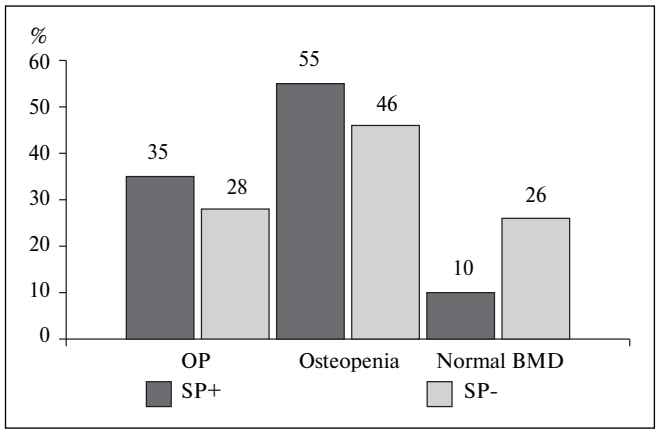

Fig. 1. *Frequency of OP in RA women depending on the presence of SP*

We evaluated the effect of the RA duration on SP and found that in our study, as well as in other studies, the duration was greater in women with SP in comparison to individuals without SP, which can explain the effect of the disease itself on the state of muscle tissue in patients with RA. At the same time, we did not find any link between the activity of the disease (DAS 28, ESR, CRP) and HAQ. People who took GCs were more common among women with SP, however, we did not observe significant differences in the cumulative dose of GCs depending on the presence or absence of SP in patients with RA. Similar results are presented in the work of Ngeuleu A. et al. [6]. We didn't see any differences in the treatment with bDMARDs between women with and without SP, but it should be noted that only 13 people used these medications. At the same time there is evidence that SP was significantly less common in patients treated with bDMARDs [14].

There is no clear answer to the question on the link between the number of falls and the presence of SP in patients with RA. In our group of patients with RA and SP falls during the year preceding the questionnaire occurred in 45% of cases, while in the group without SP only 16% of the examined mentioned falls. In the work of Torii M. et al. patients with SP fell down less frequently (26.4%) than in our group, however, in individuals without SP, the frequency of falls was significantly lower (13.9%) and almost coincided with that in patients without SP in our study [14]. There were no differences in the frequency of fractures in our study, but it was significantly greater in RA patients with SP ($p < 0.001$) in the study presented above [14].

OP was found in our group in 29.6% of cases, while its frequency was slightly higher in the group of people with SP than without it. However, these differences are insignificant. At the same time, the BMD in FN and TH was considerably lower than in the group without SP. In some studies, similar results were obtained, which reveals a series of associations between muscle mass and BMD. For example, T. Mochizuki et al. found a significant relationship between BMD in FN and SP [7]. In the work of S.E. Myasoedova et al. AMI positively correlated with T-score in LS and FN, creatinine level, and negatively – with GCs treatment and the risk of hip fracture according to FRAX® [5].

Table 3 *BMD in RA patients with and without SP*

Measurement area	SP+ (n=20)	SP- (n=61)	p
LS			
BMD, Me [25; 75 percentil] (g/cm²)	0,833 [0,738; 0,995]	0,876 [0,765; 1,007]	>0,05
T-score, Me [25; 75 percentil]	-2,0 [-2,8; -0,9]	-1,6 [-2,4; -0,4]	>0,05
FN			
BMD, Me [25; 75 percentil] (g/cm²)	0,613 [0,540; 0,685]	0,720 [0,636; 0,802]	0,0006
T-score, Me [25; 75 percentil]	-2,1 [-2,8; -1,5]	-1,3 [-2,0; -0,5]	0,0016
TH			
BMD, Me [25; 75 percentil] (g/cm²)	0,734 [0,642; 0,791]	0,788 [0,718; 0,909]	0,0061
T-score, Me [25; 75 percentil]	-1,9 [-2,5; -1,5]	-1,3 [-1,8; -0,3]	0,0027

Table 4 *The 10-year probability of osteoporotic fracture in RA patients with and without SP*

Measurement area	SP+ (n=20)	SP- (n=61)	p
10-year probability of major osteoporotic fracture, Me [25; 75 percentil] (%)	22,0 [17,0; 32,0]	14,0 [8,2; 23,0]	0,04110-
10-year probability of hip fracture, Me [25; 75 percentil] (%)	3,1 [3,0; 3,3]	0,6 [0,4; 1,6]	0,033

Table 5 *Correlations between BMD and individual factors affecting the state of bone tissue**

Factor	BMDLS	BMDFN	BMDTH
Age, r	-0,249	-0,285	-0,229
BMI, r	0,358	0,473	0,485
RA duration, r	–	–	-0,290
Years since menopause, r	-0,278	-0,308	–
Calcium, r	0,336	0,349	0,411
Creatinin, r	–	–	0,289
Uric acid, r	0,409	–	0,494
AMM, r	0,364	0,517	0,450
AMI, r	–	0,514	0,383
Grip strength (right hand), r	0,303	0,360	0,402
Grip strength (left hand), r	–	0,252	0,354
Circumference of the right shoulder, r	–	0,387	0,458
Circumference of the left shoulder, r	–	0,418	0,452

** The table presents factors that demonstrate a significant association with BMD, $p < 0.05$

Conclusion

We can conclude that SP and OP are a frequent complication in RA patients, while OP was slightly more frequently detected in RA women with SP compared to patients without SP (35.0% and 27.9 %%, respectively). Patients with SP had more frequent falls and a higher risk of osteoporotic fractures according to the FRAX®. We found out associations between BMD and some parameters of muscle tissue, which requires further research to highlight significant predictors of low BMD and low muscle mass in RA patients, and develop an integrated approach to the prevention of these complications.

