

Correlations between Serum prohepcidin level disease activity in rheumatoid arthritis and systemic lupus erythematosus

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Introduction

The aim of this study was to determine whether there is a relation between serum prohepcidin level and disease activity of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and to discover whether it has a role in the anaemia of chronic disease occurring in RA and SLE patients.

Patients and methods

This study was carried out on 30 patients suffering from RA and 30 patients suffering from SLE. In addition, 20 healthy volunteers were recruited as controls. All patients and controls were subjected to full history taking, thorough clinical examination, locomotor system examination, assessment of the disease activity in RA patients using the Disease Activity Score-28, assessment of the disease activity in SLE patients using Systemic Lupus Erythematosus Disease Activity Index, laboratory investigations, including complete blood count, erythrocyte sedimentation rate (ESR), rheumatoid factor and C-reactive protein (CRP), and measurement of serum prohepcidin levels by the enzyme-linked immunosorbant assay.

Results

The mean serum prohepcidin concentration was 395.2 ± 551.4 ng/ml in RA patients, whereas it was 381.5 ± 88.07 in SLE patients and 121.4 ± 11.1 ng/ml in healthy volunteers. The prohepcidin concentration correlated with the rheumatoid factor, C-reactive protein, ESR, disease duration, morning stiffness, tender joint count, swollen joint count, Larsen score, haemoglobin level and Disease Activity Score-28 in RA patients. There were positive significant correlations between the mean serum prohepcidin concentration and platelets number, haemoglobin level and ESR in SLE patients and insignificant correlations between the mean serum prohepcidin concentration and Systemic Lupus Erythematosus Disease Activity Index.

Conclusion

Prohepcidin could be considered as a useful marker for RA, but not for SLE. Prohepcidin may have a role in anaemia of chronic disease occurring in RA and SLE.

Keywords:

prohepcidin, rheumatoid arthritis, systemic lupus erythematosus

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that primarily affects the synovial joints. It may result in deformed and painful joints [1]. Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder characterized by loss of self-tolerance causing immune-mediated tissue destruction and various clinical presentations [2]. Anaemia is one of the common extra-articular manifestations in RA and SLE [3]. The leading causes of anaemia include chronic inflammation (ACD), iron deficiency anaemia (IDA) due to long-term use of nonsteroidal anti-inflammatory drugs and folate deficiency due to methotrexate therapy and haemolytic anaemia [4]. ACD and IDA are frequently associated with these

diseases, although their pathogenic mechanisms are different and sometimes difficult to differentiate. Moreover, ACD may coexist with IDA. ACD is associated with the pattern of a normochromic and normocytic anaemia. It is associated with a decreased serum iron and total iron-binding capacity, whereas the iron store is increased or normal. Bone marrow aspiration is considered to be the best method for the diagnosis of IDA in the presence of inflammation, but has a disadvantage of being an invasive and expensive diagnostic tool [5]. Hcpidin,

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a recently discovered antimicrobial, cysteine-rich cationic peptide, decreases the intestinal iron absorption, in addition to inhibiting the release of iron from its storage sites located in macrophages, hepatocytes and enterocytes [6]. Hepcidin synthesized by the liver, known as type II acute-phase reactant, regulates intestinal iron absorption, recycling and tissue storage. Beyond the iron regulation, it is closely linked with inflammation and infection. The inflammatory signals, chiefly interleukin-6, induce hepcidin synthesis, which decreases duodenal iron absorption and increases sequestration of iron by macrophage and may play a key role in the pathogenesis of ACD [7]. Hepcidin and its prohormone (prohepcidin) concentrations were found to be increased 100 times during inflammation, which resulted in a decrease in iron absorption and retention of iron in macrophages, decrease in serum iron and eventually causing the ACD [8].

Patients and methods

This study was conducted on 30 RA patients (24 females and six males) diagnosed according to American College of Rheumatology revised criteria [9], 30 patients (27 females and three males) suffering from SLE fulfilling the American College of Rheumatology updated classification criteria for SLE [10] and 20 age and sex-matched apparently healthy volunteers (the control group). The patients and healthy volunteers were selected from the attendants of the outpatient clinic and inpatients of the Rheumatology, Rehabilitation and Physical Medicine Department of Benha University Hospitals. All the studied members signed written informed consent before participation in this study. The study was approved by the Ethical Committee of Benha University Hospitals. Patients with haematological diseases, heart, lung, kidney, liver diseases, acute or chronic infections, malignancy, current pregnancy or delivery within 6 months and history of blood transfusion were excluded from the study. All patients were subjected to full history taking, thorough clinical examination and locomotor system examination. The disease activity using Disease Activity Score-28 (DAS-28) was used for RA patients [11]; disease activity was assessed in SLE patients by using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Activity categories were defined on the basis of no activity (SLEDAI; 0), mild activity (SLEDAI; 1–5), moderate activity (SLEDAI; 6–10), high activity (SLEDAI; 11–19) and very high activity (SLEDAI; 20) [12].

