









Serum hepcidin level and rheumatoid arthritis disease activity

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Abstract

Objective: The present study aimed to determine the relationship between the serum hepcidin level and disease activity in patients with rheumatoid arthritis (RA).

Methods: This study was conducted on 80 patients with RA (36 cases with anemia of chronic disease [ACD] and 44 patients without ACD). Disease activity was measured by the 28-joint Disease Activity Score based on the erythrocyte sedimentation rate (DAS28-ESR). According to the DAS28-ESR score, 52 and 28 cases were categorized as inactive to moderately active RA (DAS28-ESR \leq 5.1) and highly active RA (DAS28-ESR $>$ 5.1), respectively. In addition, the serum hepcidin level was evaluated in all patients to determine its correlation with the DAS28-ESR score.

Results: There was no significant difference between the RA with ACD and RA without ACD groups in terms of the median (interquartile range) hepcidin level (1207 [985.2] vs. 923.8 [677.3] ng/mL; $P=0.57$). Likewise, no significant difference was observed between the active RA and inactive to moderately active RA groups in this regard (1131.8 [991.3] vs. 1090.9 [631.4] ng/mL; $P=0.53$).

Conclusion: Heparin has no association with disease activity in RA. Therefore, it is not necessary to measure hepcidin to determine the RA activity.

Keywords: Rheumatoid arthritis, anemia, anemia of chronic disease, hepcidin, inflammation, DAS28-ESR

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Introduction

Rheumatoid arthritis (RA) is the most common autoimmune arthritis, affecting approximately 0.5%-1% of people all over the world. In RA, proliferative synovitis leads to irreversible cartilage damage and joint destruction (1). Inflammatory synovitis in RA is partially related to the overproduction of tumor necrosis factor alpha (TNF- α), interleukin-1 (IL-1), IL-6, and IL-17 (1). In particular, IL-6 plays an important role in synovitis, and its serum level is directly associated with disease activity. The IL-6 blockers have been shown as highly effective in the treatment of RA (2). Heparin is an acute-phase reactant protein synthesized in the liver. This peptide fulfills two main functions through acting as a homeostatic regulator of iron metabolism (via iron release and mobilization control in hepatocytes, macrophages, etc.) and an inflammatory mediator (3, 4). The release of hepcidin is triggered by inflammatory mediators, such as IL-6 (4). Recent studies have revealed that this peptide adjusts the immune performance with neutralizing ferroportin in macrophages, hepatocytes, and enterocytes. Moreover, hepcidin increases intracellular iron resources and reduces gastrointestinal iron absorption and serum iron (3).

Several studies have addressed the role of hepcidin in RA (5-7). The majority of these studies have focused on the anemia of chronic disease (ACD), commonly observed in RA, and its association with hepcidin. The circulating serum hepcidin level is reported to increase in the RA patients with ACD (6). Rheumatoid anemia, a type of ACD, which is prevalent in RA patients results from several factors, including ineffective erythropoiesis, abnormalities of iron metabolism, and inflammatory markers (e.g., IL-6 and TNF- α) (8, 9).

As inflammation is a chronic condition in RA, proinflammatory cytokines can affect the serum iron levels and the synthesis of ferritin and hepcidin (9). Considering those facts and interactions among IL-6 and other cytokines, rheumatoid anemia, and hepcidin, hepcidin has been studied with some clinical implications. One of them is differentiating ACD from iron deficiency anemia, which can occur in RA as a result of the

treatments addressing RA (4, 5). These observations resulted in the identification of hepcidin as a major inducer of ACD in patients with RA (3, 8). This mostly relates to the rise of hepcidin as a result of cytokines, including IL-6, and the effect of this increased circulating hepcidin level on the iron metabolism.

