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SERUM IRON PARAMETERS IN ANEMIC CASES DUE TO IRON DEFICIENCY, RHEUMATOID ARTHRITIS AND LIVER CIRRHOSIS

PERİHAN ÖZKAN GÜMÜŞKAYA[1], TEOMAN SOYSAL[2]

ABSTRACT

Objective: In this study we aimed to show the relationship between soluble transferrin receptor (sTfR) level and other iron parameters in patients with iron deficiency anemia, anemic rheumatoid arthritis and anemic liver cirrhosis, and in the combined anemias to evaluate the iron deficiency by an alternative method to gold standart bone marrow iron staining.
Methods: Our study was carried out on four groups consisting of eighteen patients with iron deficiency, eighteen patients with rheumatoid arthritis and anemia, eighteen patients with liver cirrhosis and anemia, and eighteen healthy individuals. Iron (Fe) parameters, vitamin B-12, folate, C-reactive protein (CRP), sedimentation, Thyroid stimulating hormone (TSH), urea, creatinine, alanine aminotransferase (ALT), albumin, hemogram, peripheral smear and sTfR levels were studied.
Results: In our evaluation, sTfR level was significantly higher in patients with iron deficiency anemia compared to other groups ($p<0.01$). No significant correlation was found between sTfR and other parameters in the anemic patient group with rheumatoid arthritis. Negative correlation of sTfR with platelet number, transferrin saturation (TS) and ferritin ($r=0.019$); and positive correlation of MCV with iron levels ($r=0.005$) have shown that MCV, TS, Fe and ferritin act together with sTfR in patients with liver cirrhosis to show signs of iron deficiency anemia.
Conclusion: In the diagnosis of iron deficiency accompanying chronic disease or liver cirrhosis, the evaluation of the usual iron parameters together with the sTfR level will be a more reliable and perhaps an alternative approach to the determination of invasive bone marrow iron score.
Keywords: Chronic disease, iron deficiency, sTfR

DEMİR EKSİKLİĞİ, ROMATOİD ARTRİT VE KARACİĞER SİROZUNA BAĞLI ANEMİ OLGULARINDA SERUM DEMİR PARAMETRELERİ

ÖZET

Amaç: Bu çalışmada demir eksikliği anemisi, anemik romatoid artrit ve anemik karaciğer sirozu hastalarında serum solubl transferrin reseptör (sTfR) düzeyi ile diğer demir parametreleri arasındaki ilişkiyi göstermeyi ve kronik hastalıklara eşlik eden demir eksikliğinin tanısında, altın standart kemik iliğinde demir boyamasına alternatif bir yöntem olarak değerlendirmeyi amaçladık.
Yöntem: Çalışmamız onsekiz demir eksikliği hastası, onsekiz romatoid artrit ve anemi hastası, onsekiz karaciğer sirozu ve anemi hastası ve onsekiz sağlıklı bireyden oluşan dört grup üzerinde gerçekleştirildi. Demir (Fe) parametreleri, B-12 vitamini, folat, C-reaktif protein (CRP), sedimantasyon, Tiroid uyarıcı hormon (TSH), üre, kreatinin, alanin aminotransferaz (ALT), albümin, hemogram, periferik yayma ve sTfR düzeyleri çalışıldı.
Bulgular: Çalışmamızda, demir eksikliği anemisi olan hastalarda sTfR düzeyi diğer gruplara göre anlamlı olarak yüksekti ($p<0,01$). Romatoid artritli anemik hasta grubunda sTfR ile diğer parametreler arasında anlamlı bir korelasyon bulunamadı. sTfR'nin trombosit sayısı, transferrin saturasyonu (TS) ve ferritin ($r=0,019$) ile negatif korelasyonu; MCV'nin demir düzeyi ile pozitif korelasyonu ($r=0,005$), karaciğer sirozu olan hastalarda demir eksikliği anemisi belirtileri gösterecek şekilde MCV, TS, Fe ve ferritinin sTfR ile birlikte hareket ettiğini göstermiştir.
Sonuç: Kronik hastalık veya karaciğer sirozuna eşlik eden demir eksikliği tanısında sTfR düzeyi ile birlikte diğer demir parametrelerinin de değerlendirilmesi daha güvenilir ve belki de invaziv kemik iliği demir skorunun belirlenmesine alternatif bir yaklaşım olacaktır.
Anahtar kelimeler: Kronik hastalık, demir eksikliği, sTfR

