ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of DEVELOPMENT RESEARCH

International Journal of Development Research
Vol. 4, Issue, 12, pp. 2743-2745, December, 2014

Full Length Research Article

NEW TOOLS IN DIAGNOSIS OF ANEMIA IN RHEUMATOID ARTHRITIS

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ARTICLE INFO

Article History:

Received 11th September, 2014
Received in revised form
29th October, 2014
Accepted 05th November, 2014
Published online 27th December, 2014

Key words:

Anemia,
Rheumatoid Arthritis,
Hepcidin,
Iron Deficiency,
Anemia on Chronic Inflammation.

ABSTRACT

Aim: Anemia in rheumatoid arthritis (RA) is related to the chronic inflammatory nature of the disease. The discovery of iron deficiency in patients with anemia of chronic disease (ACD) is of clinical importance because it can prevent unnecessary prescribing of preparations containing iron.
Data: We determined serum hepcidin levels using ELISA assay in patients with rheumatoid arthritis. We include 60 patients 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 Disease Activity Score calculator 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 - 15 ± 5.9 μg/L; RA with IDA - 0.7 ± 0.4 μg/L; RA with ACD – 94.6 ± 8.1 μg/L.
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.

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.

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Proinflammatory stimuli leads to the development of anemia of chronic disease by directly inhibit erythropoesis indirectly reduce iron supplied for the synthesis of heme (Weiss *et al*., 2005). 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 (Kemna *et al*., 2008; Goodnough *et al*., 2010). 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 (Sasu *et al*., 2010; Theurl *et al*., 2009; Thomas *et al*., 2011; Kroot *et al*., 2010).

MATERIALS AND METHODS

For a period 2013 - 2014 years 60 patients 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. 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 (Manolov *et al*., 2014).

RESULTS

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

Table 1. Age distribution of patients in groups

	RA no anemia	RA with IDA	RA with ACD
n	20	20	20
MIN	26	39	41
MAX	67	61	62
mean	55.1 ± 8.2	55.6 ± 10.7	57.5 ± 5.9

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	3.0	0.3	4.1	1.0	4.1	0.1
Iron(µmol/L)	15.5	5.2	5.6	1.5	11.0	2.3
Trsf (g/L)	2.7	0.5	1.5	0.3	1.6	0.3
CRP (mg/L)	10.0	5.4	9.0	0.3	88.3	14.8
Hepcidin (µg/L)	15.0	5.9	0.7	0.4	94.6	8.1

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

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.

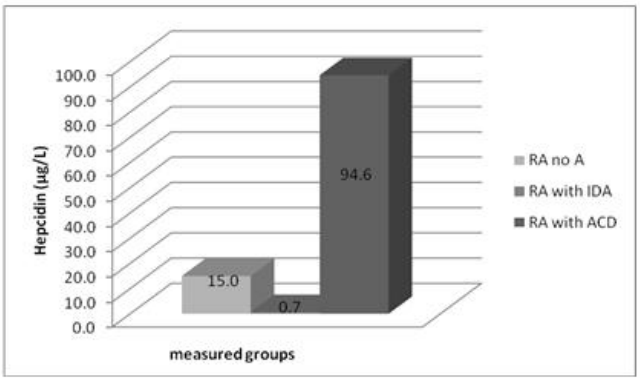

Figure 1. Serum levels hepcidin (in µg/L) in the different groups of patients with rheumatoid arthritis (RA)

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 (Manolov *et al*., 2014). 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 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 (Van Santen *et al*., 2011). Future of hepcidin is related to the possibility hepcidin antagonists and agonists can be used as a therapeutic agent in the treatment of anemia in inflammation and iron-deficiency anemia. Reducing of hepcidin levels or counteracting the biological effects of hepcidin may lead to a reduction in inflammation on erythropoesis by mobilization of stored iron and increases intestinal absorption of the element. These new therapeutic approaches could reduce or eliminate all toxic effects of treatment with parenteral iron and Co-reduction needs erythropoetin stimulating agents (ESAs). In these cases, serum hepcidin is suitable therapeutic target in the management of therapy in CKD.

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.

Acknowledgement

This project is implemented with the financial support of the Medical University - Sofia, "Grant 2014", Contract № 67/2014.

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