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A Study on the Relationship of Cartilage Glycoprotein-39 with Laboratory Markers of Inflammation in Patients and Rheumatoid Arthritis

Tamara Alexandrovna Naldikoeva[1], Aminat Turkoevna Abdulaeva[2], Aigul Rasulovna Gadzhieva[1], Anastasia Andreevna Volodikhina[3], Ekaterina Evgenievna Pugacheva[4], Salva Faekovna Dallo[5], Madina Becsoltovna Bisultanova[6], Melavinka Agubechirovna Sozaeva[1], Rinata Dzhanovna Aidarova[7], Aida Muradovna Gadzhieva[8]

[1] *North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia-Alania, RUSSIA.*
[2] *Chechen State University named after A.A. Kadyrov, Grozny, Republic of Chechnya, RUSSIA.*
[3] *Stavropol State Medical University, Stavropol, RUSSIA.*
[4] *Rostov State Medical University, Rostov-on-Don, RUSSIA.*
[5] *Russian National Research Medical University named after N. I. Pirogov, Moscow, RUSSIA.*
[6] *Saratov State Medical University named after V. I. Razumovsky, Saratov, RUSSIA.*
[7] *Moscow State University of Medicine and Dentistry Named after A.I.Evdokimov*
[8] *Dagestan State Medical University, Makhachkala, Republic of Dagestan, RUSSIA.*
**Corresponding Author (Tel: +79183500889, Email: ruslankalmykov777@yandex.ru).*

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Abstract

Rheumatoid arthritis is one of the most common rheumatic diseases characterized by chronic autoimmune inflammation and destructive damage to the joints. Despite the achievements in the treatment of rheumatoid arthritis, its early diagnosis and control of the activity of inflammation often cause difficulties for the doctor, which is the basis for continuing the search for new diagnostic solutions. The study included 52 patients (men and women) with an established diagnosis of rheumatoid arthritis aged 18 to 70 years and 20 healthy volunteers, comparable in gender and age. The examination of patients included standard clinical, laboratory and instrumental methods of investigation, as well as determination of the serum concentration of CGP-39.

Discipline: Medicine.

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1 Introduction

Rheumatoid arthritis (RA) is a chronic disease of unknown etiology, which is based on autoimmune inflammation characterized by erosive arthritis, systemic damage to internal organs and leading to early disability of the able-bodied population [1]. It is difficult to overestimate the socio-economic significance of RA, according to statistics, it affects on average 1% of the middle-aged population and 2.5% of the population over the age of 65, and during the first five years from the onset of the disease leads to persistent disability of about 40% of patients, and after 8-10 years - 60% [2-5].

Recent studies aimed at finding solutions to the problem of disability of patients and reducing life expectancy have identified the main conditions in order to reduce the activity of the disease, slow down the destruction of joints and prevent complications [5]. These conditions include early diagnosis and verification of RA, early initiation of anti-rheumatic therapy and regular monitoring of inflammatory activity [2,6].

Despite significant advances in the diagnosis and treatment of RA, which contributed to improving the prognosis of patients, the problem of its early verification, which is the key to a favorable outcome of the disease, is far from being resolved. Rather, this is due to the fact that most of the biochemical markers of RA have insufficient sensitivity and specificity [7]. There are research data according to which the sensitivity of ACCP (Antibodies to cyclic citrulline peptide) is 68%, IdMRF is 69%, and the combination of these indicators is 78% [8]. This allows us to conclude that if laboratory studies aimed at determining autoantibodies in peripheral blood give a negative result, for the diagnosis of RA at the early stages of the disease, the clinical picture should be expanded and with a high degree of inflammation activity, which implies elevated levels of CRP and ESR, which also have low specificity for RA. However, a bright clinic and high levels of inflammation indicators do not always accompany the debut of RA. In this case, it is quite difficult to differentiate RA from other forms of arthritis before the appearance of signs of erosive damage to the joints [6].