[1]DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF HEALTH SCIENCES, PROF. DR. CEMİL TASCIOGLU CITY HOSPITAL, ISTANBUL, TÜRKİYE
[2]DEPARTMENT OF HEMATOLOGY. ISTANBUL UNIVERSITY, CERRAHPASA FACULTY OF MEDICINE, ISTANBUL, TÜRKİYE

Sorumlu Yazar: PERİHAN ÖZKAN GÜMÜŞKAYA
DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF HEALTH SCIENCES, PROF. DR. CEMİL TASCIOGLU CITY HOSPITAL, ISTANBUL, TÜRKİYE

Telefon: +9050574609 52
E-mail: perihangumuskaya@hotmail.com

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INTRODUCTION

Anemia is defined as a decrease in the amount of hemoglobin in the peripheral blood below the normal values for the age and sex of the person (1). Iron deficiency anemia is the most common form of anemia in the world. Anemia of chronic disease is also a common cause of anemia after iron deficiency and the most common type of anemia in hospitalized patients. Iron deficiency anemia in chronic liver diseases is caused by varicose veins and/or bleeding due to defective synthesis of coagulation factors. In chronic diseases (like rheumatoid arthritis), combined iron deficiency anemia is common due to gastrointestinal bleeding because of the use of nonsteroidal anti-inflammatory drugs (NSAIDs); so combined iron deficiency anemia is seen frequently (2). It is possible to demonstrate anemia with simple laboratory tests; but in cases where combined anemia coexists, diagnosis becomes difficult and additional tests are required.

Low iron level is not diagnostic alone in determining iron deficiency anemia; also, MCV (mean corpuscular volume), transferrin saturation, iron binding capacity and ferritin levels should be determined. However, these parameters can be affected by infection, inflammation, malignancy and liver diseases and they can not help for diagnosis of accompanying iron deficiency anemia (2). For example, in damaged liver, ferritin storage may be depleted and serum ferritin level may increase (3). In rheumatoid arthritis, ferritin can be found to be high as an acute phase reactant, even in the presence of iron deficiency (3). 2/3 Of chronic disease anemia is normocytic. Although iron is low, since MCV>100fL due to megaloblastic change in liver patients, this parameter cannot be used. Transferrin saturation can decrease to levels (<16%) seen in iron deficiency anemia in acute and chronic inflammation (4). For all these reasons, since bone marrow iron staining, which is considered the gold standard in the definitive diagnosis of iron deficiency anemia accompanying cirrhosis or a chronic disease, is an invasive procedure, a more practical, noninvasive and reliable parameter was needed (2). This parameter is the level of "Serum Soluble transferrin receptor (sTfR)". It has been shown in many studies that serum sTfR level is not affected by chronic diseases (3). However, there are very few studies showing that this parameter is not affected by cirrhosis (5). Serum sTrF level is a reliable data in iron deficiency anemia in adults (6). It is important in the evaluation of anemic patients with high ferritin levels as an acute phase response (7). This receptor is a transmembrane protein. Cellular iron uptake occurs by endocytosis mediated by sTfR. During this endocytic cycle, TfR is externalized and a form of TfR devoid of cytoplasmic and transmembrane domains is formed in the serum. The serum sTfR concentration reflects the total body transferrin receptor level (8).

