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Research Article

Relationship Between Rheumatoid Arthritis Activation Criteria and Serum Hepcidin Levels

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Abstract

Objectives: Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease of unknown etiology. It is a chronic systemic disease primarily involving synovial joints. Evaluation of disease activity in RA is very important in terms of patient follow-up and assessing the response to drugs. Hepcidin is an acute-phase protein. It is greatly increased in inflammation or iron overload. Based on this, we aimed to reveal the relationship between Hepcidin, an acute-phase protein, and disease activity in patients with RA in this study.

Methods: Fifty individuals with rheumatoid arthritis who applied to the rheumatology outpatient clinic of Kartal Dr. Lutfı Kırdar Education and Research Hospital and 36 healthy individuals as the control group were included in the study. All patients underwent general physical examination and locomotor system examination. From routine laboratory tests, complete blood count, biochemical tests, thyroid hormone levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) measurements were performed. We divided the patients with rheumatoid arthritis into three groups as low activity, moderate activity and high activity according to the disease activity score (DAS28). The DAS 28 score was not calculated in healthy individuals because they did not have rheumatoid arthritis.

Results: Hepcidin measurements of RA and control groups included in the study were compared. There was no statistically significant difference between hepcidin values in RA group and hepcidin values in control group (p=0.518). In RA group, there was a statistically significant difference between hepcidin and CRP values (p=0.001) and between hepcidin and sedimentation values (p=0.01). There was a statistically significant difference only between hepcidin values of the users and non-users of steroid (p=0.042).

Conclusion: In conclusion, no statistically significant difference was found between patients with rheumatoid arthritis and healthy individuals in terms of hepcidin levels in our study. Although hepcidin is an acute-phase protein and increased in inflammatory events, we think that it is not appropriate to use serum hepcidin measurement to evaluate disease activity in rheumatoid arthritis.

Keywords: Disease activity score 28, hepcidin, rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease of unknown etiology. It primarily involves synovial joints. It is characterized by symmetrical, erosive synovitis. It can be seen in all races and ethnic groups. Severe deformities and disability may develop.[1–3] Evaluation of disease activity in RA is very important in terms of patient follow-up and assessing the response to drugs.

Hepcidin is a new mediator of congenital immunity. In 2001, Park et al.[4] obtained a new peptide called hepcidin from human urine during the study of antimicrobial properties of different body fluids. 'hep', the first part of the name of "hepcidin" comes from its synthesis in the liver and the second part 'cidin' from its in-vitro antimicrobial properties. Hepcidin creates an important link between body defense, inflammation and iron metabolism. Hepcidin synthesis is greatly increased in inflammation or iron overload. It has been shown in various animal and human studies that the hepcidin synthesis is significantly increased by infection and inflammation and that IL-6 is the stimulant responsible for this increase. It was observed that the excretion of hepcidin in the urine was increased 7.5-fold in volunteers infused with IL-6 in a few hours, and this increase was accompanied by a 30% decrease in serum iron and transferrin saturation.[5, 6] A 2003 study by Nemeth et al.[7] has showed that urinary hepcidin excretion is increased in patients with transfusion-induced iron overload, infection and inflammatory disease, hepcidin level is increased with in vitro IL-6 and hepcidin will be increased as an acute-phase protein in inflammatory, infectious diseases.

Based on this, we aimed to reveal the relationship between Hepcidin, an acute-phase protein, and disease activity in patients with RA in this study.

Methods

Fifty individuals with rheumatoid arthritis who applied to the rheumatology outpatient clinic of Kartal Dr. Lutfı Kırdar Education and Research Hospital and 36 healthy individuals as the control group were included in the study.

The disease was diagnosed according to the diagnostic criteria of the American Rheumatism Association for RA revised in 1987. Accordingly, patients with at least 4 positive criteria were considered having RA.

Patients included in the study did not have liver disease, renal failure, malignancy and additional inflammatory disease.

Symptoms of the patients with RA, presence of systemic disease, their drug use and family history were questioned. All patients underwent general physical examination and locomotor system examination. From routine laboratory tests, complete blood count, biochemical tests, thyroid hormone levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) measurements were performed. We divided the patients with rheumatoid arthritis into three groups as low activity, moderate activity and high activity according to the disease activity score (DAS28). The DAS 28 score was not calculated in healthy individuals because they did not have rheumatoid arthritis.

The DAS28 scores evaluating rheumatoid arthritis disease activity were calculated.[8, 9] The DAS 28 score was considered inactive if it is ≤3.2, moderately active if it is between >3.2 and ≤5.1 and very active if it is >5.1.