In addition, some studies have investigated the relationship between hepcidin and the RA disease activity based on the associations between hematological parameters (e.g., hemoglobin level) and RA disease activity (6, 10, 11). There is evidence regarding the relationship of prohepcidin (i.e., prohormone of hepcidin) and IL-1 receptor antagonist gene polymorphism with the RA disease activity assessed by 28-joint Disease Activity Score (DAS28) (12). Considering this, hepcidin was proposed as a promising tool for the diagnosis and management of ACD in patients with RA. Furthermore, in a study, the reduction of disease activity was accompanied by a decrease in serum hepcidin levels (13). However, some studies observed no relationship between the serum hepcidin and RA disease activity (7).

Hepcidin has recently gained attention in the management of patients with RA; however, the application of this protein in the routine clinical management of this disease still requires further investigation. With this background in mind, the current study was conducted to determine the relationship between the serum hepcidin level and RA disease activity among patients with RA considering the role of ACD.

Methods

Study design and setting

This descriptive-analytic cross-sectional study was conducted in our Rheumatic Diseases Research Center (RDRC) between 2015 and 2016.

Study population and eligibility criteria

The study population corresponded to a group of RA patients with and without ACD. The RA diagnosis was based on the American College of Rheumatology criteria for RA (14). Furthermore, considering the World Health Organization criteria, anemia was defined as the serum hemoglobin levels of less than 12 and 13 g/dL for females and males, respectively. The patients referred for routine visits and follow-ups of their condition, and those whose laboratory findings indicated anemia, were eligible to participate in the study.

The patients who developed anemia due to ACD were included in the research. Therefore, those with anemia due to other causes, includ-

ing iron deficiency, minor thalassemia, megaloblastic anemia, hemolysis, and drug-induced bone marrow suppression, were excluded from the study. The diagnosis of ACD was accomplished by complete iron studies, including serum ferritin, serum iron, and total iron binding capacity (TIBC).

The ACD was defined as normal to decreased mean corpuscular volume, normal to increased red cell distribution width, decreased red blood cell count, low serum iron (normal level, 60-150 mcg/dL) and TIBC, increased serum ferritin (normal level, 40-200 mcg/L), and elevated erythrocyte sedimentation rate (ESR; normal levels, 0-20 mm/h in males and 0-30 mm/h in females) (15).

The exclusion criteria entailed the following: 1) underlying chronic/inflammatory conditions that can cause anemia (e.g., malignancy, renal disease, heart failure, diabetes, and autoimmune diseases other than RA); 2) pregnancy; 3) malnutrition; 4) bone marrow suppression; and 5) (medication consumption for anemia, except for folic acid in methotrexate therapy), diabetes, and malignancy.

Research sampling

The study population was selected using the consecutive sampling technique. In this regard, the RA patients referring to the RDRC were evaluated for the inclusion criteria. Out of 268 RA patients, 36 showed pure ACD, and 44 did not have any subtype of anemia. Therefore, the study was conducted on 80 patients.

Laboratory measurements

Venous blood samples were obtained from the brachial vein. Subsequently, the samples were clotted at the room temperature and centrifuged at 3,000 rpm for 10 min. The centrifuged samples were then stored at -20°C. The serum hepcidin level was measured by the enzyme-linked immunosorbent assay. In addition, serum iron, ferritin, transferrin, TIBC, and ESR were recorded for each patient for more statistical analyses.

Clinical variables

After interviewing, the patients were subjected to clinical examinations by the researchers who were board-certified rheumatologists. The number of the swollen and tender joints was recorded for each patient. In addition, the visual analog scale was used for global health assessment. Then, the DAS28 based on ESR (DAS28-ESR) was administered to patients (16). Both DAS28-C-reactive protein and DAS28-ESR are valid and simple tools to assess disease activity in patients with RA in daily practice (17,

18). Based on the DAS28-ESR level, the included patients were categorized into two groups, namely, inactive to moderately active RA (n=52; DAS28-ESR level \leq 5.1) and highly active RA (n=28; DAS28-ESR level $>$ 5.1).

