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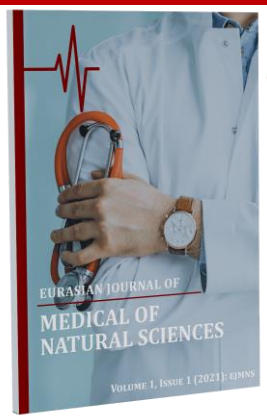

RELATIONSHIP BETWEEN ANEMIA AND HAPTOGLOBIN GENOTYPE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Despite the use of modern treatments for patients with RA, the incidence of anemia, unwanted complications, and disability in the working population remains very high. The purpose of the study is to improve the principles of proportional treatment, taking into account the structure of anemia in rheumatoid arthritis, its occurrence, and haptoglobin phenotypes. In 2016-2020, a total of 214 patients treated with a diagnosis of rheumatoid arthritis in the cardiorheumatology department of the Samarkand City Medical Association and 20 relatively healthy people as a control group were selected for the study. Examination of patients was carried out using generally accepted clinical, laboratory, and instrumental methods. Changes in iron metabolism parameters are observed in RA patients and are more pronounced in patients with anemia, and such changes depend on the degree of anemia.

ВЗАИМОСВЯЗЬ АНЕМИИ И ГЕНОТИПА ГАПТОГЛОБИНА У БОЛЬНЫХ РЕВМАТОИДНЫМ АРТРИТОМ

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ABSTRACT

несмотря на применение современных методов лечения больных РА, частота анемии, нежелательных осложнений и инвалидизации трудоспособного

Ревматоидный артрит (РА), анемия, гаптоглобин, ферритин, суставной синдром, полипатология, антитела к циклическому цитруллиновому пептиду (ААЦП)

населения остается очень высокой. Целью исследования является совершенствование принципов пропорционального лечения с учетом структуры анемии при ревматоидном артрите, ее встречаемости и фенотипов гаптоглобина. Для исследования в 2016-2020 годах было отобрано 214 пациентов, проходивших лечение с диагнозом ревматоидный артрит в кардиоревматологическом отделении Самаркандского городского медицинского объединения, и 20 относительно здоровых лиц в качестве контрольной группы. Обследование больных проводилось с использованием общепринятых клинических, лабораторных и инструментальных методов. Изменения показателей обмена железа наблюдаются у больных РА и более выражены у больных с анемией, причем такие изменения зависят от степени анемии.

Relevance. In the world, the study of the humoral and cellular immune system in rheumatoid arthritis is being carried out, which is aimed at improving the methods of diagnosis, treatment, and prevention in the early stages of this disease [1, 5, 14]. Several scientific studies have shown that rheumatoid arthritis is one of the main reasons for the widespread prevalence of anemia among the population. Determining haptoglobin phenotypes in patients is useful for early detection of disease complications, improving treatment and prevention methods, predicting the clinical course, as well as risk factors affecting severity, erosive joints. dedicated to revealing pathogenic mechanisms of destructive changes, substantiating comorbid conditions and their relationship with clinical manifestations [9, 11, 13]. It is of particular importance to improve the evaluation system of the relationship between the course of the disease and the severity of anemia in patients with rheumatoid arthritis and anemia with the haptoglobin phenotype, significant interactions between risk factors, comorbid conditions, clinical-biochemical and radiological manifestations [2, 4, 13].

The analysis of the literature shows that today the increase of RA disease among the population with high working capacity, the decrease of work capacity, the increase of the disability index, and the decrease in the quality of life of patients are one of the most urgent and not fully solved problems of rheumatology. The fact that the genetic aspects of RA are not fully studied and the early development of anemia, the lack of choosing the optimal method of treatment, and the combination of comorbid conditions make the disease severity indicator much more complicated [6, 8, 12]. Despite the use of modern treatments for patients with RA, the incidence of anemia, unwanted complications, and disability in the working population remains very high.

The purpose of the study is to improve the principles of proportional treatment, taking into account the structure of anemia in rheumatoid arthritis, its occurrence, and haptoglobin phenotypes.

