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Pathobiochemical Mechanisms Relating Iron Homeostasis with Parameters of Inflammatory Activity and Autoimmune Disorders in Rheumatoid Arthritis

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Aim: To find the correlations between the parameters of iron homeostasis, inflammatory activity and autoimmune disorders in rheumatoid arthritis (RA).

Materials and methods: The present study included 114 patients with RA and 42 healthy controls. We determined the parameters of iron homeostasis: serum iron, total iron binding capacity (TIBC), ferritin and soluble transferrin receptor (sTfR), the parameters of inflammatory activity: C-reactive protein (CRP), interleukin-6 (IL-6) and prohepcidin, and the parameters of autoimmune disorders: rheumatoid factor (RF), anti-cyclic citrullinated peptide (antiCCP) antibodies and DAS 28.

Results: The levels of sTfR, CRP, IL-6 and prohepcidin were significantly higher in RA patients than those in the controls and the level of serum iron was significantly lower in RA than that in the control group. Unlike the controls, in RA, there was a significant positive correlation of sTfR with the parameters of inflammatory activity (IL-6, prohepcidin, ESR) and with the parameters of autoimmune disorders (DAS 28, RF, antiCCP). A negative correlation of serum iron with sTfR was found only in RA patients. Prohepcidin positively correlated with the parameters of inflammation (CRP, ESR) and with the parameters for evaluation of autoimmune disorders (DAS 28 and RF) in the RA group.

Conclusion: Our study shows that the simultaneous determination of the two parameters sTfR and prohepcidin is most informative for evaluation of the changes in iron homeostasis in RA. The increase of both parameters provides information for tissue iron deficiency (assessed by the level of sTfR), caused by the inflammation when prohepcidin is expressed.

BACKGROUND

Hypoferremia is a common response to systemic infections or inflammation characterized by iron sequestration in its stores as a protective mechanism and manifestation of anemia.^{1,2} The proinflammatory cytokine interleukin-6 (IL-6) plays a key role in anemia of chronic disease (ACD), also called anemia of inflammation, through induction of the iron-regulatory hormone hepcidin, which is responsible for most of the disorders in anemia of chronic inflammatory processes.³ Hepcidin is a peptide hormone secreted by the liver in response to inflammatory stimuli and iron overload. It is synthesized

as a preproform – preprohepcidin composed of 84 amino acids.^{4,5}

Rheumatoid arthritis (RA) is a systemic autoimmune disease that involves a chronic, progressive inflammation. The changes in iron homeostasis in RA may be due to ACD, iron deficiency anemia (IDA) or both.⁶⁻⁹ As anemia in RA may cause severe symptoms and aggravation of other diseases manifestations, early detection of anemia is of vital importance.⁹

Transferrin receptor is a membrane glycoprotein composed of two monomers bound together by two disulfide bonds. The content of the soluble form of

the receptor sTfR in plasma is proportional to the amount of transferrin on the surface of hematopoietic cells¹⁰ and reflects the extent of iron deficiency. The advantage of measuring sTfR is that there are only two conditions related to high sTfR: 1) increased production of erythrocytes and; 2) tissue iron deficiency.¹¹

There is no clear evidence in literature concerning the diagnostic value of sTfR^{12,13} and serum ferritin¹⁴. Also, the comments on the associations of iron homeostasis parameters with markers of inflammatory activity and autoimmune disorders in RA differ from one another.¹⁵⁻¹⁸ This can possibly be accounted for by differences in the number of patients, their involvement in common groups with rheumatology diseases or the usage of different methods for evaluation.

AIM

The aim of the study was to find the correlations between the parameters of iron homeostasis, inflammatory activity and autoimmune disorders in rheumatoid arthritis (RA).

MATERIALS AND METHODS

PATIENTS

The present study included 114 patients with RA (16 males and 98 females, mean age 58 ± 10 yrs,) and 42 healthy controls. All patients were diagnosed as having RA according to EULAR 2010 criteria.^{19,20} The patients included in the present study had moderate ($3.2 < \text{DAS } 28 \leq 5.1$) and high ($\text{DAS } 28 > 5.1$) disease activity.