Other documented data were the RA duration and the treatment and medications the patients received. The prescribed medications mostly included oral prednisolone (5-7.5 mg per day), methotrexate (2.5 up to 15 mg per week), sulfasalazine (500-2,000 mg; in a few patients), alendronate (7 mg per week), a daily combination of calcium (1,000 mg) with vitamin D (800 IU), and folic acid (5 mg per week).

Statistical analysis

The continuous variables were presented as the mean, standard deviation, median, and interquartile range. The normality of distribution in the continuous data was assessed using the Kolmogorov-Smirnov test, Shapiro-Wilk test, and histograms. To compare the categorical variables between the RA patients with and without ACD, the Chi-square test or Fischer's exact test was employed. Furthermore, the comparison of the continuous variables between the RA patients with and without ACD, as well as between the inactive to moderately active RA and highly active RA groups, was performed using Student's t-test and the Mann-Whitney U test for the normally and non-normally distributed data, respectively.

In addition, binary logistic regression analysis (stepwise method) was run to predict the variables that could affect the DAS28-ESR score. In this analysis, the DAS28-ESR score was considered as the dependent variable. A p-value less than 0.05 was considered statistically significant for two-by-two analyses. For logistic analysis, a p-value equal to 0.1 was considered statistically significant. All data analyses were performed in the SPSS software version 20.0 (IBM Corp.; Armonk, NY, USA).

Ethical consideration

This study was in line with the Declaration of Helsinki. The research objectives were explained to the patients, and their consent was obtained prior to the study. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Results

Anemia of chronic disease

According to the results, 87.5% (n=70) of the participants were female. The mean age of the patients was 50.1 ± 13.58 years (age range, 24-80 years). The data indicated that 36 (45%)

Table 1. Comparison of the demographic and clinical characteristics of rheumatoid arthritis patients with and without anemia of chronic disease

	All patients (n=80)	RA with ACD (n=36)	RA without ACD (n=44)	Sig.
Age, year	50.15 (±13.58)	51.97 (±14.18)	48.66 (±13.04)	0.28 ^a
Gender, female	70 (87.5%)	36 (100%)	34 (77.3%)	0.002 ^b
BMI, kg/m ²	27.08 (±5.23)	25.19 (±4.69)	28.57 (±5.19)	0.004 ^a
RA duration, month	62.49 (±56.15)	48 [60]	54 [69]	0.56 ^a
RA therapy duration, month	4.78 (±4.38)	3.5 [4.8]	4 [5]	0.34 ^a
DAS28-ESR	4.51 (±1.51)	4.96 (±1.57)	4.15 (±1.37)	0.01 ^a
Serum hepcidin, ng/mL	1200.09 (±684.97)	1207 [985.2]	923.8 [677.3]	0.57 ^a
Serum iron, µg/dL	62.11 (±32.55)	53 (54)	57 (50)	0.55 ^a
Iron binding capacity, µg/dL	348 (±60.1)	349.42 (±75.15)	346.84 (±45.14)	0.93 ^a
Transferrin saturation, %	18.58 (±10.97)	14.45 [16.4]	16.46 [11.63]	0.62 ^a
Prednisolone	49 (61.3%)	21 (58.3%)	28 (63.6%)	0.62 ^b
Methotrexate	39 (48.8%)	16 (44.4%)	23 (52.3%)	0.48 ^b

RA: rheumatoid arthritis; TS: transferrin saturation; BMI: body mass index

^aStudent's t-test, data are shown as the mean±standard deviation; ^bChi-square test; *Mann-Whitney U test, data are presented as median [interquartile range]**Table 2.** Comparison of demographic and clinical characteristics of patients with rheumatoid arthritis based on disease activity measured by DAS28-ESR