Research materials and methods. In 2016-2020, a total of 214 patients treated with a diagnosis of rheumatoid arthritis in the cardiorheumatology department of the Samarkand City Medical Association and 20 relatively healthy people as a control group were selected for the study. All RA patients were divided into 2 groups based on hematological parameters: 50 (23.4%) patients without anemia, who constituted our control group; in the remaining 164 (76.6%) patients, anemia was determined according to hematological parameters, these patients formed the main group. The type and degree of anemia in RA patients was determined according to the classification recommended by WHO. SKA was observed in 94 (57.3%) patients, TTA in 65 (39.6%) patients, and in 5 patients (3.1%) both SKA and TTA occurred.

Examination of patients was carried out using generally accepted clinical, laboratory and instrumental methods. A general clinical blood test was performed. Fibrinogen and C-reactive protein indicators in the blood were studied in the "acute phase". Presence of rheumatoid factor (RO, latex agglutination reaction, ferritin, transferrin, free iron, haptoglobin amount and phenotypes) and instrumental (x-ray, UTT and MRI) tests were performed in groups.

Treatment was carried out according to the recommendations of the American Association of Rheumatologists and the standards developed by the Ministry of Health of the Republic of Uzbekistan. In the acute period of the disease, GCS pulse-therapy and non-steroidal anti-inflammatory drugs, methotrexate, delagil, leflunamide, sulfosalazine and others were given in standard doses.

When anemia was observed in RA patients, depending on the type and degree of anemia, erythropoietin (2000 TB was given subcutaneously 3-5 times a day in the hospital) and iron preparations (gynotordiferon, fercinol, venofer, irovir S) were prescribed. At home, it was recommended to take tablet forms of iron-retaining preparations for at least 1 month. Erythropoietin was administered in the above doses to patients with SKA, and in severe cases it was given together with iron preparations. Patients with TTA were prescribed tremir drugs, the form and amount of which depended on the degree of anemia.

Processing of the obtained data was analyzed using the Microsoft Excel software package of a personal computer and the "STATISTICA 6.0" software package. Descriptive statistics methods included arithmetic mean (M), mean error (μ) and mean squared deviation (s) of symbols with a normal distribution.

Results. Distribution of patients by age was carried out according to WHO recommendations. RA disease was not observed among patients under the age of 18, among patients aged 18-44 54 (29.3), 45-59 - 105 (57.1), and those over 60 - 25 (13.6 %) organized. The average age of RA patients was 49.46±0.80 years. As a result of studying the social status of patients, the following was revealed: 106 of them (57.6%) had a disability certificate, including 3 disabled persons of the 1st group, 102 of the second group, and 1 patient of the third group. It was determined that 2 patients are students, 13 are employed, 41 are temporarily unemployed, and 22 are pensioners. According to the address of the patients, 19 patients live in the districts of Samarkand region, and 195 live in the city of Samarkand.

Patients with disease duration up to 1 year were not included in the study group. The duration of RA was 1 to 5 years in 67 (31.3%) patients, and the disease duration was more than 5 years in 147 (68.7%). In our research, patients with a disease duration of more than 5 years prevailed. The average duration of the disease is 8.6±0.7 years.

When we describe RA by X-ray appearance, only 12 (5.6%) patients had I degree of joint damage, 118 (55.1%) had II degree, 79 (37%) had III degree, and 5 had IV degree. (2.3%) was observed in the patient. So, in the examined patients, mainly the second and third (92.1%) radiological stages of the disease were detected.

The distribution of patients according to BFB showed the following: grade 0 was observed in only 3 (1.4%) patients, grade I was observed in 17 (7.9%), grade II - 90 (42.1%), grade III - 91 (42.5%) and IV level - 13 (6.1%) patients. Rheumatoid nodules were found in 49 (22.9%) patients and indicate a continuous course of the disease. Therefore, mainly RA II and III levels (84.6%) were detected in RA BFB patients in our study. Among the functional disorders, 105 patients (49.1%) had high functional disorders according to the HAQ questionnaire, in addition, the number of patients with III-IV class of joint functional insufficiency was also high, making up 104 patients (48.6%).