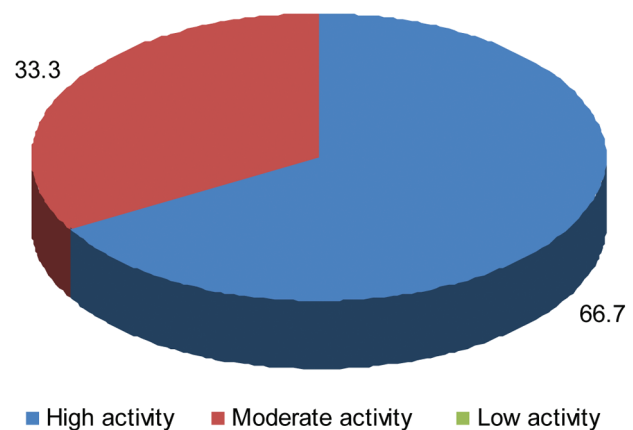
Laboratory investigations included the following: (a) complete blood picture and erythrocyte sedimentation rate (ESR), determined by using the Westergren method; (b) rheumatoid factor (RF) for RA patients (considered positive if <20 IU/ml) [13]; (c) determination of serum urea, creatinine and creatinine clearance; (d) antinuclear antibody testing [14]; (e) determination of anti-double strands DNA antibodies by enzyme immunoassay; (f) measurement of serum complement C3 and C4 (as proposed by Roitt *et al.* [15]); (g) urine analysis for casts and protein/creatinine ratio; (h) measurement of protein in 24h urine; (i) measurement of serum prohepcidin levels by using the enzyme-linked immunosorbant assay using the DRG Hepcidin Prohormone Enzyme Immunoassay K (MyBioSource, San Diego, California, USA) according to the manufacturer's instructions [16]; and (j) plain radiographs of both hands. Statistical analysis was carried out using the SPSS program, version 22 on an IBM compatible computer (SPSS Inc., Chicago, Illinois, USA).

Results

In RA patients group, the disease duration ranged between 5 months and 11 years, with a mean of 3.8 ± 3.06 years. DAS-28 ranged between 4.66 and 7.53, with a mean of 5.57 ± 0.69 . There were 21 RF-positive patients (70%) and nine RF-negative patients (30%). There were 19 C-reactive protein (CRP)-positive patients (63.3%) and 11 CRP negative patients (36.7%). The disease activity grading according DAS-28 is shown in Fig. 1. In the SLE group, the mean disease duration was

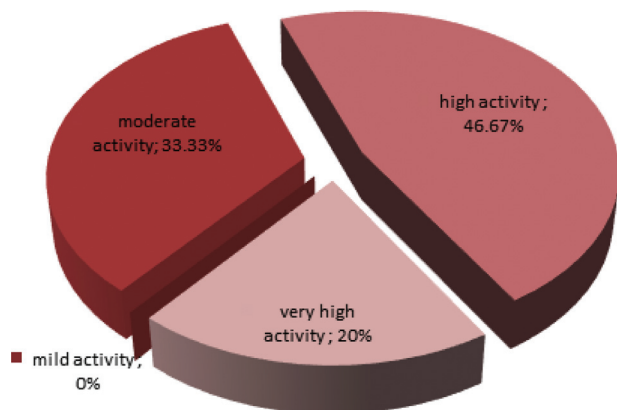
Figure 1

% of disease activity according to DAS



Disease activity grade of the rheumatoid arthritis group. DAS, Disease Activity Score.

Figure 2

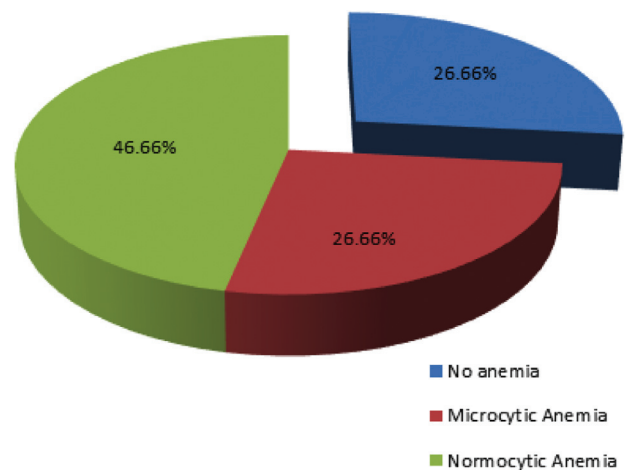


Disease activity grade of the systemic lupus erythematosus group.