The first response of cells to a decrease in iron level is an increase in transferrin receptor synthesis. Transferrin receptors are probably found on all cells, but in varying amounts. They are abundant on immature erythroid cells, placental tissue, and rapidly dividing cells (8,9). Since serum sTfR level is not affected by chronic diseases and liver cirrhosis unlike ferritin, iron treatment should be started when high serum stfr level is detected in these patients (10). In a study by Nagral et al. sTfR sensitivity was 91.6% and specificity 84.6% in the diagnosis of iron deficiency in chronic liver disease (5). Serum sTfR is a useful parameter in the determination of the treatable cause of anemia in chronic liver disease and in the detection of iron deficiency anemia in patients with anemic RA (11). A very small amount of blood sample is sufficient for the test, and sTfR, ferritin and transferrin can be evaluated in the same apparatus within 15 minutes (12). The reference range does not differ with gender and age (12). Higher concentrations were found only in black people and those living above sea level. An increase in serum sTfR is the most sensitive indicator of depleted iron stores and can be easily measured by the ELISA method (12).

In this thesis study, we aimed to show the relationship between sTfR level and other iron parameters in patients with iron deficiency anemia, anemic rheumatoid arthritis and anemic liver cirrhosis, and to evaluate it as an alternative method to gold standart invasive bone marrow iron staining.

MATERIAL AND METHOD

This study included eighteen patients with a diagnosis of iron deficiency anemia who applied to the outpatient clinic of the Department of Internal Medicine, Department of Hematology, eighteen patients with rheumatoid arthritis and anemia followed in the rheumatology department, 18 patients with anemia with liver cirrhosis followed in the hepatology department of Cerrahpaşa Medical Faculty between August 2000 and April 2001. It included eighteen healthy individuals who are compatible with age and gender characteristics. As the control group, healthy faculty students

and individuals who applied to the internal medicine outpatient clinic with nonspecific complaints and did not have any pathological findings. All groups were told that this was a thesis study and their consent was obtained. Patients with hemochromatosis or alcoholic liver cirrhosis those who use methotrexate in the treatment of RA, those who have used iron preparations in the last three months, those with hypothyroidism, and those with signs of dehydration were not included in the study. 12 Of the patients in the study were male and 42 were female, and their ages ranged from 19 to 73 (mean: 40.5±13.6). The control group consisted of 6 men and 12 women, and their ages ranged from 19 to 65 (mean: 37.4±16.2). In the study the 1. Group was patients with iron deficiency anemia, the 2. Group was anemic patients with rheumatoid arthritis, the 3. Group was anemic patients with liver cirrhosis and the 4. Group was healthy control. Iron (Fe), iron binding capacity (SIBC), ferritin, vitamin B 12, folate, C-reactive protein (CRP), sedimentation, Thyroid stimulating hormone (TSH), urea, creatinine, alanine aminotransferase (ALT), albumin, hemogram, peripheral smear and sTfR levels were studied from each person. Urea, creatinine, alt, albumin and crp parameters were studied on Olympus Au 800 autoanalyzer and Diasis Diagnostic System (dds) kits were used in the tests. iron, iron binding capacity was studied in Hitachi-704 autoanalyzer and Biotrol Diagnostic kits were used in the tests, TSH value was studied in CIBA-CORNING (ACS-180) autoanalyzer and Bayer Vital GmbH kits were used. All these blood parameters were studied on the day the blood samples were taken from the patients, and the serums separated for the sTfR level were stored at -70 degrees until the date these parameters were studied. Immunoassay (ELISA) (R&D Quantikine IVD) kits were used in the determination of sTfR.

Statistical Analysis

In the statistical analysis of the data Kruskal-Wallis test was used to determine the age distribution of the patients, the Chi-Square test was used to determine the gender distribution, ANOVA was used for the comparisons between the groups, and the Spearmen correlation test was used for the evaluation of the groups within themselves. p <0.05 was considered statistically significant.