When we analyzed comorbidities in RA patients, they were identified in 172 (80.4%) patients, and no comorbidities were identified in 42 (19.6%) patients. Among them, 36 (16.8%) patients had monopathology, 136 (64.6%) patients had 2 or more diseases. Different degrees of anemia were found in 164 (76.6%) RA patients participating in the study. Other related diseases were mainly cardiovascular diseases, chronic heart failure, and arterial hypertension. At the same time, deforming coxarthrosis and type 2 diabetes mellitus were detected in long-term RA patients. Toxic liver damage has been reported in patients treated with regular methotrexate.

The amount of hemoglobin, hematocrit, and erythrocytes in RA patients is statistically reliable 1.33 ($R<0.001$); 1.21 ($R<0.01$) and 1.34 ($R<0.001$) times decrease compared to standard indicators was observed. If there was a tendency to decrease these indicators in the comparison group, in the main group these changes were statistically reliable, 1.39 ($R<0.001$) compared to the normative indicators; 1.22 ($R<0.01$) and 1.37 ($R<0.001$) times lower. Similar changes were also observed in MCV, MCH, and MCHC indicators, indicating a decrease in morphological and hemoglobin saturation levels in erythrocytes. The number of leukocytes did not change much and remained within the normal range in all groups. However, a statistically significant increase in EC was observed in all groups.

In RA patients, haptoglobin, AACCP and SRO were statistically significantly 2.75 ($R<0.001$); An increase of 9.35 ($R<0.001$) and 6.51 ($R<0.001$) times compared to the healthy group was observed. In the comparison group, the increase of these indicators is 2.74 ($R<0.001$); 7.83 ($R<0.001$) and 6.23 ($R<0.001$) times were observed. The amount of haptoglobin, AACCP and SRO in the blood serum of RA patients with anemia was 2.75 ($R<0.001$); 9.83 ($R<0.001$) and 6.54 ($R<0.001$) times increased compared to the norm. It should be noted that the amount of haptoglobin and SRO in blood serum did not differ in all groups, although the amount of AACCP was 1.23 ($R<0.05$) times higher than the values of the group without anemia.

In patients with RA, the amount of free iron in the blood serum increased statistically significantly by 2.58 ($R<0.001$), ferritin by 1.53 ($R<0.01$), and transferrin by 1.19 ($R<0.05$).) times decreased. In the control group, iron content in blood serum decreased by 2.16 ($R<0.001$) times, ferritin content increased by 1.52 ($R<0.001$), while transferrin content did not differ from normal values. in patients in the main group, the amount of free iron in blood serum

decreased and was 2.65 (R<0.001) times lower than normal values. The amount of ferritin increased by 1.58 (R<0.001) times. The amount of transferrin in blood serum remained statistically reliable 1.22 (R<0.05) times lower. The free iron content was 1.23 (R<0.05) times lower than the comparison group, ferritin content was not significantly different, and transferrin content was 1.22 (R<0.05) times lower. Therefore, changes in iron metabolism parameters are observed in RA patients and are more pronounced in patients with anemia, and such changes depend on the degree of anemia.

Analysis of RA patients with anemia (base group) and without anemia (comparison group) by radiographic stage, radiographic stages 2, 3, and 4 were found in the main group (94.5%), and rheumatoid nodules in the joints were found in 40 (24.4%) patients. 10% of patients without anemia were found in patients.

Among people of Uzbek nationality, the haptoglobin phenotype Hp 2-1 (50.0%) predominates, while the frequency of Hp 1-1 and Hp 2-2 is 15.0 and 35% (Table 1). Frequency of Hp 1-1, Hp 2-1 and Hp 2-2 phenotypes in RA patients is 19.6; It was 55.4 and 25%, that is, the Hp 1-1 and Hp 2-1 phenotypes were slightly predominant, and the Hp 2-2 phenotype was less common. In addition, the Hp 1-1 phenotype is more common among female patients (ratio with males - 1: 5.5).

