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Original Investigation

The correlation between ferritin level and acute phase parameters in rheumatoid arthritis and systemic lupus erythematosus

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Abstract

Objective: In this study, we evaluated the relationship between ferritin levels and disease activation in rheumatoid arthritis (RA) patients.

Material and Methods: We included 44 patients with RA, 20 patients with systemic lupus erythematosus (SLE), 25 patients with infection, 22 patients with malignancy, and 20 healthy control subjects. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), whole blood count, and serum iron parameters were determined in all cases. The joint findings in RA patients were recorded, and disease activity score (DAS) was calculated. In SLE patients, antinuclear antibody (ANA) and anti-dsDNA titers and C3 and C4 complement levels were determined. SLE disease activity index (SLEDAI) score was calculated.

Results: Serum ferritin levels in the RA, SLE, and control groups were lower than those in the infection and malignancy groups ($p<0.05$). The ferritin levels in the RA group did not differ significantly from the SLE and control groups. In RA patients, serum ferritin level had a positive correlation with ESR, CRP, RF, platelet count, and DAS score and had a negative correlation with hematocrit (all p values <0.05). In SLE patients, on the other hand, serum ferritin had a positive correlation with ANA, anti-dsDNA, and SLEDAI (all p values <0.05). According to DAS, ferritin level in inactive RA patients was lower than that in active RA patients. When transferrin saturation was considered, iron deficiency anemia was a quite frequent finding in both active and inactive RA patients.

Conclusion: Interestingly, we observed that ferritin level in RA patients was similar to the control group; however, it was a good parameter of disease activation. This is because a reduction in storage iron and resultant iron deficiency anemia are very common in RA patients.

Key words: Rheumatoid arthritis, ferritin, systemic lupus erythematosus, acute phase response, inflammation

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease. The determination of disease activity is quite important in choosing the treatment modality and in following up patients. It is known that serum C-reactive protein (CRP) level in RA is a good indicator of disease activation (1). In addition, it should also be known how other acute phase proteins are affected according to the degree of inflammation during the course of the disease.

Ferritin is a high-molecular-weight protein containing iron, and it functions as an iron store complex (2). Under normal conditions, serum ferritin level is associated with the amount of iron stores (2). However, serum ferritin level may increase disproportionately to iron stores in hepatic and renal diseases, in systemic infection or inflammation, in malignancies, and in patients who are chronically transfused with erythrocyte suspensions (3, 4). Anemia-especially, iron deficiency anemia-is encountered quite often in RA. Therefore, the evaluation of ferritin levels in RA patients gains special importance (5). The chronic inflammation in RA leads to secretion of proinflammatory cytokines that influence iron metabolism. The parameters that are most affected are plasma iron levels and the production of transferrin, ferritin, and hepcidin.

In our study, we determined serum ferritin levels in RA patients and evaluated whether serum ferritin levels in RA patients were correlated with disease activation.

Material and Methods

Forty-four RA patients and 20 systemic lupus erythematosus (SLE) patients were taken as the study group. The study was conducted in Trakya University Medical Faculty, Department of Rheumatology. All RA patients were diagnosed according to the American College of Rheumatology (ACR) 1987 criteria, and all SLE patients were diagnosed according to modified ACR criteria (6, 7). The diseased control group was taken

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as 25 hospitalized patients with various infections and 22 patients with malignancies. Twenty subjects with no known disease were taken as the healthy control group. Patients who had taken oral or parenteral iron therapy or those who had any episode of bleeding within the last 3 months were not included into the study. RA and SLE patients who were pregnant or who had current infectious or malignant diseases were also excluded.

The disease activity in RA patients was calculated according to disease activity score (DAS). The modified DAS was computed according to published guidelines (8). Patients with a DAS score >3.8 were accepted to have active disease. The activity of SLE patients was calculated according to SLE disease activity index (SLEDAI) (9). All RA and SLE patients underwent a detailed physical examination, and joint findings were recorded. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), whole blood count, iron, total iron-binding capacity (TIBC), and ferritin levels of all subjects were determined. In addition, antinuclear antibody (ANA), anti-dsDNA titers, and serum C3 and C4 complement levels in SLE patients were determined. The percentage of transferrin saturation was calculated as defined by Woorwood (10). According to World Health Organization (WHO) criteria, anemia was said to be present when hemoglobin was <11 g/dL in females and when hemoglobin was <13 g/dL in males.

The study design was approved by our institution's ethical committee, and both oral and written informed consent was obtained from all subjects.