REFERENCES

1. Насонов ЕЛ, редактор. Ревматология. Российские клинические рекомендации. Москва: ГЭОТАР-Медиа; 2017. 464 с. [Nasonov EL, editor. *Revmatologiya. Rossiiskie klinicheskie rekomendatsii* [Rheumatology. Russian clinical guidelines]. Moscow: GEOTAR-Media; 2017. 464 p.]
2. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, et al. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. *Ann Rheum Dis.* 2007 Nov;66(11):1508-12. doi: 10.1136/ard.2007.070839. Epub 2007 Apr 24.
3. Таскина ЕА, Алексеева ЛИ, Дыдыкина ИС и др. Факторы риска развития остеопоропоза у больных ревматоидным артритом (предварительные результаты по материалам многоцентровой программы ?Остеопороз при ревматоидном артрите: диагностика, факторы риска, переломы, лечение?). *Научно-практическая ревматология*. 2014;52(4):393-7. [Taskina EA, Alekseeva LI, Dydykina IS, et al. Risk factors for osteoporosis in patients with rheumatoid arthritis (preliminary results according to the materials of the multicenter program ? Osteoporosis in rheumatoid arthritis: diagnosis, risk factors, fractures, treatment?). *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2014;52(4):393-7. (In Russ.)]. doi: 10.14412/1995-4484-2014-393-397
4. Rosenberg I. Summary comments. *Am J Clin Nutr.* 1989;50:1231-3. doi: 10.1093/ajcn/50.5.1231.
5. Мясоедова СЕ, Рубцова ОА, Мясоедова ЕЕ. Композиционный состав тела и минеральная плотность кости у женщин при ревматоидном артрите. *Клиницист*. 2016;10(3):41-4. [Myasoedova SE, Rubtsova OA, Myasoedova EE. Body composition and bone mineral density in women with rheumatoid arthritis. *Klinitsist*. 2016;10(3):41-4. (In Russ.)].
6. Ngeuleu A, Allali F, Medrare L, et al. Sarcopenia in rheumatoid arthritis: prevalence, influence of disease activity and associated factors. *Rheumatol Int.* 2017 Jun;37(6):1015-20. doi: 10.1007/s00296-017-3665-x. Epub 2017 Mar 3.
7. Mochizuki T, Yano K, Ikari K, Okazaki K. Sarcopenia-associated factors in Japanese patients with rheumatoid arthritis: A crosssectional study. *Geriatr Gerontol Int.* 2019 Sep;19(9):907-12. doi: 10.1111/ggi.13747
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* 2010 Jul;39(4):412-23. doi: 10.1093/ageing/afq034. Epub 2010 Apr 13.
9. Cruz-Jentoft AJ, Bahat G, Bauer JM, et al. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019 Jan 1;48(1):16-31. doi: 10.1093/ageing/afy169
10. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis.* 2010 Sep;69(9):1580-8. doi: 10.1136/ard.2010.138461
11. https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=rs
12. Barone M, Viggiani MT, Anelli MG, et al. Sarcopenia in Patients with Rheumatic Diseases: Prevalence and Associated Risk Factors. *J Clin Med.* 2018 Dec 1;7(12) pii: E504. doi: 10.3390/jcm7120504
13. Giles JT, Ling SM, Ferrucci L, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. *Arthritis Rheum.* 2008 Jun15;59(6):807-15. doi: 10.1002/art.23719
14. Torii M, Hashimoto M, Hanai A, et al. Prevalence and factors associated with sarcopenia in patients with rheumatoid arthritis. *Mod Rheumatol.* 2019 Jul;29(4):589-95. doi: 10.1080/14397595.2018.1510565. Epub 2018 Sep 11.

Received/Reviewed/Accepted
20.03.2020/18.04.2020/25.04.2020

Conflict of Interest Statement
The investigation has been conducted within the framework of scientific topic № R&D AAAA-A19-119021190150-6 ?Development of combination treatment options for musculoskeletal system diseases?. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

Dobrovolskaya O.V. *https://orcid.org/0000-0002-2809-0197*
Feklistov A.Yu. *https://orcid.org/0000-0002-7661-3124*
Efremova A.O. *https://orcid.org/0000-0002-8155-6101*
Toroptsova N.V. *https://orcid.org/0000-0003-4739-4302*
Nikitinskaya O.A. *https://orcid.org/0000-0001-6759-8367*
Demin N.V. *https://orcid.org/0000-0003-0961-9785*