We used the World Health Organization (WHO) definitions of anemia as a hemoglobin threshold of < 12 g/dl in women, and < 13 g/dl in men. On the basis of these criteria the patients were distributed in two subgroups. The first group was composed of 79 non-anemic patients and the second group was made up of 35 patients who fulfilled the criteria for anemia.

We determined the parameters of disease activity and autoimmune disorders - disease activity score 28 (DAS 28): 5.7 ± 1.2 , $n = 114$; RF: 56 (20 - 198), $n = 107$; antiCCP antibodies: 140 (54 - 246), $n = 67$.

All patients received NSAIDs and additional therapy as follows: DMARDs ($n = 83$), DMARDs and corticosteroids ($n = 10$), biological agents, DMARDs and corticosteroids ($n = 4$), corticosteroids ($n = 2$), biological agents and DMARDs ($n = 11$), biological agents and corticosteroids ($n = 3$). All patients on treatment with methotrexate alone or in

combination were receiving folic acid and the mean $\pm$ SD of MCV, MCH and MCHC were: 89 ± 7 , fl; 29 ± 3 , pg; 320 ± 34 , g/l, respectively. These results excluded folate deficiency and megaloblastic anemia.

The study was approved by the ethics committee of Medical University of Plovdiv. All participants gave informed consent before being recruited for the study.

LABORATORY ANALYSIS

The following parameters were determined: for iron homeostasis – serum iron, total iron binding capacity (TIBC), ferritin, sTfR; for inflammatory activity - C-reactive protein (CRP), IL-6, prohepcidin; for autoimmune disorders - RF, antiCCP, DAS 28.

Laboratory tests such as erythrocyte count, hemoglobin (Hb), erythrocyte sedimentation rate (ESR), TIBC were performed using standard laboratory methods.

Serum ferritin, sTfR, CRP, IL-6 were determined using commercially available kits (BioVendor – Laboratornemedicina, Czech Republic) by ELISA. The concentration of serum prohepcidin was measured by ELISA using a commercial kit (DRG Instruments, GmbH, Germany), according to the manufacturer's instructions. RF was determined with ELISA kits (Nova Tec Immundiagnostica, GmbH, Germany) and antiCCP with ELISA kits (Eurodiagnostica, Sweden).

STATISTICS

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The concentrations of the parameters of iron homeostasis, inflammation and autoimmune disorders were tested for normality with Kolmogorov-Smirnov test. Data were given as mean $\pm$ SD or as median and 25th-percentile and 75th-percentile. T-test was used to compare two groups with normal distribution and Mann-Whitney U test was used to compare groups with non-normal distribution. Correlations between data were evaluated by calculating the Pearson's or Spearman's correlation coefficient depending on the distribution of the continuous variables. $P < 0.05$ was considered as statistically significant.

RESULTS

Table 1 shows the comparison between parameters of iron homeostasis and inflammation in patients with RA and healthy controls. The sTfR, CRP, IL-6 and prohepcidin levels were significantly higher in the RA group than in the control group while the level of serum iron was significantly higher in controls compared to RA. No significant difference was

found in ferritin level and TIBC between healthy controls and RA patients.

Table 2 presents the comparison between parameters of iron homeostasis and inflammation in patients with RA according to the level of Hb. On the basis of these criteria the patients were distributed in two subgroups (No anemia and Anemia). The levels of CRP, IL-6 and probably sTfR ($P = 0.052$) were significantly higher in the group with anemia compared to the one without anemia. Serum iron was significantly higher in the group without anemia.

Table 3 shows the comparison between parameters of iron homeostasis and inflammation in patients with RA according to the degree of disease activity (DAS 28). The level of CRP was significantly higher in the subgroup with high disease activity ($\text{DAS } 28 > 5.1$) compared to the subgroup with moderate disease activity ($3.2 < \text{DAS } 28 \leq 5.1$). No significant difference was found in the level of sTfR, ferritin, IL-6 and prohepcidin in the two subgroups. TIBC and probably serum iron ($P = 0.051$) were significantly lower in the subgroup with high disease activity.