Considering the heterogeneity of the mechanisms of RA immunopathogenesis, the expansion of the spectrum of markers of the disease and rheumatoid inflammation to improve diagnostic informativeness is an urgent task of modern rheumatology. Our study aimed to study the serum levels of CGP-39 in RA patients and healthy individuals, as well as the relationship between CGP-39 and markers of inflammation.

2 Material and Methods

Location of the study: North Ossetian State Medical Academy, Vladikavkaz, Russia.

Two groups of individuals were studied: RA patients, and healthy individuals.

Inclusion criteria: men and women aged 18 and over; reliable diagnosis of RA (ACR/EULAR criteria, 2010).

Exclusion criteria: age younger than 18 and older than 70 years; the presence of other forms of arthritis other than RA; infectious diseases (HIV, hepatitis B, hepatitis C); severe degree of

somatic diseases (cardiovascular, renal, liver failure); diabetes mellitus; the presence of malignant neoplasms.

The control group consisted of healthy donors, comparable in gender and age with the main group of RA patients.

The study selected patients with a reliable diagnosis of RA that met the criteria of the American College of Rheumatology / European Alliance of Associations for Rheumatology (ACR/EULAR 2010).

Examination of patients included: assessment of disease activity by DAS28, determination of erythrocyte sedimentation rate (ESR), the concentration of C-reactive protein (CRP) and IgM RF, determination of antibodies to the cyclic citrullinated peptide (ACCP) and radiography of hands and feet. In the main and control groups, the content of CGP-39 in the blood serum was determined.

ESR was determined by the standard international method of Westergren (norm ⩽ 25 mm / h), and the study of CRP and IgM RF was carried out on an automatic biochemical analyzer VitaRei-300 by immunoturbidimetry. CRP values below 5.0 mg/l were considered normal, and RF IgM below 14.0 IU/ml. ACCP was determined by electrochemiluminescence method (norm⩽17 U/ml), and the content of CGP-39 was determined by enzyme immunoassay using ready-made kits of ELISA Kit for Glycoprotein 39 reagents [6].

Statistical processing of the results was carried out using the Statistica 12.0 software package (StatSoft, USA) and the MS Excel program (MSOffice). All data were checked for the normality of the distribution using the criteria of asymmetry and kurtosis, as well as the Shapiro-Wilk criterion. As a result of testing, it was revealed that the distribution of data is different from normal, so nonparametric methods were used for their analysis. Quantitative data are presented in the form of a median (Me) with an interquartile range [25th and 75th percentiles]. Two independent groups were compared using the Mann-Whitney U criterion, and three or more with the Kraskel-Wallis criterion. Spearman's rank correlation coefficient was used to analyze the dependence of quantitative features. Data differences and correlations between data at $p<0.05$ were considered statistically significant [9-11].

The protocol of the study was approved at the meeting of the Ethics Committee of the North Ossetian State Medical Academy. To be included in the study, all patients were informed about the progress of the study and signed a voluntary informed consent to participate and process personal data.

3 Result and Discussion

The study included 52 patients – 32 women (62%) and 20 men (38%) with an established diagnosis of RA, who were treated in the rheumatology department of the Clinical Hospital of the North Ossetian State Medical Academy and 20 healthy donors comparable in gender and age with the examined patients.

The clinical and laboratory characteristics of patients are presented in Table 1.