Kruskal-Wallis test was used in comparing serum ferritin and other acute phase parameters between the groups. Mann-Whitney U-test was used for comparisons between groups. Spearman correlation test was used to determine the relationship between ferritin and other acute phase proteins and disease activation parameters. To compare the ratios between groups, chi-square test was used.

Results

The ferritin levels in the infection and malignancy groups were significantly higher when compared to the RA, SLE, and the control groups (Table 1). The ferritin levels between the RA and SLE groups and between these groups and the control group did not differ significantly. The mean values of other acute phase proteins in all groups are seen in Table 1.

In the RA group, ferritin level showed a positive correlation with ESR (r=0.59, p<0.001), CRP (r=0.59, p<0.001), platelet count (r=0.52, p<0.001), and DAS score (r=0.34, p=0.02) and had a negative correlation with hematocrit levels (r=-0.35, p=0.02) (Table 2).

Table 1. The serum levels of ferritin, CRP, and ESR in patients with RA and other groups (values are given as means±SE)

Groups	ESR (mm/hr)	CRP (mg/dL)	Ferritin (ng/mL)
Malignancy group (n=33)	53.5±6.9	2.9±0.9	364.4±70.2*
Infection group (n=32)	57.8±6.8	12.3±1.6*	466.4±84.5*
Rheumatoid arthritis (n=44)	63.7±6.2	3.8±0.8	81.0±11.9
SLE (n=20)	50.1±7.4	1.2±0.3	191.8±85.1
Healthy control (n=21)	18.7±2.9*	0.6±0.1	80.8±14.9

ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; SLE: systemic lupus erythematosus
(*) p<0.001 Different from other groups

Table 2. Correlation between acute phase parameters and ferritin in patients with RA

	ESR (mm/hr)	Ferritin (ng/mL)	CRP (mg/dL)	RF (IU/L)	Hematocrit (%)	Platelets (/mm^3)
Ferritin	0.59*					
	<0.001a					
CRP (mg/dL)	0.69	0.59				
	<0.001	<0.001				
RF (IU/L)	0.3	0.27	0.35			
	0.049	0.07	0.02			
Hematocrit (%)	-0.46	-0.31	-0.39	-0.021		
	0.001	0.04	0.008	0.89		
Platelets (/mm^3)	0.57	0.52	0.32	0.4	-0.17	
	<0.001	<0.001	0.035	0.006	0.27	
DAS	0.69	0.34	0.64	0.3	-0.35	0.32
	<0.001	0.02	<0.001	0.047	0.02	0.03

ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; RF: rheumatoid factor; DAS: disease activity score
(*): r: Spearman correlation coefficients
(a): p

In the SLE group, serum ferritin level had a significant positive correlation with ANA titer (r=0.66, p=0.002), anti-dsDNA titer (r=0.82, p<0.001), and SLEDAI score (r=0.45, p=0.04) (Table 3).

Ten patients (6.7%) in the study had serum ferritin levels over 1000 ng/mL. Five of them had an infection, 3 had a malignancy, and 2 had SLE.

Rheumatoid arthritis patients who were inactive according to DAS score had significantly lower ferritin levels (42.1±39.5) than active RA patients (113.5±89.4) and the healthy control group (p values, respectively, 0.03 and 0.002).

Twenty-three RA patients (52.3%) had anemia. The ratio of anemic subjects (35%) among inactive RA patients was significantly lower than those in patients with active RA (66.7%) (p=0.036). Low transferrin saturation, which reflects iron deficiency, was more frequent in inactive anemic RA patients than in active RA patients with anemia (57.1% vs. 37.5%, p>0.05).

Discussion

It is known that certain acute phase proteins increase more predominantly in some inflammatory diseases and reflect disease activity better and that others are affected to a lesser degree (11). Important examples of this fact are that ferritin levels in Still's disease and CRP response in SLE are not marked. In our study, we observed that ferritin, which is an acute phase protein, together with ESR and CRP, was significantly increased in patients with malignancy and infection when compared to the control group. The differences in acute phase response among groups might probably be explained by the variability in the production and secretion of cytokines and mediators in different pathophysiologic conditions (11). It is known that ferritin synthesis is induced by interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α in hepatocytes (12). However, in SLE, there is a defect in IL-1 production, and IL-6 and TNF-α levels are increased (13). Therefore, the presence of high ferritin levels in SLE shows that IL-1 is not the major cytokine in the synthesis of ferritin.