Parameters Used in DAS 28 Calculations:

1. Number of sensitive joints: sensitivity in hands, proximal interphalangeal (PIF), metacarpophalangeal (MKF), wrist, elbow, knee and shoulder joints.
2. Number of swelled joints: swelling and arthritis findings in hands, PIF, MKF, wrist, elbow, knee and shoulder joints.
3. Overall well-being: to what extent the patient's rheumatoid arthritis was active in last seven days; overall well-being by requiring patients to give a value between 0 and 100: proximity to zero indicated lack of activity while proximity to 100 indicated high amount of activity.
4. Sediment value.

All these parameters were calculated by using calculators specially prepared for DAS 28 with a fixed formula.

DAS 28=(0.56 x √ HES) + (0.28 x √ SES) + (0.70 x Ln (ESR)) + (0.014 x GHA)

General Health Assessment (GHA)

GHA by requiring patients to put a line corresponding to their current pain on the point on a 10 cm line: 0 was evaluated as no pain, 10 cm was evaluated as irresistible pain. The point marked by the patient was used as GHA.[10]

It was paid attention that the blood of the patient was taken after 12 hours of fasting between 08:30–09:00 from the front arm vein and laboratory values received in our hospital were taken into consideration in his biochemical measurement. CRP measurement values of 0–5 mg/L was accepted as normal CRP level while CRP measurement values of 5 mg/L and above was accepted as high CRP level. Because sediment value was accepted as <ESR 20 mm/h for men and <30 mm/h for woman determined by the American Rheumatism Association's (AC) RA remission criteria and because the study and control groups in our work was composed of female patients 30 and over was accepted as high.[11]

Rheumatoid factor (RF): Between 0 and 15 IU/ml was accepted as normal (negative) value and 15 IU/ml and over was accepted as high value (positive).

Statistical Analysis

SPSS 17.0 program was used for statistical analysis of data. The independent samples t test was used to compare the mean values of the rheumatoid arthritis group and the control group. The relationship between CRP and Hepcidin values and other parameters were analyzed by correlation analysis. Spearman correlation coefficient analysis was used for the analysis of categorical data and Pearson correlation coefficient analysis was used for the analysis of measurable data. All analyzes were performed with 95% confidence interval and $p \leq 0.05$ values were considered statistically significant.

Results

50 patients with rheumatoid arthritis and 36 healthy individuals were included in the study. 75% of the control group were female (n=27), 25% were male (n=9) and 82% of RA group was female (n=41), 18% were male (n=9).

98% of RA patients were receiving at least one treatment. 32% of the patients were using NSAIDs, 30% were using hydroxychloroquine, 14% were using leflunomide, 18% were using anti TNF, 56% were using methotrexate, 28% were using salazopyrin and 38% were using steroids. 26 patients (30%) had hypertension and 7 patients (8%) had diabetes.

Hepcidin measurements of RA and control groups included in the study were compared. There was no statistically significant difference between hepcidin values in RA group and hepcidin values in control group (p=0.518) (Fig. 1).

In RA group, there was a statistically significant difference between hepcidin and CRP values (p=0.001) and between hepcidin and sedimentation values (p=0.01).

In RA group, the relationship between hepcidin values of 3 groups which were defined as low clinical activity, moderate clinical activity and high clinical activity according to the DAS 28 was examined. Hepcidin values of these three groups were not statistically significant (p=0.357). Whereas rheumatoid arthritis activity score was increased, hepcidin levels were not increased (Table 1).

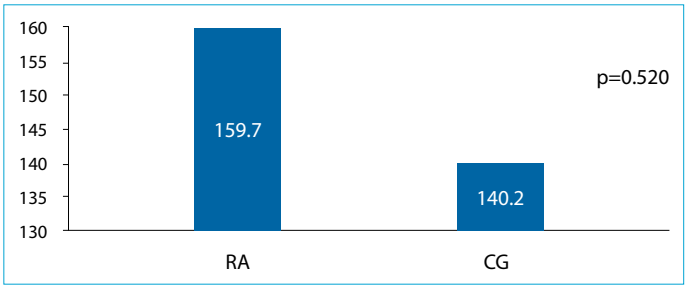

Figure 1. Hepcidin levels in study group (rheumatoid arthritis) and control group.

The mean hepcidin values of the patients using and not using NSAID, hydroxychloroquine, Leflunomide, Anti TNF, methotrexate, Salazopyrin are shown in (Table 2). There was a statistically significant difference only between hepcidin values of the users and non-users of steroid (p=0.042). There was no difference in other groups.

When evaluated according to the presence of anemia, there was no significant difference between hepcidin parameters of rheumatoid arthritis and control groups with and without anemia (p=0.83) and (p=0.383) respectively (Fig. 2).