Table 1: Clinical and laboratory characteristics of patients included in the study (n=52)

Indicator	Value
Gender n (%): Male/Female	20(38)/32(62)
Age (years),Me[25-й; 75-й percentiles]	56 (39; 67,2)
Duration of the disease (years), Me[25-й; 75-й percentiles]	7 (4,9; 12,5)
DAS 28, (points), Me[25-й; 75-й percentiles]	5,3 (4,35; 5,7)
IgM RF IU/ml, Me[25-й; 75-й percentiles]	25 (9,0; 37,5)
IgM RF positive/ IgM RF Negative, n (%)	33 (63)/19 (37)
Cyclic Citrullinated Peptide Antibodies Units/ml, Me[25-й; 75-й percentiles]	123,0 (52,0; 235,5)
Cyclic Citrullinated Peptide Antibodies positive/negative, n (%)	39 (75)/ 13 (25)
CRP, mg/l, Me[25-й; 75-й percentiles]	43 (12,8; 78,8)
ESR, mm/h, Me[25-й; 75-й percentiles]	26,5 (10,5; 46,8)
CGP – 39, pg/ml, Me[25-й; 75-й percentiles]	152,6 (54,4 – 269,2)
X-ray stage (I/II/III/IV), n	9/25/18/0

Note: DAS28 (DiseaseActivityScore) – index of disease activity in rheumatoid arthritis, ESR – erythrocyte sedimentation rate, RF – rheumatoid factor, CGP-39 – cartilage glycoprotein – 39.

The majority of patients were female, at the time of inclusion in the study, the median age of patients was 56 (39; 67.2) years, and the duration of the disease was 7 (4.9; 12.5) years.

Median (Me) of the [25th; 75th percentile] level of CRP is 43 (12.8; 78.8) mg/l, ESR is 26.5 (10.5; 46.8) mm/h. The share of seropositive for IgM of the Russian Federation was 63%, and for ACCP – 75%.

A comparison of the level of HCG39 between the group of patients with RA and the control group revealed statistically significant differences ($p<0.001$). As shown in Figure 1, the median glycoprotein value in patients was 152.6 (54.4 – 269.2) pg/ml, in healthy patients – 30.7 (7.2; 53.7).

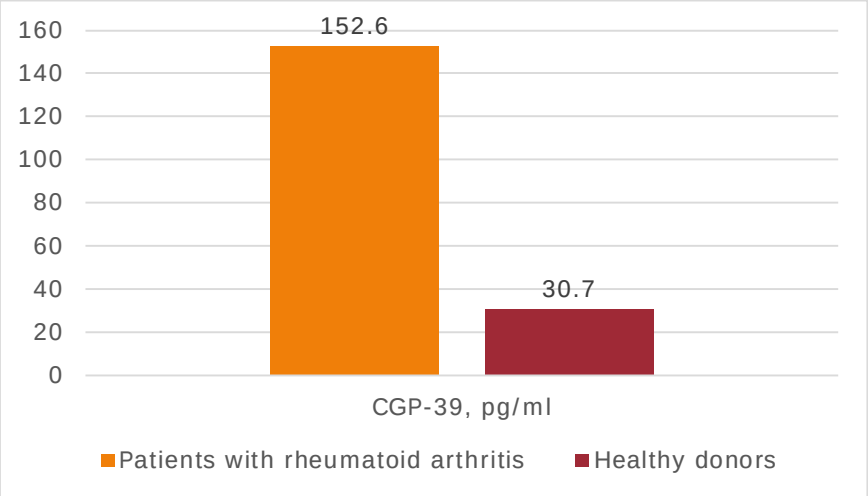

Figure 1: Concentrations of HCG39 between a group of Rheumatoid arthritis patients and healthy people.
Note: CGP-39 – cartilaginous glycoprotein – 39; values are presented as a median

To determine the relationship between CGP-39 and indicators of disease and inflammation activity, a correlation analysis was performed, the data of which are presented in Table 2.

Table 2: The results of the correlation analysis of CGP-39 and indicators of inflammation.

Variable	Correlation coefficient	p
DAS28	0,663	<0,001
C-reactive protein (CRP)	0,632	<0,001
Erythrocyte Sedimentation Rate (ESR)	0,505	0,009

As shown in the table and Figures 2 and 3, the analysis revealed statistically significant moderate direct correlations between CGP-39 and DAS28 (r=0.663, p<0.001), CRP (r=0.632, p<0.001), ESR (r=0.505, p=0.009).

