Ferrokinetics in Patients with Rheumatoid Arthritis

Eshmurzaeva A.A. Tashkent Medical Academy

Sibirkina M.V. Tashkent Medical Academy

ABSTRACT

Rheumatoid arthritis (RA) is an inflammatory disease of the joints, the main symptom of which is the development of symmetrical synovitis with a tendency to destructive changes in the joints, which affects an average of 1-2% of the world's population. The study included 134 patients, which were divided into two groups I (n=70) - RA patients without anemia and II (n=64) - RA patients with anemia. The values of hemoglobin level, total iron-binding capacity (TIBC) of blood, ferritin level, and values of soluble blood transferrin receptors were assessed. The presence of anemia in patients with RA is accompanied by noticeable changes in the exchange of iron in the blood. The most pronounced changes in peripheral blood parameters and iron metabolism parameters were observed in patients with the articular-visceral form.

Keywords: Rheumatoid arthritis, anemia, hemoglobin, ferritin, total iron-binding capacity (TIBC), values of soluble transferrin receptors

Rheumatoid arthritis (RA) is an inflammatory disease of the joints, the main symptom of which is the development of symmetrical synovitis with a tendency to destructive changes in the joints, which affects an average of 1-2% of the world's population. Along with inflammatory changes in the joints, extra-articular manifestations develop in 40% of patients [1, 2]. One of the most common comorbid manifestations of rheumatoid arthritis is anemia.

The prevalence of anemia in RA, according to epidemiological studies, ranges from 30 to 70% [4, 5]. The adverse effects of anemia in RA include a deterioration in the quality of life, an increase in the frequency of visceral lesions, the risk of complications when using certain basic drugs, and many others. According to the literature, the severity of anemia correlates with the activity of the underlying disease and is characterized by a reduced proliferative activity of the bone marrow and a reduction in the lifespan of erythrocytes [6,7].

The factors for the development of anemia in RA are diverse, which can be both the impact of the main autoimmune process and the influence of other causes [8,9]. There are reports of a decrease in the level of vitamin B12 and folic acid, the most important factors of erythropoiesis, in 24–29% of patients with RA [10,11].

It is known that anemia in patients with RA, who are often hospitalized due to the high activity of the disease, is recorded in half of the cases [3]. However, in the study of this phenomenon, there are many insufficiently studied aspects that require special analysis. Among such unresolved issues are: the study of the effect of RA activity on the development of anemia; study of the effect of anemia on various clinical and laboratory indicators of RA activity; study of the possibility of complex use of hematological and clinical-laboratory

parameters for early diagnosis of unfavorable course of RA associated with the development of anemia. The solution of the above aspects of the association of the features of the course of RA in patients with anemia syndrome formed the basis of this study.

To study the relationship between anemic syndrome and indicators of inflammation activity in patients with rheumatoid arthritis, a comparative study of the activity of rheumatoid inflammation in patients of opposite groups (RA patients with and without anemia) was carried out.

Material and methods. The study included 134 adults (combined general group) unrelated patients who were hospitalized at the 3rd clinic of the Tashkent Medical Academy with a diagnosis of RA, verified according to the criteria of ACR/EULAR (2010). In order to comply with ethical standards, informed consent to participate was obtained from all persons included in the study.

All patients, depending on the presence of anemia, were divided into two groups I (n=70) - RA patients without anemia and II (n=64) - RA patients with anemia.

The characteristics of the examined patients are presented in Table. 1.

Table 1.
Characteristics of the examined patients

Indicators	RA patients with anemia	RA patients without anemia
Number of patients, pers.	70	64
Gender (male/female)	6/64	13/51
Age (years) Under 20 20-30 31-40 41-50 51-60 61-70 over 70	 0 2 (2,8%) 12(17,1%) 11 (15,7%) 22 (31,4%) 13(18,6%) 0	 1(1,5%) 3 (4,7%) 7 (10,9%) 12 (18,8%) 25(39,0%) 12 (18,8%) 4 (6,2%)
Duration of illness (years) Under 1 1-5 5-10 10-15 Over 15	 2 (2,8%) 14 (34,3%) 15 (21,4%) 6 (15,7%) 12 (27,1%)	 2 (3,1%) 27 (42,2%) 14 (21,9%) 5 (7,8%) 16 (25,0%)
Degree of RA activity: I II III	 6 (8,6%) 45 (64,3%) 19 (27,1%)	 10 (15,6%) 47 (73,4%) 7 (10,9%)
Flow rapidly progressive slowly progressive	 1 (1,4%) 69 (98,6%)	 0 64 (100%)
Articular form Articular-visceral	42 (60,0%) 28 (40,0%)	58 (90,6%) 6 (9,4%)

