INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

Dynamics of Ferrokinetics Parameters in Patients With Rheumatoid Arthritis Associated With Helicobacter Pylori Infection on the Background of Complex Treatment Including Iron Preparations

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Abstract: Despite certain advances in understanding the pathogenesis and developing new therapeutic approaches for rheumatoid arthritis (RA), achieving stabilization of its clinical course remains challenging. The presence of comorbid conditions such as anemia and gastroduodenal involvement poses a significant risk to patients' lives and entails substantial financial costs for the treatment and prevention of RA. Modern rheumatology pays special attention to the early detection of diseases. Currently, there is evidence that the preclinical period of systemic autoimmune reaction is associated with dysregulation of immune interactions with synanthropic microflora. This article discusses the disturbances in ferrokinetics in patients with rheumatoid arthritis associated with iron-deficiency anemia and H. pylori, as well as the results of correcting the anemic syndrome with iron preparations.

Keywords: rheumatoid arthritis, anemia, ferrokinetics, Helicobacter pylori, intestinal microbiota, iron preparations.

As it is known, one of the main factors determining the social burden of diseases, especially chronic ones, is their prevalence in the population. According to several authors, the prevalence of rheumatoid arthritis (RA) in the population reaches 1%, accounting for 10% of all rheumatological diseases, and the economic losses to society are comparable to those from ischemic heart disease [1,4] (Balabanova RM, Kashevarov RY, Olyunin YA, et al., 2006). RA is characterized by extreme heterogeneity and a range of extra-articular manifestations. Anemia is one of the most common extra-articular manifestations of RA [2]. According to the literature, anemia develops in approximately 30-70% of patients with RA [3, 7]. According to S. Agrawal et al. [8], in a study of 214 patients with rheumatoid arthritis (RA), anemia was diagnosed in 71% of cases, with iron-deficiency anemia (IDA) developing in 48% of patients. In another study (Tandra M., 2010), anemia was registered in 85% of patients with RA, 60% of whom had IDA. However, anemia in patients with RA can have various origins [9]. More often, anemia of chronic disease (ACD) is diagnosed - in 25-64% of cases [5,6,10], which can be considered a systemic manifestation of RA, as it is a consequence of the inflammatory process, and the severity of anemia is directly related to the degree of disease activity [11].

The second most common cause of decreased hemoglobin in patients with RA is iron-deficiency anemia (IDA) [12,13,14]. Iron-deficiency anemia (IDA) develops and is found in 36-48.4% of patients with RA [10]. The characteristic features of current RA, established in our study, are not only a high frequency of anemia but also involvement of the gastroduodenal zone (GDZ).

According to global health statistics, pathology of the gastrointestinal tract organs is detected in 13-62% of patients suffering from RA. The nature of pathological changes in the digestive organs in RA patients is not only due to the manifestation of rheumatoid vasculitis, which contributes to endothelial dysfunction [15], based on immune disorders, but also to the damaging effects of Helicobacter pylori

infection. The aforementioned changes indicate the role of H. pylori in the pathogenesis of anemic syndrome in RA patients. At the same time, it is known that dysbiotic changes in the gastrointestinal tract as a whole, and in its individual sections, have a noticeable impact on the digestive process, disrupting the absorption of nutrients, including iron. In addition, according to several studies, Helicobacter pylori is considered a virulent agent that absorbs and utilizes a significant amount of iron for its life activities [16, 17] (Baysoy G., Ertem D., Ademoglu E., Kotiloglu E., Keskin S., Pehlivanoglu E., 2004; Roviello F., Fotia G., Marrelli D., De Stefano A., Macchiarelli R., Pinto E., 2004).

The possibility of direct lysis of cells under the influence of produced urease and mucinase, with extraction of iron from the macroorganism (human), digestion of hemoglobin, and assimilation of heme with the formation of siderophores, allowing the extraction of iron from the macroorganism, cannot be excluded.

This circumstance served as the basis for studying ferrokinetics indicators in RA patients with anemia, taking into account the colonization of the stomach by Helicobacter pylori, as well as studying their negative impact on treatment outcomes.

Research objective: To study disturbances in ferrokinetics in patients with rheumatoid arthritis associated with iron-deficiency anemia and H. pylori, and the degree of their correction with iron preparations.

MATERIALS AND METHODS: In our study, among patients with RA, women predominated - 54 (80.6%), with a mean age of 55.7±15.0 years, and a mean disease duration of 10.9±9.4 years. The RA group consisted mainly of patients with moderate disease activity, I-III radiographic stage of the disease, and the II degree of functional impairment. Systemic manifestations of the disease were rare, predominantly rheumatoid nodules. The most common complication was systemic osteoporosis. The overall activity of RA was assessed using the Disease Activity Score (DAS28), calculated using the formula: $DAS28 = 0.56 \times \sqrt{(TJC28)} + 0.28 \times (SJC28) + 0.70 \times \ln(CRP) + 0.014 \times GH$. The use of the DAS28 index as a baseline method for assessing disease activity was recommended during the development of the classification of RA at the meeting of the Russian Association of Rheumatologists (ARR) in 2007. Disease activity is considered high with DAS28 > 5.1, moderate with DAS28 between 3.2 and 5.1, low with DAS28 between 2.6 and 3.2, and remission with DAS28 < 2.6. All patients underwent clinical blood analysis, fibrinogen determination, C-reactive protein (CRP) measurement, and iron metabolism parameters were assessed: serum iron, transferrin saturation, soluble transferrin receptor, and ferritin. The concentration of serum iron and the total iron-binding capacity of serum were determined using the "Mindray" semi-automatic biochemical analyzer, using "HUMAN" kits (Germany).

