POINT OF VIEW

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THE RELATIONSHIP BETWEEN MARKERS OF BONE REMODELING AND THE RISK OF BONE FRACTURE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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The aim of the study was to study the possibility of predicting bone fractures by determining the concentration of markers of bone remodeling in patients with rheumatoid arthritis (RA). **Materials and methods.** We observed 88 patients with a reliable diagnosis of RA. The diagnosis was made based on the classification adopted at the 2010 EULAR / ACR meeting. Depending on the presence of osteoporetic fractures detected by collecting anamnestic data, the patients were divided into 2 groups: RA patients with osteoporotic fractures (n = 11) and RA patients without a history of fractures (n = 77). Commercial ELISA reagent kits were used to determine CrossLaps, P1NP and 25-OH vitamin D in serum.

Results. We examined the diagnostic value of in vitro determination of bone remodeling markers (CrossLaps, P1NP, and serum 25-OH vitamin D) using a characteristic curve (ROC curve). Laboratory determination of type I collagen C-telopeptide for predicting the risk of fractures in RA is of good quality (area under the ROC-curve 0.751, specificity 44.16%, sensitivity 100.0%). Laboratory determination of P1NP is of good quality, which confirms the value of the area under the ROC-curve (0.788), test sensitivity 81.82%, specificity 66.23%. Laboratory determination of 25-OH vitamin D for predicting the risk of fractures in RA has an area under the ROC-curve of 0.753, sensitivity 63.64%, specificity 88.31%.

Findings. Thus, the proposed method for predicting the development of low-energy bone fractures in patients with RA using the laboratory determination of markers of bone remodeling makes it possible to more accurately assess the risk of developing low-energy fractures as one of the complications of RA.

Keywords: rheumatoid arthritis, osteoporosis, markers of bone remodeling

Introduction. According to the WHO, rheumatoid arthritis (RA) ranks second among rheumatic diseases. In the world of RA, about 58 million people are affected [1, 2]. Although the etiology of the disease is not fully understood, the pathogenesis of RA is characterized by the activation of cells of the immune system [3].

According to the data available to date, up to half of RA cases (up to 48.6%) are complicated by the development of osteopenia and osteoporosis (OP), which leads to the appearance of bone pain, fractures with minor trauma, changes in posture, early disability in patients of working age [6 , 8]. The pathogenetic reasons for the development of secondary OP in RA are the intake of glucocorticosteroids (GCS), the presence of a chronic immune-inflammatory process, and low physical activity. Due to insufficient knowledge of the etiology, pathogenesis, lack of specific clinical and laboratory signs of the disease (especially in the early stages), the practitioner often faces difficulties both at the stage of diagnosing AP in RA patients and when choosing the optimal treatment strategy [3].

At the present stage, laboratory, histological and radiation research methods are used to diagnose OP, identify disorders of bone metabolism and predict the development of low-energy bone fractures. In clinical practice, the determination of many parameters in blood serum is used to study the state of bone tissue metabolism, for example, the determination of the concentration of proteins and peptides characterizing resorption and bone formation: C-terminal telopeptide of type I collagen (Cross Laps), osteocalcin, osteoprotegerin, total amino-thermal type I propeptide daprocollagen (P1NP) [4, 5]. The role of vitamin D is of great importance [7]. These techniques are characterized by minimal invasiveness and are available for use in the vast majority of clinical diagnostic laboratories.

The aim of our study was to investigate the possibility of predicting bone fractures by determining the concentration of bone remodeling markers in patients with RA.

Materials and methods. We observed 88 patients with RA (women aged 21 to 81 years). When diagnosing RA, we were guided by the clinical classification adopted at the 2010 EULAR / ACR meeting (European League Against Rheumatism / American College of Rheumatology). The patients were followed up by specialists of the A. B. Rheumatology Research Institute of Clinical and Experimental Rheumatology". The majority of patients were between 41 and 55 years old. According to the degree of RA activity, patients were distributed as follows: with activity 0 (DAS28<2.6) there were 19 patients in the study (21.59%), with a low degree of activity I (2.6<DAS28<3.2) - 10 people (11.36%), with an average degree of activity II (DAS28≥3.2 - 5.1) - 52 people (59.09%), with a high degree of activity III (DAS28>5.1) there were 7 patients (7.96%).

Depending on the presence of osteoporetic fractures, identified by collecting anamnestic data, the patients were divided into groups: 1st - RA patients with osteoporotic fractures (n = 11), 2nd - patients with RA without a history of fractures (n = 77).