The values of hemoglobin level, total iron-binding capacity (TIBC) of blood, ferritin level, and values of soluble blood transferrin receptors were assessed.

The method for determining serum iron using a set of reagents from La Hema Bio-La-Test "Zhelezo" (Czech Republic), the level of soluble transferrin receptor was determined on an automatic ELISA analyzer by enzyme-linked immunosorbent assay, using a set of "BioKhimMak" (Russia).

The data obtained were statistically processed using the OpenEpi 2009, Version 9.3 software package.

Results and discussion.

To determine the number of affected joints and the severity of the inflammatory process in them, the following were used: joint score, the results of assessing the intensity of pain in the joints (by the patient) were analyzed using visual analogue scales (VAS), the duration of morning stiffness was also determined, and the degree of activity in terms of Disease Activity Score 28 (DAS28). To assess the nature of the course of RA, we used generally accepted criteria for assessing the severity of the course of this disease.

The results of these studies are presented in Table 2.

Table 2. Initial data of the studied parameters in RA patients with and without anemia

Indicators	RA patients with anemia n=64	RA patients without anemia n=70
Pain level according to VAS (cm)	6,39 ±0,48	5,18 ±0,35 *
Number of painful joints	19,63 ±0,81	11,49±0,64 *
Number of swollen joints	11,49 ±0,24	8,05 ±0,38 *
Morning stiffness (min)	111,28±5,4 9	63,58 ±4,21*
ESR, (mm/h)	45,7 ±2,75	30,7 ±2,238*
DAS28	3,6±0,25	4,9±0,35*

Note: * - significance of the difference P <0.05

Analyzing the clinical picture of the articular syndrome in patients with RA, we drew attention to the fact that all examined patients had pain syndrome at the time of admission to the clinic, which, according to the pain index, was 5.18 ± 0.35 in the group of RA patients without anemia, in patients with rheumatoid arthritis associated with anemia 6.39±0.48. As can be seen from the results obtained, before the start of treatment, in the group of RA patients with anemia, there was a statistically significant increase in the level of pain assessed by VAS by 19% (p <0.05).

Similar changes in the severity of RA in the presence of anemia were found when assessing such indicators as: the total number of painful (p <0.05) and swollen joints (p <0.05). Thus, in patients with RA associated with anemia, compared with RA patients without anemia, the number of painful joints exceeded by 41.5%, swollen joints by 30%.

As follows from the analysis of the obtained data, in the group of RA patients with anemia, there was a significantly longer duration of morning stiffness (p <0.05) by 43%.

Similar differences took place with respect to the DAS28 index. This indicator was significantly higher in RA patients with anemic syndrome. Therefore, according to the specified criteria, RA patients with anemia have a greater severity of the inflammatory process. This is confirmed by laboratory data, in particular, the ESR, which was significantly (p <0.05) higher by 32.8% in RA patients with anemia (Table 2).

At the same time, there was no clearly proven relationship between anemia and the radiological stage; in the comparison groups, this indicator did not have statistically significant differences. At the same time, the articular-visceral form of rheumatoid arthritis was 2.7 times more common in RA patients with anemic syndrome.

In the course of the study, we obtained results confirming the close relationship between the clinical manifestations of RA and

disorders in the state of the erythroid germ of hematopoiesis, namely with the development of anemia.

The analysis of the indicators of the general blood test showed the presence of registration of anemia in terms of the level of hemoglobin and erythrocytes in both groups of patients with RA. In particular, among patients with the articular form of RA, the hemoglobin level ranged from 78 to 110 g/l, with an average value of 97.3 ± 5.7 g/l. Among patients with visceral manifestations of RA, this indicator was in the range of 72–94 g/l, with a median of 89.4 ± 5.8 g/l (Table 3).