	DAS28-ESR ≤5.1 (n=52)	DAS28-ESR >5.1 (n=28)	p
Age	47.91 ±13.18	54.56 ±13.5	0.04 ^a
Gender, female	44 (84.61%)	26 (92.85%)	0.15 b
BMI, kg/m ²	26.71 ±5.1	27.84 ±5.5	0.39 ^a
RA duration, month	48 [57]	36 [96]	0.91 ^a
RA therapy duration, month	4 [4]	3 [7.09]	0.83 ^a
Anemia of chronic disease	18 (34.61%)	18 (64.28%)	0.005
Serum hepcidin, ng/mL	1090.9 [631.4]	1131.8 [991.3]	0.53 ^a
Serum iron, µg/dL	57 [51]	46 [46]	0.09 ^a
TIBC, micg/dL	352.42 (60.62)	339.33 (59.24)	0.36 ^a
Transferrin saturation, %	16.86 [15.67]	14.01 [11.55]	0.2 ^a
Prednisolone	37 (71.15%)	12 (42.85%)	0.02 b
Methotrexate dosage	3.75 [2.5]	1.25 [1.56]	0.01 ^a

RA: rheumatoid arthritis; BMI: body mass index; TIBC: total iron binding capacity

^aStudent's t-test, data are shown as the mean±standard deviation; ^bChi-square or Fischer's exact test; *Mann-Whitney U test, data are presented as median [interquartile range]**Table 3.** Input variables in the multiple logistic regression model recognized as significant predictors of active rheumatoid arthritis (DAS28-ESR>5.1)

	B	SE	p	Adjusted OR
Methotrexate dosage	-0.72	0.39	0.06	0.48
Constant	0.16	1.002	0.86	1.18

SE=standard error; OR=odds ratio

patients had ACD. Table 1 tabulates the clinical characteristics of the participants and comparison of the variables between the two groups with and without ACD.

All of the RA patients with ACD were female and had a significantly lower body mass index, higher number of tender joints, more active disease (i.e., a higher DAS28-ESR score), and higher ESR, compared to those without ACD. However, these groups were comparable in terms of other variables. The median serum hepcidin level was higher in the RA with ACD group, compared to that in the RA without ACD group; however, this difference was not statistically significant (p=0.57).

28-joint Disease Activity based on erythrocyte sedimentation rate (DAS28-ESR)

Table 2 presents the comparison of the studied variables between the inactive to moderately active RA and highly active RA groups. As the results demonstrated, the RA patients with active disease were older and more likely to have ACD with a lower serum iron level. However, the serum hepcidin level was not significantly different between the two groups.

Predictors of active rheumatoid arthritis

The variables included in the binary logistic regression analysis were age, ACD, serum iron, serum hepcidin, and methotrexate dosage. Table 3 summarizes the results of the regression analysis. Methotrexate dosage remained a significant predictor of active RA (i.e., DAS28-ESR score>5.1).

Discussion

Hepcidin is a small peptide associated with the red blood cell kinetics and inflammation in healthy individuals. This peptide acts as a major regulator of iron absorption in the intestines and iron recycling via macrophages (19). Hepcidin is considered to be an acute-phase reactant. The diagnostic significance of hepcidin has been reported in several conditions, such as inflammation, neoplastic diseases, and diabetes mellitus (20, 21).

Anemia is a major contributor to morbidity in RA (3). In the current study, we evaluated the serum hepcidin level in patients with RA and its correlation with inflammation and anemia. Based on our findings, hepcidin showed no association with the RA activity, and it could not significantly predict active RA. These results are somehow inconsistent with some of the previously reported studies, which suggested that serum hepcidin may act as a surrogate marker

for RA activity (6, 11, 12). However, these comparisons should be made cautiously as the design of studies and the way that the findings were interpreted are different. The mature form of hepcidin in erosive RA is reportedly correlated with RA activity. This is mainly due to the association of hepcidin with inflammatory markers, such as ESR (7). Thus, hepcidin cannot be introduced as an independent marker for RA activity and radiologic progression of joint erosion.