4.05 ± 2.04 years; in total, 16 patients (53.3%) had malar rash, 11 patients (36.6%) had photosensitivity, 15 patients (30%) had oral ulcer, 14 patients had arthritis (46.6%), one patient (3.3%) had pericarditis, three patients (10%) had lupus nephritis based on the presence of proteinuria and none of the patients had pleurisy or effusion. The disease activity grading according to SLEDAI was as follows: 10 patients with moderate activity (33.3%), 14 patient (46.67%) with high activity, six patients with very high activity (20%) and none of the patients with mild activity (Fig. 2).

According to the distribution of anaemia among SLE patients, normocytic normochromic was found in 46.66%, microcytic hypochromic in 26.66% and no anaemia in 26.6% of the patients (Fig. 3). Mean prohepcidin concentrations were higher in the RA patients group (395.2 ± 51.4) and the SLE group (381.5 ± 88.07) than in the control group (121.4 ± 11.1), with a highly statistically significant difference ($P \leq 0.001$) (Table 1). Mean serum prohepcidin concentrations were highest in both RA and SLE patients with normocytic anaemia (ACD), with a highly statistically significant difference ($P \leq 0.001$) (Tables 2 and 3). In RA patients, there were statistically significant correlations between serum prohepcidin and disease duration, morning stiffness, tender joint count, swollen joint count, DAS-28, Larsen score, haemoglobin and ESR ($P \leq 0.001$). There were insignificant correlations between mean serum prohepcidin and visual analogue scale, RF titre, CRP titre, white blood cells and platelet count ($P \geq 0.05$) (Table 4). In SLE patients, there were positive significant correlations between mean serum prohepcidin concentrations and platelets, haemoglobin and ESR ($P \leq 0.001$), and insignificant correlations between serum prohepcidin concentrations,

Figure 3



Distribution of anaemia among systemic lupus erythematosus patients.

SLEDAI, CRP titre and white blood cells ($P \geq 0.05$) (Table 5).

Discussion

It seems reasonable to determine more specific biomarkers in correlation with the disease activity in RA and SLE patients to monitor disease progression and assess the effects of therapies, and to identify more biomarkers for measuring disease activity and damage [1]. Anaemia frequently affects most RA and SLE patients at some time in the course of their disease. Multiple mechanisms contribute to the development of anaemia, including inflammation, renal insufficiency, blood loss, dietary insufficiency, medications, haemolysis, hypersplenism and aplastic anaemia [17]. In addition, ACD may occur in those patients resulting from suppressed erythropoiesis because of chronic inflammation [18]. Furthermore, hepcidin synthesis is greatly induced during inflammation, trapping iron in the macrophages causing ACD [19]. The assays for measuring hepcidin have lacked precision, accuracy and internal validation. Many studies have relied on the measurement of hepcidin mRNA concentrations in the liver, and, although this correlates well with the concentration of mature hepcidin in the serum, hepatic biopsies are clinically indicated in only a limited number of cases [20]. Although antibodies to hepcidin-25 have been proven to be difficult to be generated, prohepcidin is far more immunogenic, and a prohepcidin enzyme-linked immunosorbant assay is commercially available [21]. In ankylosing spondylitis, serum prohepcidin and hepcidin levels are closely associated with disease activity and might play a role in the pathogenesis of associated ACD [6]. Serum hepcidin and prohepcidin

Table 1 Mean serum prohepcidin concentrations in the studied groups

Variable	Patients group (N=30)		'Z' of MWU test	P value
	Mean±SD	Median (IQR)		
Prohepcidin in RA patients (ng/ml)	395.2±51.4	213.8 (126.7–441.4)	4.57	0.001*
Prohepcidin in SLE patients (ng/ml)	381.5240±88.07152	372.85 (130–450)	14.95	0.015*
Control grouping/ml	121.4±11.1	116.6 (113.1–134.5)		

IQR, inter quartile range; MWU, Mann–Whitney *U*-test; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

*Significant.

Table 2 Mean serum prohepcidin concentrations according to type of anaemia in SLE patients

Group	n	Prohepcidin (mean±SD)	KW test	P value
SLE without anaemia	8	360.8113±97.79894	17.47	0.02*
SLE with microcytic anaemia	8	386.5586±82.79068		
SLE with normocytic anaemia	14	393.4263±95.59035		
Control group	20	83.7300±13.64301		

KW test, Kruskal–Wallis test; SLE, systemic lupus erythematosus.

P > 0.05: insignificant.