Discussion

The etiology of rheumatoid arthritis, which is one of the most common inflammatory joint diseases, is currently unknown. It is a chronic systemic disease primarily involving synovial joints, characterized by symmetrical, erosive syn-

Table 1. Hepcidin levels according to disease activity in RA patients

	n	Mean	p
Hepcidin (ng/ml)			
Low activity	9	136.0±295.4	
Moderate activity	21	223.5±451.2	0.357
High activity	20	103.2±219.4	

Table 2. Relation between treatment drugs and hepcidin levels in Rheumatoid artritis patients

Drugs	n	Hepcidin (ng/ml)	p
Steroid			
Negative	31	114±264.4	
Positive	19	234±442.6	0.042
Sulfasalazine			
Negative	36	132±300.4	
Positive	14	229±460.3	0.078
Methotrexate			
Negative	22	158±382.4	
Positive	28	160.7±345.9	0.066
Anti-TNF therapy			
Negative	41	143.9±319.8	
Positive	9	231.2±498.2	0.596
Leflunomide			
Negative	43	141±328.5	
Positive	7	274.3±472.9	0.149
NSAID			
Negative	34	146.9±339.5	
Positive	16	186.7±402.4	0.755
Chloroquine			
Negative	35	180±399.7	
Positive	15	112.2±220.2	0.491

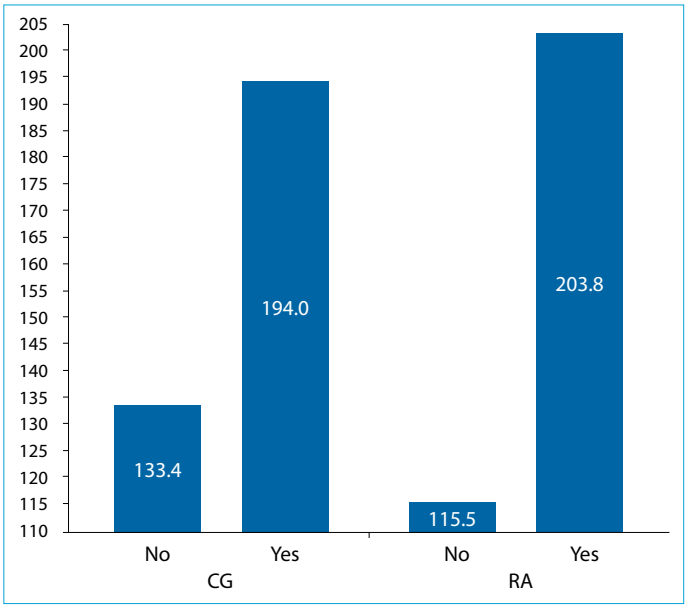

Figure 2. Hepcidin levels in RA and control group according to the presence of anemia.

ovitis, which can be seen in all race and ethnic groups, and may develop serious deformities and disability.[1–3]

Hepcidin is an acute-phase protein synthesized in the liver. Hepcidin is greatly increased in inflammation or iron overload. It has been shown in various animal and human studies that the synthesis of hepcidin is significantly increased by infection and inflammation and that IL-6 is the stimulant responsible for this increase.[5, 6] A 2003 study by Nemeth et al.[7] has showed that urinary hepcidin excretion is increased in patients with transfusion-induced iron overload, infection and inflammatory disease, hepcidin level is increased with in vitro IL-6 and hepcidin will be increased as an acute-phase protein in inflammatory, infectious diseases. Based on these data, we predicted that hepcidin levels would be high in RA group. However, no statistically significant difference was found between the RA group and healthy individuals in terms of hepcidin levels. We think that the reason is that serum hepcidin levels may change due to dietary iron intake and dietary habits, or that the individuals in the control group in our study may have an unknown disease that has not yet been identified and that affects the inflammatory process.

In a study by Jayaranee S. et al.[12] prohepcidin concentrations in patients with RA were evaluated. No significant difference was found between patients with RA and healthy group in terms of prohepcidin measurements. Similarly, no statistically significant difference was found between patients with RA and healthy group in terms of hepcidin levels in our study. In the same study, it has been shown that there was a significant correlation between anemia and hepcidin levels in anemic patients with RA. As for our study, although negative correlation between hepcidin and hemoglobin was found in the RA group, there was no statistical significance. With regard to the presence of anemia in RA group, there was no significant difference between patients with and without anemia in terms of hepcidin measurements. This may be due to the coexistence of anemia of chronic disease and iron deficiency in some patients with rheumatoid arthritis.

In a study by Serdar Koca et al.[13] prohepcidin levels were evaluated in patients with SLE and RA. It was found that prohepcidin levels were significantly higher in RA group compared to SLE and healthy group. Prohepcidin levels were not correlated with the DAS 28 and hemoglobin levels in patients with RA. In our study, no correlation was found between hepcidin levels and the DAS 28 levels in accordance with this study.