Table 1

Frequency of meeting haptoglobin phenotypes in RA patients

Groups	Hp 1-1		Hp 2-1		Hp 2-2	
	n	%	n	%	n	%
Healthy, n=20	3	15,0	10	50,0	7	35,0
General RA, n=214	36	19,6	102	55,4	46	25,0
RA, n=50	7	35,0	13	65,0	0	0,0
RA + anemia, n=164	29	17,7	89	54,3	46	28,0
RA +SKA, n=94	13	13,8	51	54,3	30	31,9
RA +TTA, n=65	15	23,1	37	56,9	13	20,0
RA +SKA+TTA, n=5	1	20,0	1	20,0	3	60,0

It should be noted that Hp 1-1 phenotype was found in 35% of RA patients without anemia, Hp 2-1 phenotype increased to 65%, and Nr 2-2 phenotype was not found. In patients with anemia, the Hp 1-1 phenotype was 2 times more frequent than in the above group, and the occurrence of the Nr 2-2 phenotype increased to 28%. In RA patients, Hp 1-1 phenotype was found in the lowest percentage (13.8%) in patients with SKA, compared to patients without anemia, the tendency of meeting Hp 2-1 phenotype was found to decrease, the number of patients with Hp 2-2 increased to 31.9%. In the group of patients with TTA, the number of patients with Hp 1-1 phenotype increased approximately 2-fold compared to patients with SKA, and the occurrence of Hp 2-2 phenotype increased to 20%. The highest incidence of this phenotype was observed in RA+SKA+TTA patient group (60%).

So, the phenotypic features of the organism of RA patients determine the tendency to develop anemia, and also make it possible to predict what type of anemia may develop.

When we analyzed the distribution of haptoglobin phenotypes according to the degree of anemia, Hp 1-1, Hp 2-1 and Hp 2-2 phenotypes were 20.3; We observed it in 61.0 and 18.6%. It

was found that the frequency of Hp 1-1 and Hp 2-1 phenotypes decreases, and Hp 2-2 increases as anemia becomes more severe. So, Hp 2-2 phenotype indicates severe anemia.

Studies have shown that the phenotypic characteristics of RA patients determine the predisposition to develop anemia, and predict the type of anemia that may develop. While the seropositive form of RA is mainly characterized by the Hp 2-1 and Hp 2-2 phenotypes of haptoglobin, patients with the Hp 2-2 phenotype are characterized by high activity and severe course of the disease according to DAS, but the level of biological functions of patients does not depend on the phenotype of haptoglobin.

Anti-inflammatory and anti-anemic treatments resulted in some improvement, but not normalization, of hematological parameters. The most positive results were observed when erythropoietin and iron preparations were used together. Antianemic treatment in RA patients was mainly observed in the 3rd and 4th degree of anemia. This, in our opinion, may be due to the use of erythropoietin in combination with iron preparations in such patients. In our opinion, the use of erythropoietin in combination with iron supplements is effective in the treatment of severe anemia in RA patients. However, it should be said that the phenotypic changes of patients do not significantly affect the fertility of erythropoietin and iron preparations.

Conclusions. 53.7% of RA patients have anemia of chronic diseases, 39.6% have iron deficiency anemia, and 3.1% have their co-occurrence. SKA is characterized by the aggravation of the main disease, profound changes in hematological indicators, and a decrease in the quality of life. Ferrokinetic changes were observed in RA patients, characterized by a decrease in the amount of free iron in the blood serum, an increase in transferrin and ferritin. The development of anemia in RA depends on the haptoglobin phenotype. SKA and its severity were higher in patients with Hp 2-2 and Hp 2-1, and anemia in Hp 1-1 phenotype was found to be characteristic of TTA type.

In addition to the complex treatment of RA patients, the use of anti-anemic drugs enhances their anti-inflammatory effect, allows achieving stable remission and improving the quality of life of patients.

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