The complete blood count analysis was performed using the "Sysraex KX-2 IN" analyzer, which measured hemoglobin levels, erythrocyte count, erythrocyte indices (MCV and MCH), platelet count, leukocyte count, and ESR. The leukocyte differential count and reticulocyte level were also evaluated. Radiography of the clinically most affected joints was performed in all RA patients to determine the stage of RA according to Steinbrocker. To exclude visceral involvement, additional tests such as ECG, chest X-ray, urinalysis, abdominal ultrasound, upper gastrointestinal endoscopy, and immunological determination of H. pylori were performed if necessary. All patients were divided into two groups. The first group consisted of RA patients with anemia (38), and the second group consisted of RA patients with anemia associated with H. pylori infection (32). The groups were comparable in terms of gender, age, clinical characteristics of the underlying disease, and severity of anemia.

RA patients with hemoglobin levels below 110 g/L were included in the standard treatment for the studied pathology, which included a 3-valent iron-containing iron supplement - Ferlatum, at a dose of 80 mg per day for 60 days.

The results of the study were statistically analyzed using standard methods of variation statistics, applying the t-test using the "Excel Office 2010" software on a Pentium IV computer.

Results and discussion:

We examined the indicators of ferrokinetics in patients with rheumatoid arthritis (RA) and anemia, taking into account the presence of Helicobacter pylori infection in the stomach. The results of these studies are presented in Table 1.

Table 1: Indicators of ferrokinetics in patients with rheumatoid arthritis and anemia depending on the presence of Helicobacter pylori infection

Indicator	Control n=14	Patients with RA Нв<110 g/l	Patients with RA Нв<110 g/l
		H.p.assotiated n=32	H.p. not associated n=38
RBC (1x10^6/ml	4,51±0,31	4,08+0,24	4,19+0,34
MCV (fl)	88,4±3,56	80,9+5,73	80,32+7,01
MCH (pg)	29,01±0,89	24,9+2,01	25,23+1,56
MCHC (pg)	33,18±6,78	31,80 +11,23	32,6+9,55
RDW (%)	11,9±0,51	15,6+0,43	14,67+0,73
Erythrocyte morphology	normal	Moderate hypochromia	Moderate hypochromia
Serum iron (mkm/l)	24,7±2,01	20,2+1,47	21,86+1,83
Total iron-binding capacity (TIBC) (mkm/ml)	66,91±5,05	75,9+4,86	71,56+ 4,78
Ferritin (ng/ml)	87,6±4,78	107,4+7,61	100,4 +1,56
Soluble transferrin receptor (ng/ml)	1,89±0,12	4,63+0,21	3,98+0,31
C-reactive protein (mg/l)	5,01±0,44	8,81+1,04	6,18+0,45

Note: * - significance of difference P<0.05

As evident from the presented data, patients with rheumatoid arthritis (RA) and anemia experience certain changes in iron transport and absorption depending on the presence of Helicobacter pylori in the stomach. While the iron content in the blood is lower in both groups of patients compared to the control group, it is 8% lower in the group with Helicobacter pylori infection compared to the group without the infection. Therefore, the presence of Helicobacter pylori contributes to an even greater iron deficiency in the blood. Similar, but more pronounced, shifts are observed in terms of total iron-binding capacity (TIBC). In the group of RA patients without Helicobacter pylori, the TIBC value is 7% higher compared to the control, while in the group of RA patients with Helicobacter pylori, it is 13.4% higher, respectively.

The level of blood ferritin undergoes significant shifts in the presence of Helicobacter pylori in patients with RA. The values of ferritin become 22.6% higher than the control and 7% higher compared to the group of RA patients without Helicobacter pylori, respectively. Identical shifts are observed in relation to soluble transferrin receptor and C-reactive protein (Table 12). Therefore, the presence of Helicobacter pylori in the gastric mucosa has a negative impact on the iron content and its transport in the blood of RA patients, contributing to the severity of anemia.

The study of the qualitative and quantitative characteristics of blood erythrocytes under the conditions of Helicobacter pylori presence was of particular interest to us. Since the presence of this pathogen in the gastric mucosa, by increasing the iron deficiency in the blood, contributes to the strained work of the blood's iron transport system, it is evident that there is a likelihood of certain changes occurring in the blood erythrocytes as well. As can be seen from the data presented in Table 1, the colonization of the gastric mucosa by Helicobacter pylori in patients with RA (Rheumatoid Arthritis) leads to the emergence of certain shifts in the morphology of erythrocytes. Meanwhile, the deficiency of erythrocytes in the peripheral blood becomes comparatively pronounced. The mean corpuscular

volume (MCV) and the volume of hemoglobin in it (MCH) become even smaller. Similar shifts are also observed in the concentration of hemoglobin in the erythrocytes (MCHC). However, these differences are not statistically significant (Table 1). Nevertheless, they indicate the presence of a negative trend concerning the morphological characteristics of erythrocytes and the necessity to consider these shifts and seek ways for their correction.