As can be seen from the data presented in Table 1, in patients of both groups with RA, there is a clear trend towards a decrease in the content of blood erythrocytes (RBC), which in terms of severity corresponds to the level of hemoglobin in the blood (group 1 - 3.87±0.27 x106/ml; 2 - group - 3.36±0.25 x106/ml). A similar picture can be traced in relation to the average volume of erythrocytes (MCV). At the same time, the value of the latter in patients with RA in the 1st group (86.1±3.19 fl) practically does not differ from the reference values (88.4±3.56 fl), while in patients in the 2nd group it turned out to be lower than the reference values by 8.5% (80.91±5.73 fl). Consequently, as the level of hemoglobin in the peripheral blood decreases, the number of small erythrocytes increases.

In conditions of RA with anemia in the peripheral blood, not only the appearance of small erythrocytes takes place, but also an increase in erythrocytes with a smaller amount of hemoglobin. Thus, in patients with RA of the 2nd group, there is a decrease in the average volume of hemoglobin in erythrocytes (MSV) by 14% (24.96±2.01 pg). Along with this, there is a tendency to reduce the average concentration of hemoglobin in erythrocytes (MCHC) from 331.86±6.78 pg in the control to 326.6±8.24 pg in the 1st group and 318.0±11.23 pg in the 2nd group. th group of patients with RA.

Table 3.
Parameters of the general blood test in patients with rheumatoid arthritis

Indicators	Reference values	Patients with RA with articular form, n=42	Patients with RA with articular-visceral form, n=28
Hb, г/л	129,6 ± 3,5	97,3 ± 5,7	89,4 ± 5,8
RBC (x10^6/мл)	4,51±0,31	3,87±0,27	3,36±0,25
MCV (фл)	88,4±3,56	86,1±3,19	80,91±5,73
MCH (пг)	29,01±0,89	28,63±1,81	24,96±2,01
MCHC (пг)	331,86±6,78	326,6±8,24	318,0±11,23
RDW (%)	11,9±0,51	12,10±1,07	15,6±0,43*
ЦП	0,95±0,5	0,8±0,5	0,75±0,5

It should be noted that in patients with RA, along with a change in the qualitative characteristics of erythrocytes, changes are also noted in the indicator of the calculated width of the erythrocyte distribution curve. At the same time, the values of the latter increase in comparison with the reference values, in the presence of more pronounced anemia in the 2nd group by 31.1% (15.6±0.43%). Consequently, the severity of anemia in patients with RA is manifested by the most noticeable qualitative and quantitative changes in peripheral blood erythrocytes, reflecting iron deficiency in the blood serum.

An important laboratory sign of IDA is a low color index (hypochromia), which, as a

rule, is clearly manifested when the hemoglobin level decreases in the 2nd group (0.75±0.5 against the reference values - 0.95±0.5). However, in the initial stages of anemia development, this indicator is often within the normal range, and in this regard, this indicator cannot be used for early diagnosis of anemia.

Along with changes in the general blood test, a slight decrease in serum iron was found to 22.63±1.01 μmol/l in the 1st group and to 18.23±1.35 μmol/l in the 2nd group of patients with RA. Therefore, under the conditions of the studied pathology, there is an iron deficiency in the blood, which is most pronounced among patients with articular-visceral manifestations of the disease, which is possibly associated with the redistribution of iron in the body or its use for other needs of the body, due to the development and progression of the pathological process (table 4).

Table 4.

Ferrokinetic parameters in patients with rheumatoid arthritis

Indicators	Reference values	Patients with RA with articular form, n=42	Patients with RA with articular-visceral form, n=28
Serum iron (μmol/l)	24,7±2,01	22,63±1,01	18,23±1,35
Total iron-binding capacity (TIBC) (μmol/ml)	66,91±5,05	68,94±4,31	74,56±4,78
Ferritin (ng/ml)	87,6±4,78	106,4±1,56*	98,9±2,07
Soluble transferrin receptor (ng/ml)	1,89±0,12	2,13±0,12	4,63±0,21*

*Note: *- significant difference P <0.05*

The study of the value of the total iron-binding capacity (IBC) of the blood shows (table 2) that as the concentration of hemoglobin in the blood decreases, its value increases. So, if in patients with RA of the 1st group, the value of FBC does not change significantly (68.94±4.31 μmol/l) compared with the reference values (66.91±5.05 μmol/l), then in patients with RA during In the 2nd group, the level of TIBC increases to 74.56±4.78 μmol/L. Therefore, under the conditions of the studied pathology, there is an increase in the ability of serum to bind iron. Apparently, this is aimed at compensating for iron deficiency in the blood of RA patients.

