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The relationship between hemoglobin level and disease activity in patients with rheumatoid arthritis



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ABSTRACT

Objectives: This study aims to investigate the relationship of hemoglobin level with disease activity in patients with rheumatoid arthritis (RA).

Patients and methods: The hemoglobin level, the 66/68 joint count, the Disease Activity Score 28 joints (DAS28), the Health Assessment Questionnaire (HAQ), the Visual Analog Scales (VAS), the Modified Sharp Score (MSS), and the disease duration in 89 patients with RA were used to analyze the possible relationship. The World Health Organization (WHO) criteria for anemia uses a hemoglobin threshold of < 120 g/L for women and < 130 g/L for men. Pregnant or breastfeeding patients, patients with a history of other inflammatory or no inflammatory arthritis, malignancies, chronic infectious and inflammatory diseases and other diseases in the stage of decompensation were excluded from the study.

Results: Anemia was observed in 64% of the patients (1st group); the other group (2nd group) had normal levels of hemoglobin. There was a statistically significant negative correlation between hemoglobin level and swollen and tender joints' count, DAS28, HAQ score, VAS, MSS, and disease duration ($p < 0.001$). DAS28, HAQ score, VAS, MSS, swollen and tender joints' count and disease duration were significantly ($p < 0.001$) higher in 1st versus 2nd group.

Conclusion: In conclusion, we determined that low hemoglobin level was significantly related to disability and impairment, disease activity, articular damage, pain and disease duration in RA patients in our study. We believe that by keeping disease activity under control, therefore preventing articular damage, the disability in RA patients can be lessened or possibly even eliminated.

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Relação entre o nível de hemoglobina e a atividade da doença em pacientes com artrite reumatoide

R E S U M O

Palavras-chave:

Artrite reumatoide

Objetivos: Este estudo tem como objetivo investigar a relação entre o nível de hemoglobina e a atividade da doença em pacientes com artrite reumatoide (AR).

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Anemia
Atividade da doença

Pacientes e métodos: Avaliou-se a possível relação existente entre o nível de hemoglobina, a contagem de 66/68 articulações, o Escore de Atividade da Doença – 28 articulações (DAS28), o Questionário de Avaliação de Saúde (HAQ), a escala visual analógica (EVA), o Escore de Sharp modificado (MSS) e a duração da doença de 89 pacientes com AR. Os critérios para anemia da Organização Mundial de Saúde (OMS) consideram um limite de hemoglobina < 120 g/L para as mulheres e < 130 g/L para os homens. Pacientes grávidas ou amamentando, pacientes com história de outra artrite inflamatória ou não inflamatória, neoplasias, doenças crônicas infecciosas e inflamatórias e outras doenças descompensadas foram excluídas do estudo. **Resultados:** A anemia foi observada em 64% dos pacientes (1° grupo); o outro grupo (2° grupo) apresentou níveis normais de hemoglobina. Houve uma correlação negativa estatisticamente significativa entre o nível de hemoglobina e a contagem de articulações inchadas e sensíveis, DAS28, HAQ, EVA, MSS e duração da doença ($p < 0,001$). O DAS28, escore HAQ, EVA, MSS, contagem de articulações inchadas e sensíveis e duração da doença foram significativamente maiores ($p < 0,001$) no primeiro grupo em comparação com o segundo. **Conclusão:** Determinou-se que o baixo nível de hemoglobina está significativamente correlacionado com a deficiência e incapacidade, atividade da doença, lesão articular, dor e duração da doença em pacientes com AR. Acredita-se que, mantendo a atividade da doença sob controle, evitando danos articulares será possível diminuir ou, possivelmente, até mesmo eliminar a incapacidade em pacientes com AR.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by inflammation in the synovium of joints, malaise, morning stiffness and fatigue.^{1,2} It is associated with progressive joint destruction and, depending on the severity, may be accompanied by systemic manifestation including effects on the blood.³ In particular, anemic syndrome is a very common manifestation of rheumatoid inflammation that could increase RA activity and decrease patient's quality of life.⁴ Unfortunately, anemia is not considered a major problem in rheumatoid arthritis RA by the vast majority of physicians. This statement is based on the fact that studies on anemia in RA are sparse, with few systemic reviews, and no extensive literature on its prevalence and effect on various clinical and functional outcomes, including morbidity, mortality, and quality of life. Some results suggest that anemia is associated with a negative impact on both RA symptoms and quality of life. Thus the question needs to be raised of why so little research on anemia-related outcomes has been conducted. This gap in the literature is strange because anemia is a common comorbidity in patients with RA. Additional large-scale studies on prevalence and anemia-related outcomes are needed to support the importance of anemia screening and treatment in RA.

