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Correlation between DAS28 and Serum Hepcidin Levels in Patients with Anemia and Rheumatoid Arthritis

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Abstract: ***Aim: Anemia in rheumatoid arthritis (RA) is related to the chronic inflammatory nature of the disease. It occurs as iron deficiency, mostly due to drug-induced gastrointestinal bleeding and disorders as well as iron redistribution into inflamed joint structure. We tried to find a correlation between disease activity score (DAS28) and serum hepcidin levels in order to identify and find the right treatment approach for iron deficiency in patients with anemia of chronic disease. Data: We determined serum hepcidin levels using ELISA assay in patients with rheumatoid arthritis. Number of patients included – 50. They were diagnosed with RA in the University Hospital "St. Ivan Rilski", Clinic of Rheumatology for a period 2013 – 2014 year. Activity of the disease was determined by DAS 28 for RA. Patients were divided into three groups: RA without anemia; RA with iron deficiency anemia (IDA) and RA with ACD. Results: We found statistically significant differences in serum hepcidin levels between measured groups: RA without anemia – 14.9 ± 7.6 μg/L; RA with IDA - 0.7 ± 0.3 μg/L; RA with ACD – 88.0 ± 9.7 μg/L. We found a significant negative correlation between serum hepcidin levels and DAS28 in patients with RA without anemia (r = -0.834, P < 0.05); and significant positive correlation between serum hepcidin levels and DAS28 in patients with RA with ACD (r = 0.679, P < 0.001). Conclusions: We conclude that our results may support the right choice of a therapeutic approach to the iron-deficiency anemia or anemia of chronic inflammation in rheumatoid arthritis.***

Keywords: anemia, rheumatoid arthritis, hepcidin, iron deficiency, anemia on chronic inflammation

1. Introduction

Anemia in rheumatoid arthritis is a process associated with chronic inflammatory disease. It occurs as iron deficiency, mostly due to drug-induced gastrointestinal bleeding and disorders as well as iron redistribution into inflamed joint structure. Identifying and finding the right treatment approach for iron deficiency in patients with anemia of chronic disease is of great clinical importance because it can prevent unnecessary spelling of therapy with iron preparations.

Proinflammatory stimuli leads to the development of anemia of chronic disease by directly inhibit erythropoesis indirectly reduce iron supplied for the synthesis of heme [1]. This process is associated with increased levels of regulatory peptide hepcidin due to inflammation. Elevated hepcidin decreased intestinal iron absorption. Due to the occurrence of changes in the molecule of the cell iron exporter – ferroportin, occurs iron retention in macrophages and iron sequestration in the reticuloendothelial system [2,3]. Consequently, the total content of iron in the body is normal, but less is supplied for erythropoesis. Opposite is the mechanism for the development of iron deficiency anemia. When it is observed absolute iron deficiency, hepcidin secretion is suppressed, leading to stimulation of the absorption of iron in the intestine. The establishment of the different behavior of hepcidin inflammatory and iron deficiency suggests that it could be a potential biomarker for identification of iron deficiency in patients with inflammatory conditions [4-7].

2. Materials and Methods

For a period 2013 - 2014 years 50 patients (15 male and 35 female), diagnosed with rheumatoid arthritis from the Department of Rheumatology at "St. Ivan Rilski" hospital were observed. Disease activity was determined by Disease Activity Score calculator for rheumatoid arthritis [DAS 28-CRP]. Patients with anemia were divided into three groups by identifying clinical and laboratory indicators of inflammation and iron deficiency.

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In patients with rheumatoid arthritis and anemia we classified anemia as iron deficiency (IDA) and anemia of chronic disease (ACD) by the following conditions:

- IDA - no active inflammation (level of CRP < 10 mg/L), transferrin saturation < 20% and the level of ferritin < 30 ng/mL.
- ACD - if there is active inflammation (level of CRP > 10 mg/L), transferrin saturation < 20% and ferritin > 100 ng/mL.
- Patients with rheumatoid arthritis without anemia defined as controls.

We measure hepcidin levels using verified ELISA method [8].

3. Results

Age distribution of patients in the different groups is shown in Table 1.

Table 1: Age distribution of patients in groups

	Male	*Female*
n	15	35
mean (age)	49.7	53.2
SD (age)	7.3	8.4

Patients were signing the informed consent according to the Declaration of Helsinki (Directive 2001/20 / EC).
The results of laboratory parameters are presented in Table 2.

Table 2: Laboratory parameters in studied groups

	RA no anemia		*RA with IDA*		*RA with ACD*	
	mean	*SD*	*mean*	*SD*	*mean*	*SD*
DAS28	2.96	0.4	3.48	0.7	4.8	0.8
CRP (mg/L)	10.0	5.4	9.0	0.3	88.3	14.8
Hepcidin (µg/L)	14.9	7.6	0.7	0.3	88.0	9.7

The results obtained from the serum hepcidin are presented in Figure 1.