Table 4 shows the correlations between parameters of iron homeostasis and inflammation in RA patients and healthy controls.

Table 5 shows the correlations between parameters of inflammation and autoimmune disorders in patients with RA.

Table 6 shows the correlations between param-

eters of iron homeostasis, inflammation and autoimmune disorders in patients with RA.

In RA patients the mean of Hb was 126.45 ± 13.05 , $n = 114$ and the median of RBC: 4.44 (4.16 – 4.72), $n = 106$. We found the following positive correlations: serum iron and Hb ($n = 57$, $r = 0.457$, $P < 0.001$); serum iron and RBC ($n = 53$, $r = 0.450$, $P = 0.001$); Hb and RBC ($n = 106$, $r = 0.628$, $P < 0.001$). Hb and RBC negatively correlated with fibrinogen (**Table 6**). The level of Hb negatively correlated with ESR, CRP and IL-6 (**Table 6**).

DISCUSSION

ACD may be diagnosed by determination of serum parameters of iron homeostasis – serum iron, TIBC (saturation of transferrin with iron), transferrin concentration, ferritin and sTfR.¹⁷ In RA the form of anemia may be ACD, IDA or both (ACD + IDA). Since anemia in RA may cause severe complications, researchers are making efforts to find appropriate methods for early detection, monitoring and treatment of the condition. Unlike “pure iron deficiency”, in anemia of chronic inflammation, the target for therapy is the major disease process.^{21,22}

The sTfR level in serum is considered a key marker in ACD research.²³ The studies show also that sTfR is a reliable laboratory index of IDA and in distinguishing IDA from ACD.¹³ According to some authors, anemia of chronic inflammation

Table 1. Comparison between parameters of iron homeostasis and inflammation in patients with RA and healthy controls

Parameters	Controls	RA	P
sTfR, $\mu\text{g/ml}$	0.77 (0.58 – 0.91) $n = 42$	1.04 (0.67 – 1.50) $n = 114$	<0.001
Ferritin, ng/ml	31.4 (18.0 – 59.8) $n = 42$	40.5 (22.3 – 78.7) $n = 114$	NS
Serum iron, $\mu\text{mol/l}$	18.8 ± 6.1 $n = 21$	14.6 ± 6.8 $n = 57$	0.014
TIBC, $\mu\text{mol/l}$	63.7 ± 8.9 $n = 21$	59.3 ± 10.0 $n = 57$	NS
CRP, $\mu\text{g/ml}$	2.0 (1.9 – 2.5) $n = 42$	2.7 (1.9 – 10.3) $n = 114$	0.003
IL-6, pg/ml	1.51 (0.76 – 2.30) $n = 21$	4.00 (1.17 – 11.95) $n = 59$	0.002
Prohepcidin, ng/ml	997 ± 477 $n = 42$	1262 ± 796 $n = 114$	0.013

Table 2. Comparison between parameters of iron homeostasis and inflammation in patients with RA according to the level of Hb (No anemia and Anemia)

Parameters	No anemia	Anemia	P
sTfR, µg/ml	0.99 (0.59 – 1.39) n = 79	1.14 (0.88 – 1.61) n = 35	0.052
Ferritin, ng/ml	39.9 (22.4 – 77.9) n = 79	43.7 (21.8 – 84.3) n = 35	NS
Serum iron, µmol/l	16.1 ± 6.5 n = 41	10.8 ± 6.4 n = 16	0.007
TIBC, µmol/l	59.5 ± 7.6 n = 41	58.8 ± 14.7 n = 16	NS
CRP, µg/ml	2.2 (1.9 – 5.8) n = 79	10.3 (2.3 – 53.5) n = 35	<0.001*
IL-6, pg/ml	2.96 (0.96 – 6.79) n = 43	9.42 (2.26 – 22.42) n = 16	0.022*
Prohepcidin, ng/ml	1189 ± 711 n = 79	1427 ± 952 n = 35	NS