Mehmet D. Demirağ et al.[14] found that serum hepcidin levels were higher in active RA group than inactive RA group in their study. Positive correlation was found between serum hepcidin levels and disease activity in RA group. In our study, there was no statistically significant difference between the groups in terms of hepcidin levels in patients with RA, which is inconsistent with this study. In the same study, positive correlation was found between serum hepcidin levels and CRP levels and negative correlation was found between serum hepcidin and hemoglobin levels in patients with RA. In accordance with this study, positive correlation was found between CRP levels and hepcidin levels in patients with RA in our study; however, there was no significant correlation between hepcidin and hemoglobin levels.

Kim HR et al.[15] found positive correlation between serum prohepcidin levels and serum CRP, sedimentation levels and DAS 28 score in patients with rheumatoid arthritis in their study. Hepcidin levels were higher in active RA group compared to inactive RA group. In accordance with this study, hepcidin levels were positively correlated with serum CRP and sedimentation levels in our study; however, there was no statistically significant difference between hepcidin levels examined according to disease activity.

When hepcidin levels were examined according to the drugs used in RA treatment; there was no statistically significant difference between patients taking and not taking drugs in all drug groups except corticosteroids (MTX, hydroxychloroquine, leflunomide, NSAID, anti-TNF). There was a statistically significant difference between patients with RA taking and not taking steroids (p=0.042). Despite the anti-inflammatory and immunosuppressive effect, the high levels of hepcidin in patients using steroids led us to

think that hepcidin levels may remain high and be affected in other ways.

Conclusion

In conclusion, no statistically significant difference was found between patients with rheumatoid arthritis and healthy individuals in terms of hepcidin levels in our study. Although hepcidin is an acute-phase protein and increased in inflammatory events, we think that it is not appropriate to use serum hepcidin measurement to evaluate disease activity in rheumatoid arthritis since it may be affected by other factors such as dietary habits and diet content.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.T.B.; Design – D.A.T.; Supervision – N.D.; Materials – E.T.B.; Data collection &/or processing – Ö.V.; Analysis and/or interpretation – E.T.E.; Literature search – E.T.B.; Writing – E.T.B.; Critical review – M.A.

References

1. Fuchs HA, Sergent JS, Rheumatoid arthritis: The clinical Picture. In: Koopman WJ, (ed). Arthritis and Allied Conditions. 13th ed, Pennsylvania, Williams and Wilkins, 1997:1041–70.
2. Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. In: Ruddy S, HarrisED, Sledge CB, (eds). Kelley's Textbook of Rheumatology. Sixth ed, Philadelphia, WB Saunders, 921–966, 2001.
3. Albani S, Carson DA. Etiology and pathogenesis of rheumatoid arthritis. In: Kopman WJ (ed). Arthritis and Allied Conditions. Thirteenth edition, Pennsylvania, Williamsand Wilkins, 1997;979–92.
4. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a Urinary Antimicrobial Peptite Synthesized in The Liver. The Journal Of Medicine Biological Chemistry 2001;276:7806–10.[CrossRef]
5. Ganz T. Hepcidin and ıts Role in Regulating systemic Iron Metabolism. Hematology 2006;29–35. [CrossRef]
6. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood 2003;102:783–8.
7. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type 2 acute-phase protein. Blood 2003;101:2461–3. [CrossRef]
8. Bingham S, Emery P. Resistant rheumatoid arthritis clinics--a necessary development? Rheumatology 2000;39:2–5. [CrossRef]
9. Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R; EMECAR Study Group. Value of Disease Activity Score 28 (DAS28) and DAS 28- 3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. J Rheumatol 2004;31:40–6.
10. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther 2016;18:25. [CrossRef]
11. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15. [CrossRef]
12. Jayaranee S, sthaneshwar P, Sokkalingam S. Serum prohepcidin concentrations in rheumatoid arthriti. Deparment of Pathology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, Pathology 2009;41:178–82. [CrossRef]
13. Suleyman Serdar Koca, Ahmet Isik, Bilal Ustundag, Kerem Metin and Kader Aksoy Fırat üniversitesi, Tıp fakültesi, Romatoloji Bölümü, inflammation 2008;31;146–53. [CrossRef]
14. Mehmet Derya Demirag, Seminur Haznedaroglu, Banu Sancak, Ceyla Konca, Ozlem Gulbahar, M. Akif Ozturk, Berna Goker. Department of Internal Medicine, Gazi University School of Medicine, Ankara, Turkey, Inter Med 2009;48:421–6.
15. Kim HR, Kim KW, Yoon SY, Kim SH, Lee SH. Serum Prohepcidin Could Reflect Disease Activity in patients with rheumatoid arthritis. J Koreon Med Sci 2010:348–52. [CrossRef]