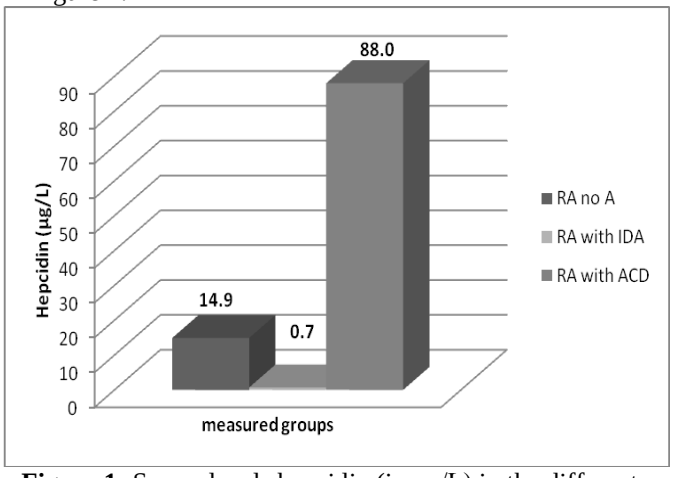


Figure 1: Serum levels hepcidin (in µg/L) in the different groups of patients with rheumatoid arthritis (RA)

The results from calculated DAS28 are presented in Figure 2.

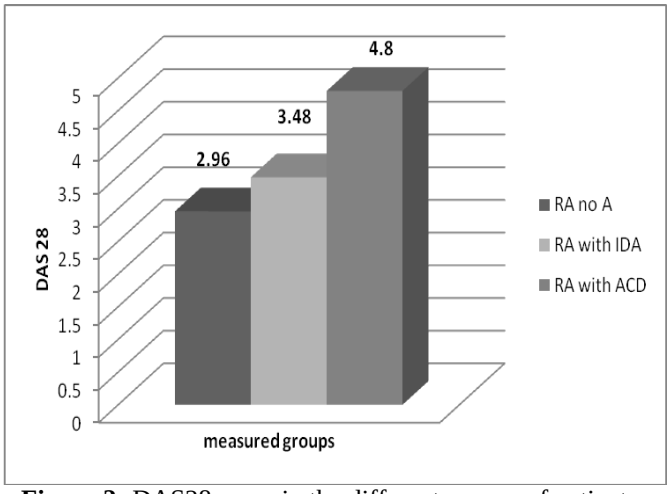


Figure 2: DAS28 score in the different groups of patients with rheumatoid arthritis (RA)

We found a significant negative correlation between serum hepcidin levels and DAS28 in patients with RA without anemia ($r = -0.834$, $P < 0.05$); and significant positive correlation between serum hepcidin levels and DAS28 in patients with RA with ACD ($r = 0.679$, $P < 0.001$).

Table 3 presents DAS28 score's correlation between measured groups.

Table 3: Correlation of DAS28 score between measured groups patients with rheumatoid arthritis (RA)

DAS28	**r**	**p**
RA no A **to** RA with IDA	0.515	0.07
RA no A **to** RA with ACD	-0.637	0.01
RA with IDA **to** RA with ACD	-0.263	0.06

We found a significant positive correlation between patients with RA without anemia and RA with IDA ($r = 0.515$, $P < 0.1$); and a significant negative correlation between patients with RA without anemia to patients with ACD ($r = -0.637$, $P < 0.05$).

4. Discussion

Patients with inflammatory and reduced hepcidin are expected to have an iron deficiency. In contrast, those with high level of hepcidin are diagnosed with ACD.

Using serum hepcidin levels would help in assessing the need for the application of preparations containing iron. The results suggest that patients with IDA may be subjected to treatment with such drugs, while patients with ACD do not need them.

Rheumatoid arthritis is a multifactorial condition that is associated with ACD [9]. It may also include iron deficiency due to bleeding in the gastrointestinal tract caused by applied therapy; distribution in synovial tissue. Establishment of iron deficiency in populations with ACD is clinically relevant because: 1) iron-deficiency anemia (IDA) is treatable, 2) diagnosis can precede further investigation of the cause of anemia, and 3) can prevent unnecessary supplementation with iron. Data from our study indicated a significant increase in serum hepcidin in RA and ACD

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compared with the control group. Serum hepcidin is a reliable marker for distinguishing IDA mixed state IDA/ACD and ACD. It may be part of the selection algorithm of RA patients, in which it is appropriate to use iron therapy to correct anemic syndrome [10].

5. Conclusion

Determination of serum hepcidin is still a novelty in Bulgarian medical practice. The introduction of a reliable routine method for the study of hepcidin in biological fluids is a step forward in the treatment of diseases with impaired iron homeostasis. Our study in patients with RA and different anemia confirms the ability of verified immunochemical method to differentiate the increase and decrease in serum hepcidin in patients with RA. It provides a basis for choosing the correct therapeutic approach in the treatment of anemia.

6. Acknowledgement

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