Thus, the aim of our study was to investigate the relationship between hemoglobin level and disease activity in patients with rheumatoid arthritis (RA) by using the 66/68 joint count, the DAS 28, the HAQ, the VAS, the MSS, and duration of disease.

Patients and methods

The study was comprised of 89 Ukrainian patients (females; mean age 51.7 ± 10.3 years) who were diagnosed with RA

according to the American College of Rheumatology (ACR) classification criteria,⁵ and written informed consent was obtained from all of the participants. The patients were assigned to one of two groups on the basis of their hemoglobin concentration. The first group was composed of 57 female patients who fulfilled the criteria for anemia. The World Health Organization (WHO) criteria for anemia use a hemoglobin threshold of < 120 g/L for women, and < 130 g/L for men. The second group was made up of 32 non-anemic female patients. The 66/68 joint count, the DAS 28 joints, the HAQ, the VAS, the MSS and disease duration of each group were used to analyze the possible relationship. Pregnant or breastfeeding patients, patients with a history of other inflammatory or non-inflammatory arthritis, malignancies, chronic infectious and inflammatory diseases and other diseases in the stage of decompensation were excluded from the study. The local ethics committee of the National Medical University in Donetsk, Ukraine, gave their approval.

Blood samples were collected using the Sarstedt tube system (Sarstedt Inc., Nümbrecht, Germany). The blood count was then measured electronically by the ABX Micros ES 60 hematology analyzer (Horiba ABX SAS, Montpellier, France).

The 66/68 joint count includes the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints of the hands, the metatarsal phalangeal and distal interphalangeal joints of the feet and the shoulder, elbow, wrist, hip, knee, ankle, tarsus, and temporomandibular, sternoclavicular and acromioclavicular joints.

Disease activity was determined with the DAS 28 and calculated using the following equation: $DAS\ 28 = 0.56 \times \sqrt{(\text{tender } 28 \text{ joint count})} + 0.28 \times \sqrt{(\text{swollen } 28 \text{ joint count})} + 0.70 \times \ln(\text{erythrocyte sedimentation rate (ESR), mm/hr}) + 0.014 \times \text{general health}.$ ⁶ General health is subject global assessment using a 100 mm VAS.

The level of disability was investigated using the HAQ,⁷ which consists of 20 questions in eight subcategories: dressing

Table 1 – Comparison of the RA activity of the two groups.

Parameters	P-values	1 st Group (57 patients)	2 nd Group (32 patients)
Duration of RA, years	0.004	11.62 ± 3.54	7.63 ± 3.48
Swollen joint	0.002	28.67 ± 9.01	16.53 ± 8.27
Tender joint	0.001	31.42 ± 10.07	18.52 ± 11.28
DAS28	0.001	5.2 ± 1.3	2.8 ± 1.1
HAQ	0.02	1.4 ± 0.6	1.98 ± 0.55
VAS (pain assessment), mm	0.004	68.11 ± 12.34	37.17 ± 9.48
VAS (global assessment of disease activity), mm	0.004	71.21 ± 15.42	44.56 ± 11.41
MMS	0.001	235.37 ± 24.82	137.54 ± 19.61

and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Responses in each functional area are scored from 0 (without any difficulty) to 3 (unable to do). The highest score recorded for any question in a category is the score for that category, unless aids, devices, or help from another person is required. Dependence on aids or devices or help from others results in a minimum category score of 2. The HAQ score is calculated as the sum of the category scores divided by the number of categories scored, giving a possible range of scores from 0 to 3.

Patients were asked to assess their average pain during the past week on a VAS (0 to 100 mm). The scale ranges from 0 (no pain) to 100 (severe pain). Patients were also asked to assess their disease progression on a VAS (0 to 100 mm). They marked on a VAS their overall assessment of how their RA has affected them, rating how they are managing from 0 (very well) to 100 (very poorly). The VAS scores were measured in millimeters.⁸

The MSS was used in our study to evaluate structural articular damage via plain X-rays taken of both hands and feet.⁹ The erosion score per each joint of the hands ranges from 0 to 5, and, per each joint of the feet, ranges from 0 to 10. The maximum total erosion score for two hands is 160, the highest narrowing score is 120, and the maximum MSS score is 280. The maximum total erosion score for feet is 120, the highest narrowing score is 48, and the maximum MSS score is 168. The maximum total score for one patient is 448.