Table 3. Comparison between parameters of iron homeostasis and inflammation in patients with RA according to the degree of disease activity

Parameters	DAS28≤5.1	DAS28>5.1	P
sTfR, µg/ml	0.79 (0.56 – 1.36) n = 38	1.10 (0.86 – 1.55) n = 76	0.062
Ferritin, ng/ml	38.1 (21.6 – 82.9) n = 38	43.4 (22.4 – 75.4) n = 76	NS
Serum iron, µmol/l	16.6 ± 6.9 n = 25	13.1 ± 6.5 n = 32	0.051
TIBC, µmol/l	64.5 ± 9.7 n = 25	55.2 ± 8.2 n = 32	<0.0001
CRP, µg/ml	2.0 (1.7 – 3.0) n = 38	3.4 (2.2 – 22.4) n = 76	<0.0001
IL-6, pg/ml	2.44 (1.15 – 5.10) n = 26	4.77 (1.20 – 14.74) n = 33	0.078
Prohepcidin, ng/ml	1103 ± 651 n=38	1341 ± 852 n=76	NS

proceeds with decreased level of sTfR and that distinguishes it from the anemia caused by insufficient dietary intake of iron.²¹ Other authors report that increased level of sTfR is a feature of functional iron deficiency, despite the adequate iron stores as it is in chronic inflammatory processes.²⁴ Our results confirm the latter finding (**Table 1**). Iron deficiency

in RA is confirmed by the increase of sTfR level not only in patients compared to controls but also in the subgroup with anemia compared to the subgroup without anemia (**Table 2**). The study of the correlations of sTfR with the other parameters of iron homeostasis, inflammatory activity and autoimmune disorders show that sTfR provides most

Table 4. Correlations between parameters of iron homeostasis and inflammation in RA patients and healthy controls

Parameters	RA			Controls		
	n	r	P	n	r	P
Ferritin / TIBC	57	-0.606	<0.001	21	-0.415	NS
Ferritin / Serum iron	57	0.152	NS	21	0.437	0.048
Ferritin / IL-6	59	0.083	NS	21	-0.213	NS
sTfR / Serum iron	57	-0.306	0.020	21	-0.110	NS
sTfR / Ferritin	114	-0.124	NS	42	-0.001	NS
sTfR / TIBC	57	0.045	NS	21	0.202	NS
sTfR / Prohepcidin	114	0.338	<0.001	42	0.070	NS
sTfR / CRP	114	0.451	<0.001	42	0.441	0.003
sTfR / IL-6	59	0.456	<0.001	21	-0.127	NS
Prohepcidin / CRP	114	0.265	0.004	42	0.253	NS
Serum iron / CRP	57	-0.416	0.001	21	-0.099	NS
Serum iron / IL-6	57	-0.378	0.004	21	-0.460	0.036
CRP / IL-6	59	0.553	<0.001	21	0.049	NS
TIBC / CRP	57	- 0.297	0.025	21	-0.247	NS

evidence as it links the pathogenetic mechanisms of iron metabolism with the autoimmune disorders in RA (**Tables 4** and **6**). The comparison with healthy controls clearly indicates that only in RA there is a positive correlation of iron requirement (sTfR) with the release of the proinflammatory cytokine IL-6 and the hormone hepcidin (assessed by the prohepcidin content) (**Table 4**). The same associations are observed between sTfR and the parameters of evaluation of the disorders in RA - DAS 28, ESR, RF and antiCCP (**Table 6**). The negative correlation of serum iron with sTfR level also confirms the informative value of the parameter - the adaptive pathologic mechanism of iron sequestration in its stores, due to the chronic inflammation in RA, causes cellular iron deficiency and in response the cells increase the expression of transferrin receptors. Such correlation was not observed in the control group (**Table 4**).