RESULTS

In our evaluation, there was no significant difference between the groups in terms of hemoglobin, hematocrit levels and also age and sex. While MCV was significantly lower in iron deficiency than the other patient and control groups, it was found to be significantly higher in liver cirrhosis than rheumatoid arthritis and the control group (p<0.05). RDW was found to be significantly higher in the patient groups than the control group. There was no significant difference between the patient groups. Iron levels were found to be significantly lower in iron deficiency anemia than in liver cirrhosis cases and control group, whereas in RA cases, liver cirrhosis cases and control group; It was also found to be significantly lower in liver cirrhosis than the control group (p<0.01). In iron deficiency anemia, ferritin levels were found to be significantly lower than the other groups, while the differences between the other groups were not significant. SIBC was found to be higher in iron deficiency anemia cases than in all groups, and lower in RA and cirrhosis cases than controls. In the intergroup evaluation, transferrin saturation was found to be significantly lower in iron deficiency anemia than RA (p<0.05), liver cirrhosis (p<0.01) and control groups (p<0.01). Transferrin saturations of RA patients were found to be lower than those of cirrhosis and healthy patients. sTfR level was 51.67+/-17.08nM/L in the control group. sTfR level was significantly higher in patients with iron deficiency anemia compared to other groups (p<0.01). These results were shown in table 1 and figure 1.

Table 1. Serum soluble transferrin receptor level in the groups

	Iron Deficiency	Rheumatoid Arthritis	Liver Cirrhosis	Control	P Value
sTfR	155.29 ± 66.4	81.72 ± 42.5	93.61 ± 50.44	5 1 . 6 7 ±17.08	p< 0.01

sTfR levels (nM/L)

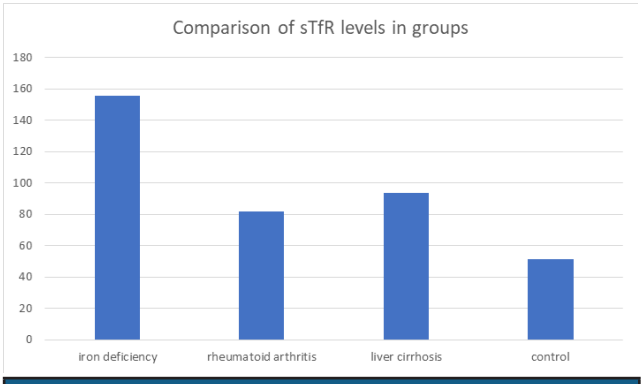

Figure 1. Comparison of sTfR levels ((nM/L)) in groups

No significant correlation was found between sTfR and other parameters in the anemic patient group with rheumatoid arthritis. Negative correlation of sTfR with platelet number, transferrin saturation (TS) and ferritin (r=0.019); and positive correlation of MCV with iron levels (r=0.005) have shown that MCV, TS, Fe and ferritin act together with sTfR in patients with liver cirrhosis to show signs of iron deficiency anemia.

DISCUSSION

Anemia is frequently encountered in hospitalized or outpatient patients as a result of the high prevalence in the community and the routine usage of blood count in almost every health institution (4). Iron deficiency anemia is the most common anemia in the world. Anemia of chronic disease and the differential diagnosis of iron deficiency with inflammation are among the problems encountered. Almost all patients with RA develop anemia of chronic disease and iron deficiency is encountered in up to 75% of these patients (13,14). Iron deficiency anemia is frequently seen in patients with liver cirrhosis due to bleeding. On the other hand, the reliability of parameters such as MCV, RDW, serum iron and SIBC levels, and ferritin in the diagnosis of iron deficiency in chronic disease anemia and chronic liver diseases are controversial. MCV is one of the frequently used parameters in the diagnosis of anemia.