Statistical analyses were performed using the MEDSTAT version 4.0 for Windows software program (The MEDSTAT Group, Inc., Ann Arbor, MI). The Shapiro-Wilk normality test was employed to assess whether or not the data was normally distributed and descriptive data was presented as mean ± standard deviation (SD) because the data was distributed normally. Correlations between hemoglobin level and swollen and tender joint count, the DAS28, HAQ score, VAS, MSS, and disease duration were investigated with Spearman's rank correlation test. A P-value of less than 0.05 was considered to be statistically significant.

Results

Anemia was observed in 57 (64%) of the patients (1st group). The others (2nd group) had normal levels of hemoglobin (135.5 ± 10.7 g/l). The patients from the 1st and 2nd groups were statistically similar with regard to age ($p = 0.21$). The clinical parameters of the patients are shown in Table 1. The DAS 28, HAQ score, VAS, MSS, swollen and tender joint count, disease duration were significantly ($p < 0.001$) higher in 1st group

compared to the 2nd. The results of a correlation analysis between the hemoglobin level and the clinical parameters of RA activity are shown in Table 2. There were statistically significant negative correlations between the hemoglobin level and the swollen and tender joint, DAS 28, HAQ, MSS, VAS, and disease duration ($p < 0.001$).

Discussion

We found that duration and activity of RA were significantly ($p < 0.05$) higher in patients with anemia compared to patients with normal hemoglobin level. In 2009, Furst et al.¹⁰ reported that anemic syndrome in RA patients could be a marker of high activity and severity of disease. Similarly, Borah et al.¹¹ reported that RA activity, according to the DAS 28 and HAQ score, was significantly higher in patients with anemia compared to patients with normal hemoglobin level (6.85 ± 0.64; 1.41 ± 0.44 and 4.76 ± 1.29; 0.7 ± 0.25, respectively; $p < 0.05$). Results of other studies have shown that patients with low hemoglobin level had higher number of affected joints than patients without anemia.¹² Similar to the current literature, we found negative correlation between the hemoglobin level and the swollen/tender joint, DAS 28, HAQ, MSS, VAS, and disease duration.

The well established relationship between inflammation and anemia was confirmed in different studies by significant associations between lower hemoglobin concentrations and higher DAS 28, and by faster hemoglobin normalization after TNF- α blockade. Anemia in RA may be caused by a shortened red blood cell lifespan, pathologic iron homeostasis

Table 2 – The results of a correlation analysis between the hemoglobin level and the clinical parameters of RA activity.

Laboratory test	Correlation coefficient (r)	P-values
Duration of RA, years	-0.62	$p < 0.001$
Swollen joint	-0.61	$p < 0.001$
Tender joint	-0.59	$p < 0.001$
DAS 28	-0.57	$p < 0.001$
HAQ	-0.48	$p < 0.001$
VAS (pain assessment), mm	-0.52	$p < 0.001$
VAS (global assessment of disease activity), mm	-0.59	$p < 0.001$
MMS	-0.61	$p < 0.001$

induced by hepcidin, and blunted response to erythropoietin. Cytokines also have a direct toxic effect on erythropoietin. Kullich et al.¹³ found that TNF- α level was significantly higher in RA patients who had anemia, than in those without it. Similarly, Zhu et al. reported that patients suffering from RA and anemia had increased TNF- α level and decreased serum erythropoietin concentration. This allowed the authors to suggest that TNF inhibits the production of erythropoietin. Interestingly, erythropoietin treatment reduced disease activity in RA patients and tissue damage in collagen-induced arthritis models. Hepcidin may trigger functional iron deficiency upon induction by TNF- α , interleukin-6, resulting in reduced intestinal iron uptake at the mucosal barrier, and iron retention in the reticulo-endothelial system via internalization of the same exclusive cellular iron exporter ferroportin on both cell types. Corticosteroids may carry an increased risk of anemia due to toxic mucosal drug effects or a bias by indication.

In summary, these results indicate that anemia may serve as predictor of worse outcome in RA patients. Our data suggest that anemia is associated independently of common disease activity outcome measures. This report may add clinical background to recent discoveries at the nexus of inflammation, hematopoiesis and iron metabolism, and highlights the clinical implications of anemia in RA. Diagnosis of anemia in RA should prompt a thorough search for subclinical disease activity, after exclusion of other frequent causes.

Conflicts of interest

The author declares no conflicts of interest.

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