The individual acute phase proteins provide less information for evaluation of the disease process in RA. Therefore specific parameters that comprise these proteins in total are accepted. An example of such a parameter is DAS 28.²⁵ Probably because ferritin is both an iron binding protein and an acute

phase protein¹⁴, its informative value for evaluation of iron homeostasis in RA is limited. Some authors report that ferritin level is significantly higher in RA patients compared to controls and is positively associated with DAS 28.²⁶ In our study no significant difference was found in ferritin level between healthy controls and RA patients although the median in the RA group was higher (**Table 1**). The results we obtained showed no significant association of sTfR and serum iron with serum ferritin in RA, while in healthy controls ferritin positively correlated with serum iron and reflected iron stores (**Table 4**). Serum ferritin had a negative correlation with TIBC in RA which indicated inability for usage of the stored iron (**Table 4**). A negative correlation of TIBC with serum ferritin and CRP (**Table 4**) and with specific rheumatoid disorders DAS 28 and antiCCP was found in RA patients only (**Table 6**). These results indicated that TIBC reflected the grade of inflammation and autoimmune process but not the grade of iron deficiency, which was in agreement with the findings of other authors.²⁷

Some authors reject the informative value of serum iron determination as a parameter of anemia in RA.¹⁸ Our results indicate that serum iron reflects

Table 5. Correlations between parameters of inflammation and autoimmune disorders in patients with RA

Parameters	RA		
	n	r	P
Prohepcidin / DAS 28	114	0.266	0.004
Prohepcidin / RF	107	0.316	0.001
Prohepcidin / ESR	114	0.232	0.013
Prohepcidin / CRP	114	0.265	0.004
CRP / DAS 28	114	0.435	<0.001
CRP / RF	107	0.232	0.016
CRP / antiCCP	67	0.266	0.029
CRP / IL-6	59	0.553	<0.001
CRP / ESR	114	0.450	<0.001
IL-6 / DAS 28	59	0.335	0.009
IL-6 / ESR	59	0.344	0.008
ESR / DAS 28	114	0.396	<0.001
ESR / Fibrinogen	108	0.436	<0.001
Fibrinogen / RF	102	0.511	<0.001
DAS 28 / RF	107	0.304	0.001
DAS 28 / antiCCP	67	0.341	0.005
RF / antiCCP	66	0.623	<0.001

Fibrinogen: 4.25 ± 1.38 , n = 108, ESR: 36 (28 – 58), n = 114

the iron deficiency and inflammatory activity: the amount of serum iron was significantly higher in healthy controls compared to RA ($P = 0.014$) (**Table 1**), and in the subgroup without anemia compared to the subgroup with anemia. These findings confirmed the hypoferremia condition in RA patients. Serum iron negatively correlated with IL-6 in healthy controls and in RA (**Table 4**). We found a significant negative correlation of serum iron with CRP, ESR and DAS 28, which confirms the relationship between the impaired iron metabolism and inflammation in RA (**Tables 4 and 6**).

There is evidence that transferrin receptor modulates the expression of hepcidin.²⁸ Some authors propose the determination of serum prohepcidin as a new diagnostic index for ACD in RA.^{29,30} The available information in the scientific literature on the informative value of prohepcidin for evaluation of the iron status is rather confusing.³¹⁻³³ According to Kim et al.³¹ serum prohepcidin correlates with the activity of the major disease process but not

with the anemia condition. On the other hand, in another study³³, the iron deficiency in RA patients is related with the serum concentration of prohepcidin. The results obtained in our study indicated that the parameter was informative for evaluation of iron deficiency and inflammatory activity in RA: prohepcidin level was significantly higher in RA patients ($P = 0.013$) (**Table 1**) and reflected hypoferremia condition in inflammation since it positively correlated with sTfR and with CRP only in RA but not in the controls (**Table 4**). Prohepcidin is also a sensitive parameter for disorders in RA expressed as its positive correlation with ESR, DAS 28 and RF (**Table 5**). We didn't find a correlation of prohepcidin with IL-6 which is probably due to the involvement of additional regulatory mechanisms in the conversion of the precursor prohepcidin in hepcidin. Our findings indicate that the pro-inflammatory markers CRP and IL-6 are associated with the changes in iron metabolism in RA since their levels are significantly higher in RA patients compared to controls