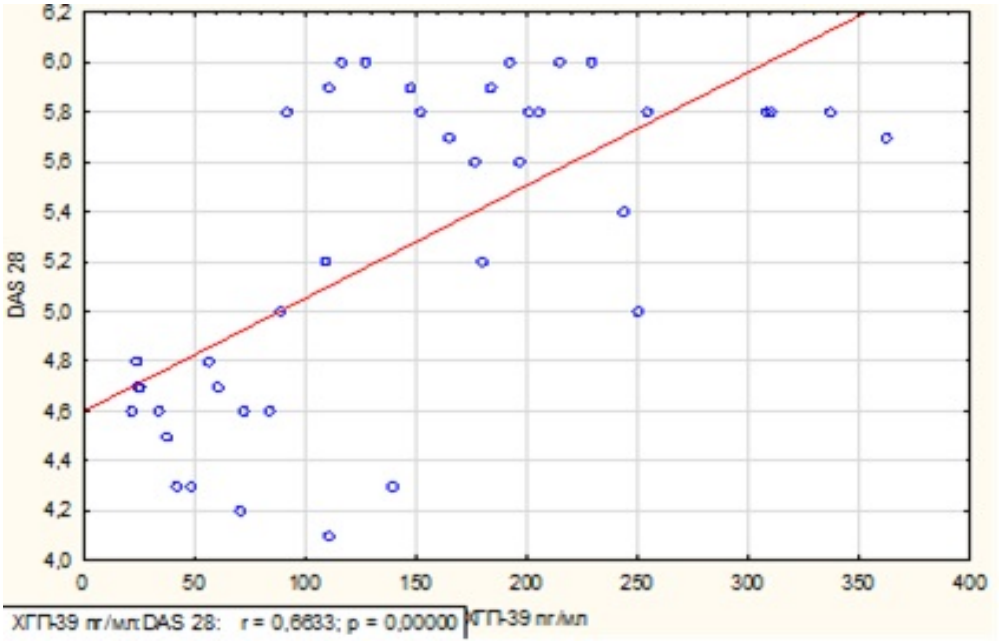

Figure 2: Correlation between HCG39 and DAS28 in patients with rheumatoid arthritis.m

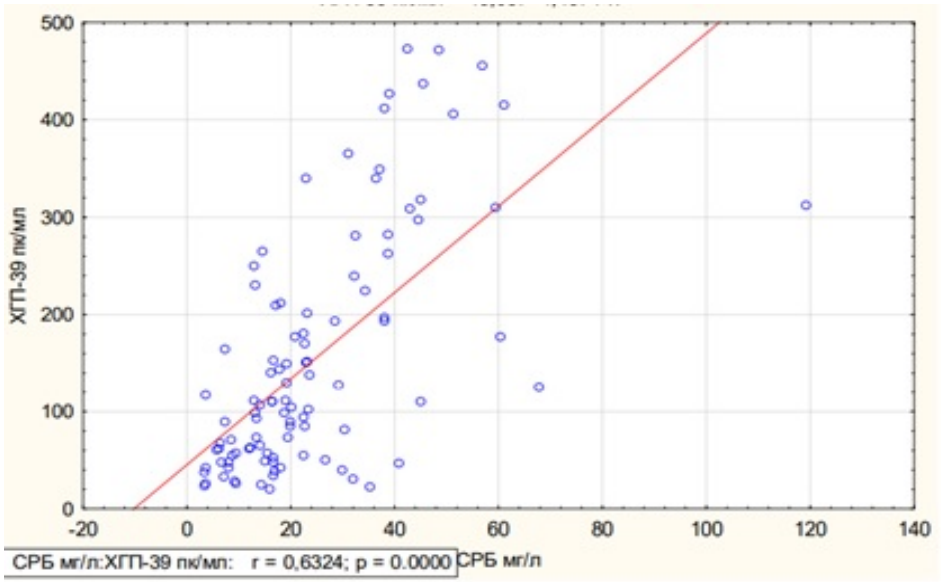

Figure 3: Correlation between HCG-39 and CRP in patients with rheumatoid arthritis