To determine Cross Laps, P1NP and 25-OH vitamin D in blood serum, we used commercial ELISA reagent kits (Cross Laps ELISA Kit (IDS, UK), kit Procollagen I N-terminal Propeptide (PINP) SEA-957Hu (CLOUD-CLONE CORP., USA), 25 (OH) Vit D ELISA).

For the statistical processing of the

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data, the software packages "STATISTICA 10.0 for Windows" were used. The significance of differences between groups was compared using statistical variation analysis (ANOVA). The results were considered statistically significant at p <0.05. For the reliably significant studied indicators, an ROC analysis of the curves was carried out, the areas under the curves were calculated, and new points for making a diagnostic decision were selected.

Results. We have investigated the diagnostic value of laboratory determination of markers of bone remodeling in order to predict the risk of bone fractures.

To analyze the diagnostic accuracy of laboratory tests, a characteristic curve (ROC curve) was used, the method for evaluating ROC curves was the calculation of the area under the curve (AUC - Area Under Curve), which varies from 0.5 (no diagnostic effectiveness of the test) to 1.0 (maximum test efficiency). This calculation allows us to conclude about the predictive value of the laboratory test.

The curve for determining the diagnostic value of type I collagen C-telopeptide in blood serum is shown in Figure 1. The data on the area under the curves, the points of making the diagnostic decision (cutoff points) are presented in the tables below (tables 1, 2).

Based on the performed calculations, it can be concluded that the laboratory determination of type I collagen C-telopeptide for predicting the risk of fractures in RA is of good quality, which confirms the value of the area under the ROC-curve (0.751). The point corresponding to the optimal sensitivity / specificity ratio is the C-telopeptide value of type I collagen equal to 0.488 ng / ml. This value corresponds to a specificity of 44.16%, and a sensitivity of 100.0%.

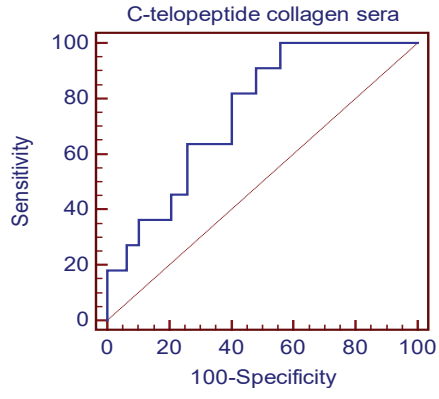
By evaluating similar ROC curves, the diagnostic value of determining type I N-terminal propeptide daprocollagen (P1NP) and 25-OH vitamin D in serum was studied for predicting the risk of fractures in RA.

The laboratory determination of P1NP was found to be of good quality, which confirms the value of the area under the ROC curve (0.788). In this case, the point corresponding to the optimal sensitivity / specificity ratio is the P1NP value equal to 51.76 ng / ml. This value corresponds to a sensitivity of 81.82%, a specificity of 66.23%.

Also, based on the performed calculations, it was concluded that laboratory determination of 25-OH vitamin D for predicting the risk of fractures in RA is of good quality, which confirms the value of the area under the ROC curve (0.753). In this case, the point corresponding to the optimal sensitivity / specificity ratio is the value of 25-OH vitamin D equal to 31.185 ng / ml. This value corresponds to a sensitivity of 63.64%, a specificity of 88.31%.

Findings. It is known that the currently used methods for diagnosing OP and predicting the risk of fractures in RA do not always reflect the true state of bone tissue. Often, low-energy fractures develop in RA patients with normal bone mineral density, assessed by densitometry or absorptiometry, which indicates the insufficient effectiveness of these methods for diagnosing OP. At the same time, the results of our study are consistent with the literature data that the methods for determining markers of bone synthesis and resorption have sufficient sensitivity and specificity for practical use in order to predict the risk of fractures. It can be assumed that the wider clinical use of these markers for diagnostic purposes, including their combined use with instrumental methods (densitometry), will improve the accuracy of predicting the risk of low-energy fractures.

Thus, the proposed method for predicting the development of low-energy bone fractures in patients with RA using the laboratory determination of markers of bone remodeling makes it possible to more accurately assess the risk of developing low-energy fractures as one of the complications of RA. Qualitative diagnos-



ROC-curve characterizing the diagnostic value of the determination of type I collagen C-telopeptide in blood serum for predicting the risk of fractures in RA.