Thus, the results of the conducted research indicate the presence of certain disturbances in the ferrokinetics parameters in patients with RA, which become more pronounced as the level of blood hemoglobin decreases. The presence of Helicobacter pylori in the gastric mucosa of patients with RA has a negative effect on the iron content and its transport and exacerbates anemia, which undoubtedly points to the necessity of considering these shifts and seeking ways for their correction.

Since the presence of helicobacteriosis in the stomach exacerbates the course of anemia in patients with RA, we were particularly interested in studying the ferrokinetics parameters in patients with RA with anemia associated with Helicobacter infection during dynamic comprehensive treatment, including iron supplementation. The results of these studies are presented in Table 2.

As can be seen from the data presented in the table, in patients with RA associated with Helicobacter infection, the initially disturbed ferrokinetics parameters undergo noticeable shifts during the treatment.

Despite the therapy with an iron supplement, the level of iron in the blood does not significantly change by the end of the first month of treatment compared to its baseline value. By the end of the second month, it even begins to decrease. At this observation period, the latter's value becomes 23% lower than in the control. Therefore, under the conditions of helicobacter invasion, in the patients we studied, even the use of iron supplements does not lead to the normalization of the blood iron level.

Along with the decrease in iron content in the blood in the study group, there is a tendency to increase the total iron-binding capacity (TIBC). Apparently, this is a manifestation of a compensatory reaction aimed at replenishing the iron deficiency in the blood.

In the study group, during the dynamic treatment, there is a further increase in the level of ferritin in the blood (Table 2). At the same time, the level of the latter exceeds the control by 26.2% after two months of therapy. To a greater extent, during this observation period, the values of the soluble transferrin receptor change. Thus, the value of the latter by the end of the observation period becomes 2.2 times higher than the control. Therefore, the shifts in the iron transport parameters in the blood we identified once again confirm the negative impact of Helicobacter invasion on the course of anemia, the clinical-laboratory manifestations of which, despite treatment with iron supplements, not only do not improve but even worsen.

Table 2 Ferrokinetics parameters in patients with rheumatoid arthritis associated with Helicobacter infection during dynamic comprehensive treatment.

Indicator	Control n=14	Patients with RA Нв<110 g/l n=32		
		Before treatment	After treatment	
			After 1 month	After 2 months
RBC (1x10^6/ml	4,51±0,31	4,08+0,24	3,68+0,26	3,88+0,22
MCV (fl)	88,4±3,56	80,9+5,73	78,65+6,51	78,98+5,49
MCH (pg)	29,01±0,89	24,9+2,01	25,12+2.01	25,83+1,63
MCHC (pg)	33,18±6,78	31,80+11,23	32,23+9,02	32,84+8,76
RDW (%)	11,9±0,51	15,6+0,43	15,24+0,73	14,08+0,78

Erythrocyte morphology	normal	Moderate hypochromia	Moderate hypochromia	Moderate hypochromia
Serum iron (mkm/l)	24,7±2,01	20,2+1,47	20,93+1,73	19,04+1,56
Total iron-binding capacity (TIBC) (mkm/ml)	66,91±5,05	75,9+4,86	76,4+6,01	77,01+6,54
Ferritin (ng/ml)	87,6±4,78	107,4+7,61	109,3+8,01	110,6+7,61
Soluble transferrin receptor (ng/ml)	1,89±0,12	4,63+0,21	4,24+0,32	4,09+0,24
C-reactive protein (mg/l)	5,01±0,44	8,81+1,04	5,54+0,46	5,13+0,51

Note: * - significance of differences P<0.05

Indeed, the study of the qualitative and quantitative characteristics of peripheral blood erythrocytes, as seen from Table 24, shows that against the background of comprehensive treatment including an iron supplement in patients with RA associated with Helicobacter infection, negative shifts are observed. At the same time, the content of blood erythrocytes decreases by 10% compared to the baseline by the end of the 1st month of treatment, which constitutes 81.6% of its content in the control group. Moreover, the low volume of blood erythrocytes present before the start of treatment remains unchanged even after therapy with iron preparations.

In patients of the studied group, there is no positive dynamics concerning the values of mean volume and concentration of hemoglobin in erythrocytes and the width of the erythrocyte distribution curve (Table 2). Therefore, the analysis results of the qualitative and quantitative characteristics of patients' blood erythrocytes also indicate the absence of positive dynamics.

Conclusion.

Based on the conducted studies, the following conclusions can be drawn:

1. The inclusion of Ferlatum in the comprehensive therapy for RA with an anemic syndrome helps to restore the disturbed ferrokinetics parameters.
2. The presence of Helicobacter invasion in patients with RA with an anemic syndrome reduces the anti-anemic effect of Ferlatum included in the comprehensive therapy of this pathology.

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