Given the variability of some indicators of iron metabolism, many authors recommend using a set of studies that include a number of indicators, in particular, serum ferritin, for a more accurate diagnosis of iron deficiency. The analysis of the obtained results, as can be seen from the data presented in Table 2, revealed an increase in the level of ferritin in patients with RA, both in the 1st (98.9±2.07 ng/ml) and in the 2nd group (106.4±1. 56 ng/ml) of patients with RA. At the same time, compared with the reference values, the level of serum ferritin in the 1st group of patients becomes higher by 12.9%, and in the 2nd group it increases by 21.5%, respectively. If we take into account that ferritin belongs to the acute-phase proteins of inflammation, then it becomes obvious that its level increases in conditions of RA, which is a chronic inflammatory pathology of the joints of an autoimmune nature. Along with an increase in the blood content of ferritin in the examined patients, there are noticeable changes in the value of soluble transferrin receptors, the value of which increases as the level of hemoglobin in the blood decreases. So, if in patients of the 1st group its value exceeds the reference level by 12.7% (2.13±0.12 ng/ml), then in patients of the 2nd group l - by 1.5 times (4.63± 0.21 ng/ml). Therefore, as

anemia worsens in patients with RA, the affinity of receptors for transferrin also sharply increases.

Thus, the results of the conducted studies allow us to conclude that anemia in RA conditions is characterized by manifestations not only of qualitative and quantitative changes in blood erythrocytes, but also by violations of iron metabolism in the body, as an indicator of impaired absorption of iron, reflecting the response of iron-consuming cells to its developed deficit.

Thus, based on the results obtained, a reasonable conclusion can be made about a more severe course of RA in patients with anemia.

We have analyzed the effectiveness of traditional therapy in patients with RA without anemia and in patients with RA associated with anemic syndrome.

Clinical manifestations of rheumatoid arthritis in the patients examined by us were evaluated 10 days after the start of treatment (Table 10). At the same time, it was found that in patients with RA without anemia, the level of pain according to VAS, compared with the baseline, decreased by 38.2%. In RA patients with anemia, this indicator decreased by 15.5%. The number of painful joints, compared with the values before treatment, decreased in RA patients without anemia and with anemia by 45.2% and 26.2%, respectively. A more pronounced decrease in the number of swollen joints was noted in the group of RA patients without anemia. In this group, after treatment, a decrease in the studied indicator by 44.1% was observed, in patients with RA associated with anemia, the number of swollen joints decreased by 21.2%. Similar dynamics can be traced in relation to other criteria for the activity of the articular process. This is confirmed by the dynamics of the duration of morning stiffness, the ESR index and the DAS28 index (Table 5).

Table 5. Dynamics of controlled parameters in patients with RA on the background of traditional therapy

Indicators	RA patients without anemia n=64		RA patients with anemia n=70	
	Before treatment	After treatment	Before treatment	After treatment
Pain level according to VAS (cm)	5,18 ± 0,35	3,2 ± 0,33*	6,39 ± 0,48	5,4 ± 0,35*
Number of painful joints	11,49±0,64	6,29±0,54*	19,63 ±0,81	14,49±0,64*
Number of swollen joints	8,05 ±0,38	4,5 ±0,31*	11,49 ±0,24	9,05 ±0,38*
Morning stiffness (min)	63,58 ±4,21	33,58 ±2,21*	111,28±5,4 9	63,58 ±4,21*
ESR, (mm/h)	30,7 ±2,238	20,7 ±2,238	45,7 ±2,75	30,7 ±2,238*
DAS28	3,6±0,25	2,8±0,25	4,9±0,35	3,6±0,25*

Note: * - significance of the difference P <0.05

Therefore, during this period of observation, there is a clear trend towards a greater regression of the clinical manifestations of RA against the background of traditional therapy in RA patients without anemia.