In the literature, there are conflicting data about serum ferritin levels in RA. In one study comparing ferritin levels in RA and osteoarthri-

Table 3. Correlation between acute phase parameters and ferritin in patients with SLE

	ESR (mm/h)	Ferritin (ng/mL)	CRP (mg/dL)	Antinuclear antibody titer	Anti-dsDNA titer	C3	C4
Ferritin	-0.003*						
	0.99a						
CRP	0.74	0.3					
	<0.001	0.2					
Antinuclear antibody	-0.22	0.66	-0.04				
	0.35	0.002	0.85				
Anti-dsDNA	-0.23	0.82	-0.06	0.86			
	0.4	<0.001	0.83	<0.001			
C3 complement level	-0.13	-0.16	-0.14	-0.01	-0.25		
	0.6	0.5	0.56	0.96	0.35		
C4 complement level	-0.09	-0.05	-0.23	-0.12	-0.13	0.6	
	0.7	0.83	0.32	0.6	0.63	0.005	
SLEDAI	0.02	0.45	-0.02	0.36	0.51	-0.08	-0.26
	0.92	0.04	0.93	0.13	0.04	0.72	0.26

ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; SLEDAI: SLE disease activity index
(*): r: Spearman correlation coefficients.
(a): p

tis (OA) patients, high serum ferritin levels were found in RA patients (14). In another study, serum ferritin levels in RA were not different from those in controls (15). However, in both of these studies, ferritin levels in the synovial fluid of RA patients were higher than those in OA. In the study of Ota et al. (14), the molecular structures of ferritin produced in synovial fluid and serum were seen to be different, and it was proposed that this was because of local ferritin production in the inflamed joint in RA. In another study comparing serum ferritin levels between active RA patients and healthy controls, no difference was found (16). In our study, ferritin levels in RA patients were not different from controls. However, when RA patients who were in remission according to DAS score were taken as a subgroup, it was observed that ferritin levels in those subjects were lower than those in controls and also in active RA patients.

In our RA patients, there was a significant correlation between serum ferritin levels and CRP, ESR, and platelet count, which reflect disease activation. In the study of Hannonen et al. (17), it was detected that serum ferritin level in RA correlated with disease activity; however, Koman et al. (15) observed that only synovial ferritin levels, not serum levels, had a correlation with CRP. The conflicting data in these studies might probably be explained by the inclusion of an insufficient number of RA patients. In our study, interestingly, serum ferritin levels in RA were similar to controls; however, they had a good correlation with parameters that reflect disease activation. Another finding that supports the relation with disease activation is the lower ferritin levels in inactive RA patients than in controls. Iron deficiency was more frequent in our inactive RA patients. This shows that low ferritin levels in these patients are because of the higher frequency of iron deficiency anemia. In our study, the gold standards for the diagnosis of iron deficiency in RA, which are bone marrow iron stain and serum transferrin receptor analysis, could not be performed. However, recent studies report that determination of transferrin receptor in anemic RA patients is not diagnostic by itself in the absence of iron stores (18). In addition, synovial ferritin production in active RA contributes to the increase of ferritin in active disease. As a result, we might conclude that ferritin level in RA increases in correlation with other acute phase proteins in the case of disease activity and that the low basal ferritin level in inactive RA does not reach that in SLE.

We observed that serum ferritin level in our SLE group was higher than in the control group, and it had a significant positive correlation with ANA, anti-dsDNA titer, and SLEDAI score. On the other hand, ferritin level in this group had no significant relation with acute phase parameters. Nishiya et al. (19) stated that ferritin levels in SLE were higher than in controls and had a positive correlation with anti-dsDNA and a negative correlation with complement levels. Another study about this subject concluded that the change in serum ferritin level was associated with a change in therapy; in contrast, it was not associated with changes in ESR, CRP, and anti-dsDNA (20). One recent study, including few patients, observed that ferritin levels increased in >70% of SLE activations according to SLEDAI scores (21). In the series of Lim et al. (20), ferritin levels in SLE patients with hematologic findings and serositis were increased more prominently. Data on more patients are necessary to determine the features associated with extremely high ferritin levels in SLE.

As a result, we observed that interestingly, ferritin levels in our RA patients were not different from controls; however, it was a good parameter that reflected disease activation. The most important reasons for this result are probably the high frequency of iron deficiency in these patients and ferritin levels, which were lower than controls in inactive RA patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University Faculty of Medicine.

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

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