Table 3 Mean serum prohepcidin concentrations according to type of anaemia in the RA group

Group	n	Prohepcidin (mean±SD)	KW test	P value
RA without anaemia	2	194.48±43.491	22.5	<0.001*
RA with microcytic anaemia	7	220.41±143.493		
RA with normocytic anaemia	21	472.55±643.118		
Control	20	121.43±11.131		

KW test, Kruskal–Wallis test; RA, rheumatoid arthritis.

levels are significantly altered in patients with irritable bowel disease (IBD) compared with healthy controls [22]. Previous studies have suggested a substantial role of these two hormones in the development of anaemia in IBD and concluded that hepcidin seems to have a lower efficacy than do other parameters in the detection of disease activity of IBD [23]. The present study revealed that prohepcidin concentrations were higher in SLE patients and RA patients than in controls, with a highly statistically significant difference ($P < 0.001$). These findings were in agreement with those of a study by Koca *et al.* [24], who found that prohepcidin levels were higher in RA and SLE patients than in healthy controls. Moreover, our findings support those of a study by Kim *et al.* [25], who reported the same results.

Our study demonstrated a positive significant correlation between the serum prohepcidin concentrations and DAS-28 ($P < 0.001$) in RA patients, which was in line with the findings of a study by Adriana *et al.* [26]. In our study, we found insignificant correlations between serum prohepcidin concentrations and SLEDAI score ($P = 0.061$), which was in agreement with the findings of Dagli and colleagues, who concluded that serum prohepcidin was not associated with the disease activity in SLE patients [3]. On the other hand, in their study, Koca

and colleagues stated that the serum prohepcidin levels did not correlate with disease activity scores in the RA and SLE groups [25].

In our study, serum prohepcidin concentrations were highest in patients with normocytic anaemia either in RA or SLE, with a highly statistically significant difference ($P < 0.001$ and $P = 0.002$, respectively). The previous findings were consistent with those of Means [27], who found that serum prohepcidin concentrations were significantly higher in RA patients with ACD.

The previous findings were in contrast to those of a study by Kemna *et al.* [21], who postulated that serum prohepcidin could not represent the bioactive hepcidin and did not reflect the actual anaemic parameters. Furthermore, our data were in contrast to those of a study by Roe *et al.* [28], who conducted their studies on healthy individuals and suggested that serum prohepcidin had no role to play in iron haemostasis. Moreover, Nagy *et al.* [29] concluded that serum prohepcidin level determination in itself was not a satisfactory diagnostic or prognostic measure in anaemia of chronic inflammatory bowel diseases. Although our findings were in agreement with those of Emerah *et al.* [30], who concluded that serum prohepcidin reflects the disease activity and thus

Table 4 Correlations of mean serum prohepcidin concentrations with clinical findings and laboratory investigations of RA patients

	Patients' group (N=30)	
	r	P value
Age (years)	-0.129	0.49
Disease duration (years)	0.57	0.001*
Morning stiffness (min)	0.52	0.009*
TJC	0.755	<0.001*
SJC	0.637	<0.001*
VAS	0.209	0.26
DAS-28	0.629	<0.001*
Larsen score	0.453	0.012*
RF titre (N=27)	0.038	0.85
CRP titre (N=19)	0.073	0.077
ESR	0.639	<0.001*
Hb	-0.402	0.028*
HCT (%)	0.64	0.73
MCV (fl)	0.157	0.41
MCH (pg)	-0.148	0.43
MCHC (g/dl)	-0.233	0.21
WBCs ($\times 10^3$)	0.334	0.07
PLTs ($\times 10^3$)	-0.112	0.55

CRP, C-reactive protein; DAS-28, Disease Activity Score-28; Hb, haemoglobin; HCT, haematocrit; ESR, erythrocyte sedimentation rate; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; PLT, platelet; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; WBC, white blood cell. *Significant. $p > 0.05$: insignificant. $p < 0.05$: significant.

Table 5 Correlations of serum prohepcidin concentrations and laboratory investigations of SLE patients

Variable	Prohepcidin in SLE patients (N=30)	
	r	P value
Age (years)	0.040	0.835
Disease duration (years)	0.001	0.970
Hb (g/dl)	0.257	0.0171*
MCV (fl)	0.252	0.179
MCH (pg)	0.221	0.241
WBCs ($\times 10^3$)	0.140	0.462
Platelets ($\times 10^3$)	0.436	0.016*
CRP titre (N=19)	0.267	0.153
ESR (mm/h)	0.450	0.013*
SLEDAI score	0.927	0.061
Creatinine (mg/dl)	0.115	0.546
24 h urine protein	0.205	0.276

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; WBC, white blood cell. $P > 0.05$: insignificant. $P < 0.05$: significant.

prohepcidin could be used as another useful marker for RA disease activity, we disagreed on one point, which was that, in their study, they could not find any difference in prohepcidin concentration between the patients with RA and those without.

Conclusion

Our findings suggested that serum prohepcidin concentration may be strongly associated with disease activity in RA patients but not in SLE patients. Prohepcidin could play a role in ACD associated with RA and SLE.

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Conflicts of interest

None declared. The authors have declared no conflicts of interest.

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