Although it differs with age and gender, values below 80 fL were evaluated as low in our study. MCV<80 was found in all cases in group 1, MCV<80 fL in six cases in group 2, MCV> 80 fL in 12 cases. 80fL, only two cases in group 3 had MCV<80fL. In the study of Punnonen et al. it was stated that MCV is a reliable parameter in demonstrating iron deficiency (r=0.88) (15). In our study, MCV was found to be 68.33 ± 68.33 fL in group 1, 80.49 ± 6.41fL in group 2, 91.32 ±8.9fL in group 3, and 84.69 ± 3.74 fL in group 4. Although sTfR and MCV showed a significant (-) correlation (r=0.038) in group 1, no such correlation was observed in group 2, but 6 cases with low MCV values in this group, in 5 of them, the sTfR value was found to be above the mean sTfR value found in the controls (51.6 ±17). Ferritin value was not below normal limits in any of these cases. In our study, the fact that MCV did not show a significant correlation with sTfR, which is an important indicator of iron deficiency in this case group, may be related to the low number of cases. MCV value was found to be significantly higher in patients with anemic cirrhosis than in all groups (p<0.05). This finding is consistent with the general character of anemia in liver cirrhosis. However, when the relationships between the parameters belonging to the same patient group were examined, it can be thought that MCV value in this case group moved in the same direction as serum iron, in other words, towards defining iron deficiency. No similar information about MCV was found in the literature. RDW is one of the frequently used parameters in anemia. The RDW value was found to be 16.9 ± 2.22% in the 1. group, 16.44± 2.52 % in 2. Group, 16.4 ±2.68% in the 3rd group, 12.38 ± 0.64% in the 4. Group. In the control group it was found to be significantly lower than the other subjects (p<0.05), between the first, second and third groups. No significant difference was observed. Although it can be thought that RDW can be used to support iron deficiency anemia with these findings, it should be kept in mind that it produces similar changes in other disease groups, therefore it should be evaluated together with other diagnostic parameters. When serum iron is taken into account, there is no difference between the iron deficiency anemia group and the group with chronic disease and anemia, which is not different from the classical data, on the other hand, it is seen that SIBC differs significantly between these two groups, and when iron deficiency anemia, liver cirrhosis and controls are compared, there are significant differences in terms of both serum iron and SIBC. In patients with RA and liver cirrhosis, serum iron and SIBC were also found to be significantly lower than controls. These findings are related to the general diagnostic features of the case groups. SIBC was found to be significantly higher in group 1 than the other groups (p<0.01). this is an expected finding and is consistent with the literature There was no significant difference between groups 2 and 3, but a significant decrease was observed in both groups compared to the control group (p<0.01). SIBC was not found to be associated with sTfR in group 2, and it is thought to be unreliable in the diagnosis of iron deficiency accompanying RA. On the other hand, in the 3rd group, it was observed that SIBC showed a (-) correlation with TS and ferritin. This finding suggests that SIBC may be suitable to define iron deficiency in patients with liver cirrhosis.

CONCLUSION

In the diagnosis of iron deficiency accompanying chronic disease or liver cirrhosis, the evaluation of the usual iron parameters together with the sTfR level will be a more reliable and perhaps an alternative approach to the determination of bone marrow iron score. In order to reach more precise judgments on this issue, studies

with larger case numbers are needed that will allow in-group comparisons.

Conflict of Interest
The authors have no conflicts of interest to declare.

Author Contributions
Medical Practice – P.O.G.; Concept - P.O.G., T.S.; Design - P.O.G. Data Collection and/or Processing - P.O.G.; Analysis and/or Interpretation - P.O.G.; Literature Review - P.O.G.,T.S.; Manuscript Writing - P.O.G. All authors agree with all aspects of the final manuscript.

Ethical Approval
All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (National Thesis Center Acceptance Number:108208).

Informed Consent
Informed consent was obtained from all participants included in the study.

Declaration of Data Availability
Data supporting the findings of this study are available upon request from the corresponding author. Data are not publicly available due to confidentiality or ethical constraints.

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