It is known from recent studies that cartilage glycoprotein-39 is an inflammatory protein expressed by cells with high metabolic activity, such as macrophages, synoviocytes, chondrocytes, neutrophils and oncocytes [12-14]. Elevated glycoprotein levels were detected in the blood serum of

patients with diseases such as osteoarthritis, chronic obstructive pulmonary disease, bronchial asthma, liver fibrosis, endothelial dysfunction - diseases based on chronic inflammation [15-18]. Researchers believe that CGP-39 plays a significant role in the processes of inflammation, tissue remodeling, promoting differentiation of macrophages, migration and adhesion of cells to the focus of inflammation [19-22]. Elevated concentrations of CGP-39 were found in the synovial fluid of patients with osteoarthritis [23]. In the same study, the concentrations of CGP-39 in the synovial fluid and in the blood serum of patients were compared, as a result, a direct correlation was revealed between the indicators, the higher the glycoprotein in the synovial fluid, the higher the values were determined in the blood serum.

4 Conclusion

The aim of our study was to study cartilage glycoprotein in RA patients and to evaluate its relationship with indicators of disease activity and rheumatoid inflammation.

As a result of our study, we found elevated concentrations of CGP-39 in RA patients, compared with the control group. And when conducting a correlation analysis of quantitative indicators, a statistically significant positive association of CGP-39 with disease activity (DAS28) was found. Therefore, positive correlations between CRP and ESR were found. Given the data obtained, it can be assumed that cartilaginous glycoprotein-39 plays the role of a pro-inflammatory agent in the pathogenesis of rheumatoid arthritis.

In the course of the study, it was revealed that the level of CGP-39 is statistically significantly higher in the blood serum of RA patients and directly correlates with the activity of the disease and laboratory indicators of inflammation, based on which we conclude that cartilage glycoprotein-39 can be used as an additional indicator of the activity of inflammation in RA to increase diagnostic informativeness.

5 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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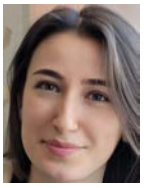
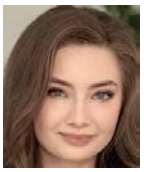


Tamara Alexandrovna Naldikoeva, Student of North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia-Alania, Russia

Aminat Turkoevna Abdulaeva, Student of the Chechen State University named after A.A. Kadyrov, Grozny, Republic of Chechnya, Russia

Aigul Rasulovna Gadzhieva, Student of North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia-Alania, Russia

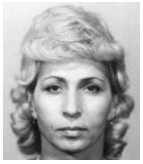
Anastasia Andreevna Volodikhina, Student of Stavropol State Medical University, Stavropol, Russia



Ekaterina Evgenievna Pugacheva, Student of Rostov State Medical University, Rostov-on-Don, Russia

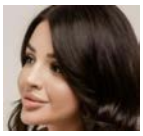
Salva Faekovna Dallo, Student of the Russian National Research Medical University named after N. I. Pirogov, Moscow, Russia

Madina Becsoltovna Bisultanova, Student of Saratov State Medical University named after V. I. Razumovsky, Saratov, Russia



Melavinka Agubechirovna Sozaeva, lecturer of North Ossetian State Medical Academy, Vladikavkaz, Republic of North Ossetia-Alania, Russia

Rinata Dzhanovna Aidarova, Student of Moscow State University of Medicine and Dentistry Named after A.I.Evdokimov, Moscow, Russia



Aida Muradovna Gadzhieva, Student of Dagestan State Medical University, Makhachkala, Republic of Dagestan, Russia