Considering that the main manifestation of the body's response to the inflammatory process is pain, we analyzed the dynamics of the pain syndrome in patients with RA, depending on the presence or absence of an anemic syndrome. At the same time, we paid attention to such characteristics of the pain syndrome as the index and intensity of pain. The results of the analysis are shown in Figure 5.

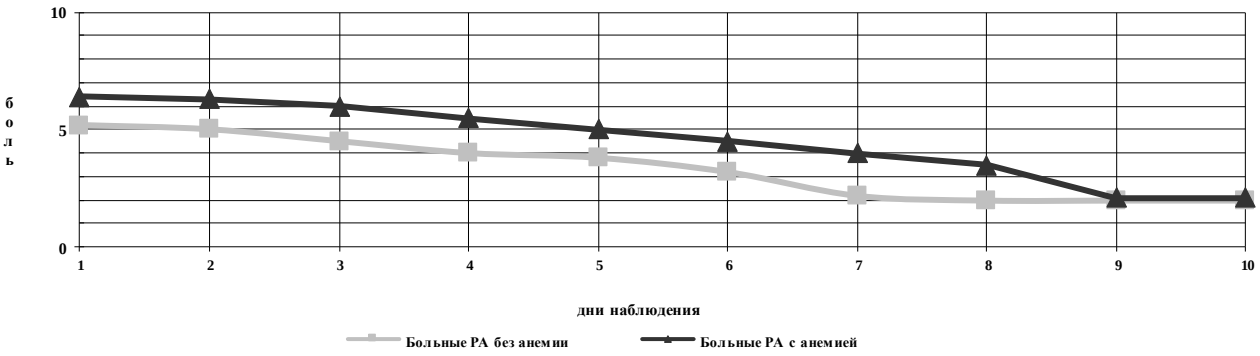

Figure 5. Dynamics of pain syndrome repression in patients with and without anemic syndrome

As can be seen from the data presented in Figure 1, the dynamics of pain level indicators according to VAS in the studied groups has some differences. Thus, in patients with RA associated with anemia, a noticeable decrease in pain sensation begins from the 5th day of treatment, and in patients with RA without anemia, from the 3rd day (Fig. 1). In addition, the pain level recorded by us at the end of the observation period (10 days) in the group of RA patients without anemia reached this value on the 7th day of observation, in RA patients with anemia on the 9th day. Therefore, the analysis of the dynamics of pain in patients with RA against the background of ongoing treatment indicates that in the group of patients with RA without anemia, there is a tendency to earlier repression of the pain syndrome, compared with the group of patients with RA associated with anemia.

The study of the intensity of the pain syndrome in the examined groups of patients also indicates the presence of certain differences in these groups. However, after the treatment, certain differences were found in the groups according to the studied indicator. At the same time, the pain syndrome actually disappeared in 21% of RA patients without anemia. At the same time, the proportion of patients with no pain in patients with RA associated with anemia is 13%.

By the end of the observation period in all the studied groups, the proportion of patients with minor and moderate pain were actually comparable and occurred in every third and fourth patients, respectively. Consequently, a decrease in the proportion of patients with a severe degree of pain syndrome prevailed in the group of RA patients without anemia compared with RA patients with an anemic syndrome.

Conclusion. Thus, based on the results obtained, a reasonable conclusion can be made about a more severe course of RA in patients with anemia.

Under conditions of RA, the features of the manifestations of anemia in the peripheral blood are a decrease in the concentration of hemoglobin, the number of erythrocytes, a color index, the appearance of small erythrocytes in volume and an increase in erythrocytes with a low hemoglobin volume, which also indicates a violation of hemoglobin synthesis in the bone marrow of patients. In addition, the presence of anemia in patients with RA is accompanied by noticeable changes in iron metabolism, reflecting iron deficiency in the blood serum. Meanwhile, it is important to note that the most pronounced changes in both peripheral blood parameters and those reflecting iron metabolism were recorded in patients with the articular-visceral form. The severity of these changes in this group of RA patients is associated with the aggravation of the underlying pathological process, which spreads not only in the area of the joints, but also beyond.

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