Table 6. Correlations between parameters of iron homeostasis, inflammation and autoimmune disorders in patients with RA

Parameters	RA		
	n	r	P
sTfR / DAS 28	114	0.308	0.001
sTfR / RF	107	0.427	<0.001
sTfR / antiCCP	67	0.400	0.001
sTfR / ESR	114	0.252	0.007
Serum iron / DAS 28	57	-0.375	0.004
Serum iron / ESR	57	-0.545	<0.001
TIBC / DAS 28	57	-0.374	0.004
TIBC / antiCCP	24	-0.424	0.039
CRP / Hb	114	-0.303	0.001
IL-6 / Hb	59	-0.343	0.008
ESR / Hb	114	-0.430	<0.001
ESR / RBC	106	-0.302	0.002
Hb / Fibrinogen	108	-0.401	<0.001
RBC / Fibrinogen	101	-0.275	0.005

and in the subgroup with anemia (**Tables 1 and 2**). IL-6 is involved in autoimmunity by altering the balance between Th17 cells and Treg cells. IL-6 also acts on changing lipid concentrations in blood and on inducing the production of hepcidin which causes iron deficiency. In conclusion, IL-6 is a major player in the pathogenesis of RA, and current evidence indicates that the blockade of IL-6 is a beneficial therapy for RA patients.^{3,34} Our results confirm the participation of IL-6 both in the hyposideremia (positive correlation with sTfR and negative with serum iron and Hb) (**Tables 4 and 6**) and in the inflammatory and autoimmune disorders in RA (positive correlation of IL-6 with ESR, CRP and DAS 28) (**Table 5**).

CONCLUSION

Our study shows that the simultaneous determination of two parameters, sTfR and prohepcidin, is most informative for evaluation of the changes in iron homeostasis in RA. The increase of both parameters provides information for tissue iron deficiency (assessed by the level of sTfR), caused by the inflammation when prohepcidin is expressed. This contention is confirmed by the positive cor-

relation of sTfR with prohepcidin only in RA but not in the healthy controls.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Патобиохимические механизмы - показатели взаимосвязи гомеостаза железа с параметрами воспалительной активности и аутоиммунными нарушениями при ревматоидном артрите

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Цель: Целью настоящего исследования является установление корреляций между параметрами гомеостаза железа, воспалительной активностью и аутоиммунными нарушениями при ревматоидном артрите (РА).

Материалы и методы: В настоящем исследовании обследовано 114 больных с РА и 42 здоровых лица в качестве контрольной группы. Нами были определены параметры гомеостаза железа: сывороточное железо, общая железосвязывающая способность (ЖСС), феритин и растворимый рецептор трансферрина (sTfR), параметры воспалительной активности: С-реактивный белок (CRP), интерлейкин - 6 (IL-6) и прогепсидин и параметры аутоиммунных нарушений: ревматоидный фактор (РФ), антитела к циклическому цитруллиновому пептиду (антиCCP) и DAS 28.

Результаты: Уровни sTfR, CRP, IL-6 и прогепсидина оказались значительно более высокими у больных с РА по сравнению с контрольной группой, уровень сывороточного железа оказался значительно более низким в случаях РА по сравнению с контрольной группой. В отличие от контрольной группы, у больных с РА установлена значительная положительная корреляция sTfR с параметрами воспалительной активности (IL-6, прогепсидин, ESR) и с параметрами аутоиммунных нарушений (DAS 28, РФ, антиCCP). Отрицательная корреляция сывороточного железа с sTfR была установлена только у больных с РА. Прогепсидин коррелирует положительно с параметрами воспаления (CRP, ESR) и с параметрами оценки аутоиммунных нарушений (DAS 28 и РФ) в группе больных с РА.

Заключение: Наше исследование устанавливает, что одновременное определение двух параметров sTfR и прогепсидина является наиболее информативным при оценке изменений гомеостаза железа при РА. Повышение обоих параметров предоставляет информацию о тканевом дефиците железа (измеренном в соответствии с уровнем sTfR) вызванном воспалением с экспрессией прогепсидина.