In a study by Demirag et al. (6), 40 RA patients with anemia (19 cases) and without anemia (21 cases) were included. Among 19 patients with anemia, anemia in only 10 patients was attributed to iron deficiency. The current sample size (36 patients) was higher than in the mentioned study. The authors reported that serum hepcidin in the RA group with non-iron deficiency anemia (619 ng/mL) was higher in comparison to other groups. One of the differences between the presented results and the significant difference observed in Demirag et al. (6) study could be a larger sample size in our study. In addition, in contrast to our analyses where the RA activity was measured using the ESR level, the authors calculated DAS28 based on CRP, and based on this definition of the RA activity, they showed that hepcidin was significantly higher in active RA.

In another study (12) investigating the correlation between hepcidin and RA disease activity, the authors found that the serum hepcidin was higher in patients with active RA (similar to the current study, active RA was defined as DAS28 >5.1) when compared to inactive to moderate RA (128 vs. 73 ng/mL). The frequency of anemia in the active RA group (91.2%) was also higher than in the inactive to moderate RA group (48.7%). However, the authors did not perform more analyses in subcategories of patients with anemia in either group. Furthermore, anemia type, whether due to iron deficiency or as the result of RA, was not clearly defined in the report.

The main objective of our study was to find significant predictive factors for the RA activity rather than anemia. Accordingly, after a thorough evaluation of complete blood count and implementation of iron tests, only patients with ACD were included, and those with iron deficiency anemia were excluded. Even after the adjustment for the effect of ACD, hepcidin was not recognized as the main predictor of RA activity. In the current study, a wide set of possible variables contributing to RA activity (e.g., RA duration and medications) were investigated.

Hepcidin has gained attention in RA studies owing to the involvement of IL-6 as a major multifunctional cytokine in this disease, which induces the hepcidin production (22, 23). Given the significant role of IL-6 in joint destruction, acute-phase reactant induction, and overall disease activity (24), blocking this interleukin reduces the RA activity (25). The IL-6 has been also introduced as the central ACD mediator (26). This interplay among IL-6, disease activity, and serum hepcidin has been the main reason to concentrate on the hepcidin level as a marker that could be used to evaluate the RA activity.

In the current study, the DAS28-ESR cut-off value of 5.1 was used to divide the patients into the low and high RA activity groups, following previous studies (11). In this report, the authors showed that, in agreement with our results, the hepcidin level was not different in RA with and without ACD cases. However, hepcidin showed a moderate correlation with disease activity ($r=0.4$). In the mentioned study, ESR had a higher correlation with disease activity ($r=0.53$) than hepcidin.

Given more evidence on the possible role of hepcidin in chronic inflammation, several studies have been conducted to elucidate other possible applications of hepcidin in clinical practice. For example, some efforts have been made to use hepcidin in discriminating ACD from iron deficiency anemia; however, hepcidin was not applicable in this regard (4). In addition, this peptide has been used to determine the clinical efficacy of some therapeutic interventions (27).

The RA duration can be also considered as a significant contributor when evaluating hepcidin and anemia in RA. In this regard, hepcidin was reported to show no correlation with changes in the hemoglobin level at the earlier RA stages (13). In the present study, the RA duration was not a significant predictor for the RA activity. Although the hepcidin level was higher in the RA with ACD group than that in the RA without ACD group, the difference was not statistically significant.

However, this result was in line with those from the previous studies demonstrating the elevation of the hepcidin level in the presence of ACD (6). The serum iron level could be normal or increased in patients with ACD. In the current study, serum iron was within the normal range in all participants, and it did not differ between the two groups based on the presence or absence of ACD.

Strengths and limitations

One of the limitations of the current study was a relatively small sample size. However, we included a wide array of variables that can affect the RA activity to investigate a possible role of hepcidin considering the confounding effect of ACD.

Conclusion

The findings of the present study indicate that there is no association between the serum hepcidin level and the ACD or RA activity. It seems that it is premature to include the hepcidin level in clinical practice to evaluate the disease activity in patients with RA, with or without ACD.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Mashhad University of Medical Sciences.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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