Table 1

Basic descriptive characteristics of the ROC curve

Area under the ROC curve (AUC)	0.751
Standard error [a]	0.0671
95% Confidence interval [b]	0.647 to 0.837
Z statistics	3.738
Significance level P (Площадь = 0.5)	0.0002

[a]DeLongetal.. 1988
[b]Binomial accuracy

Table 2

Criteria values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
>=0.2	100.00	71.5 - 100.0	0.00	0.0 - 4.7	1.00	
>0.488	**100.00**	**71.5 - 100.0**	**44.16**	**32.8 - 55.9**	**1.79**	**0.00**
>0.508	90.91	58.7 - 99.8	44.16	32.8 - 55.9	1.63	0.21
>0.547	90.91	58.7 - 99.8	51.95	40.3 - 63.5	1.89	0.18
>0.549	81.82	48.2 - 97.7	51.95	40.3 - 63.5	1.70	0.35
>0.646	81.82	48.2 - 97.7	59.74	47.9 - 70.8	2.03	0.30
>0.667	63.64	30.8 - 89.1	59.74	47.9 - 70.8	1.58	0.61
>0.746	63.64	30.8 - 89.1	74.03	62.8 - 83.4	2.45	0.49
>0.752	45.45	16.7 - 76.6	74.03	62.8 - 83.4	1.75	0.74
>0.786	45.45	16.7 - 76.6	79.22	68.5 - 87.6	2.19	0.69
>0.796	36.36	10.9 - 69.2	79.22	68.5 - 87.6	1.75	0.80
>1.024	36.36	10.9 - 69.2	89.61	80.6 - 95.4	3.50	0.71
>1.062	27.27	6.0 - 61.0	89.61	80.6 - 95.4	2.62	0.81
>1.244	27.27	6.0 - 61.0	93.51	85.5 - 97.9	4.20	0.78
>1.284	18.18	2.3 - 51.8	93.51	85.5 - 97.9	2.80	0.88
>1.621	18.18	2.3 - 51.8	100.00	95.3 - 100.0		0.82
>1.993	0.00	0.0 - 28.5	100.00	95.3 - 100.0		1.00

tics in this case makes it possible to determine an adequate amount of therapy and pharmacological correction of disorders of bone metabolism. The inclusion of bone resorption markers in the standard examination program for RA patients can reduce the risk of developing low-energy fractures and improve the quality of life of patients.

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PERSPECTIVES FOR THE STUDY OF ACTIVE LONGEVITY AMONG RESEARCHERS

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Along with the increase in life expectancy in most countries of the world, including in Russia, the proportion of people in older age groups is growing. The authors carried out a scientific review of the problem of "active longevity" and the prospects for its study in a group of researchers. Currently various components of the question of "active longevity «are widely studied. However, in relation to researchers, most of its problems have not been studied systematically, there are practically no justified preventive measures, as well as measures to normalize the functions that have already been violated in a particular researcher. The development of the problem of active longevity of researchers will help to formulate a set of measures to extend the effective professional longevity of researchers and ensure scientific continuity.

Keywords: active longevity; professional longevity; researchers; scientists; cognitive abilities; quality of life.

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Introduction. Simultaneously with the increase in life expectancy in most countries of the world, including Russia [34-35], the share of older people in the population is growing. Since 2003, the average life expectancy in the Russian Federation for those born in 2020, according to the State Statistics Committee, is 73.4 years [30], and according to the conservative forecast, it will reach 75.4 years by 2035.

One of the areas of activity where the proportion of older workers is high is science. The development of science is one of the priority goals in the Russian Federation. In 2018, the National Project "Science" was approved, the goals of which are [30]:

1) ensuring the presence of the Russian Federation among the five leading countries of the world engaged in research and development in the field of priority areas for scientific and technological development areas;

2) ensuring the attractiveness of work in the Russian Federation for leading Russian and foreign scientists and young promising researchers;

3) outstripping the increase in domestic spending on research and development, compared with the growth of the country's gross domestic product.

To achieve these goals, the project "Science" sets the following tasks [18]:

1) Creation of at least 15 world-class scientific and educational centers based on the integration of universities and scientific organizations and their cooperation with organizations operating in the real sector of the economy;

2) creation of world-class scientific centers, including a network of international mathematical centers and genomic research centers;

3) updating at least 50 percent of the instrument base of the leading organizations performing research and development;

4) development of advanced infrastructure for research and development,