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The significance of soluble transferrin receptors in diagnosing iron deficiency anemia

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Abstract

Introduction. *In recent years, determination of soluble transferrin receptor levels has been emerging as a test that can reliably indicate iron deficiency in various states, and that is non-invasive and easy to use. The aim of this study was: to determine reference values of soluble transferrin receptor concentrations in serums in our population, to examine the reliability of this method in the diagnosis of anemia due to iron deficiency and associated iron deficiency in anemia accompanying malignant hemopathies, and to identify possible limitations of the test in certain conditions.*

Material and Methods. *The prospective research included 86 patients with anemia: 46 patients with iron deficiency anemia, and 40 patients with malignant hemopathies. The control group consisted of 40 healthy persons aging over 18.*

Results. *Ferritin values were reduced in 76.1% of patients, while higher levels of soluble transferrin receptors appeared in 100% of patients with iron deficiency anemia. In patients with reduced serum ferritin levels, the soluble transferrin receptor/log ferritin index was statistically significantly higher than in patients in whom ferritin concentration was in the normal range ($p < 0.001$). ROC analysis of patients with iron deficiency anemia showed that the soluble transferrin receptor/log ferritin index (AUC 0.977) and levels of soluble transferrin receptors (AUC 0.931) occupied the largest area under the curve. The best diagnostic parameter for detecting iron deficiency in patients with malignant hemopathies by ROC analysis is the soluble transferrin receptor/log ferritin index (AUC 0.770).*

Conclusion. *Soluble transferrin receptors are useful in the diagnosis of iron deficiency anemia, especially when ferritin values are not reduced. The calculation of soluble transferrin receptor/log ferritin index is even more reliable. In patients with malignant hemopathies, the associated iron deficiency could be best indicated by soluble transferrin receptor/log ferritin index.*

Keywords*: soluble transferrin receptors;ferritin;iron deficiency;anemia*

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Introduction

The Iron Deficiency Anemia (IDA) is the most frequent form of anemia in human population. In the United States of America, around 5% of women and 2% of men are affected by the iron deficiency anemia [1]. In developing countries, the frequency percentage is much higher.

The IDA increases both the morbidity and the mortality [2]. In children, it might be responsible for a slower development and the appearance of cognitive dysfunction [3]. In adults, it affects the work ability and the quality of life. For that reason, it represents a significant problem and a great challenge for all public health systems.

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In most cases it is relatively simple to establish an anemia diagnosis. The World Health Organization (WHO) defines anemia to exist when the hemoglobin (Hgb) values are below 130g/L in men, or below 120g/L in women. However, it is not always easy to prove that the cause of anemia is iron deficiency. When establishing the diagnosis, we must mainly rely on laboratory analyses.

The reports of microcytosis, hypochromia and increased erythrocyte distribution width (RDW) elevated values may refer to iron deficiency, but up to 40% of patients with IDA have normal mean corpuscular volume of erythrocytes (MCV). Normocytosis, consequently, does not exclude the iron deficiency, and microcytosis may be found in other kinds of anemia, too. For that reason, it is necessary to perform some additional biochemical analyses to confirm the iron deficiency. There are already routine procedures of determining the concentration of serum iron, total (TIBC) and unsaturated iron binding capacity (UIBC) and saturation of transferrin and, increasingly, ferritin. The concentration of serum iron is usually low in patients with IDA, but it may be normal, as well. The serum iron concentration is impacted by numerous physiological and pathological conditions. In physiological conditions, iron displays a diurnal rhythm, so it is necessary to have all the analyses made from a blood sample taken in the morning [4]. Lower iron concentrations are present in malignant diseases, but also in acute or chronic inflammatory processes [5]. Therefore, this test may not be considered reliable. In iron deficiency anemia, TIBC is often increased. However, exceptions are quite frequent, thus reducing the diagnostic value of this test. Since its introduction during the 70s of the last century, the serum ferritin, as a diagnostic method, has been occupying an important place in the diagnosis of iron deficit, because it was found that it correlated with the total iron stores in the body [6]. Based on the serum ferritin level, the iron deficiency may be diagnosed with certainty only if the values are lower than 20 ng/mL, while if the values exceed 100ng/mL, iron deficiency is considered not to exist [7]. The existence of comorbid conditions often prevents establishing the IDA diagnosis only by determining the serum ferritin values. Ferritin behaves as an acute-phase reactant and its level is increasing within the response to inflammation, that is, the inflammatory response modifies the iron regulation [8].

For that reason, the need emerged for a test that would indicate the iron deficiency with certainty, and that would be noninvasive and easily applicable at the same time. In recent years, determining the level of soluble transferrin receptors (sTfR) has been imposed as the test to meet all these criteria. Iron transport in the plasma is carried out by transferrin and iron is delivered to the cells through the transferrin receptor (TfR), which is located in the cell membrane. This receptor is a 760-amino acid glycoprotein. Iron deprivation results in the induction of TfR synthesis. [9] The highest density of TfR is found in erythroid cells and its soluble form is a truncated membrane receptor which is shed in the plasma mostly from the maturating erythroid cells. It has been shown that sTfR correlates with transferrin receptor concentration in the cell membranes [10]. While ferritin values indicate the state of iron stores, sTfR concentration gives us information on the iron functional status [11]. In IDA patients, there is an increase of sTfR level, and it is one of the first indicators of iron deficiency in conditions without anemia. Its reliability is also verified in relation to bone marrow staining, which is considered to be the gold standard [12]. Since various inflammatory conditions do not affect the sTfR level, it is used in differentiating the IDA from the anemia of chronic disease (ACD) [13]. The reaction in patients with malignant diseases has not been fully examined, but previous results indicate that, generally, there is

no increase of sTfR level. Chronic lymphocytic leukemia (CLL) is an exception, with the increase of sTfR level, which may be considered as the marker of disease progression rather than of the iron deficit [14]. However, we would expect higher values of sTfR in IDA patients as compared to healthy persons, as well as compared to malignant hemopathies (MH), in which higher sTfR levels are not expected, except in cases of associated IDA.

The aim of this study was to define the reference values of serum sTfR concentration in our population, to test the reliability of this method in diagnostics of IDA and associated iron deficiency in MH, to establish possible test limitations in certain conditions, and to investigate the value of combinations with other tests in the diagnostics of the mentioned types of anemia.

Material and Methods

The research represents a prospective clinical and experimental study which covered 86 patients with anemia, composing a clinical group with two subgroups. Subgroup I comprised 46 patients with IDA, and subgroup II comprised 40 patients with MH (11 with acute leukemia, 11 with non Hodgkin lymphoma, 3 with chronic myeloid leukemia, 4 with myelodysplastic syndrome, 7 with multiple myeloma, 4 with CLL). The control group included 40 healthy persons aged over 18 years (23-79 years of age), of which 18 were of male and 22 of female gender. The preconditions for including patients in the study Subgroup I were that they had a diagnosis of IDA (Hgb <120 g/l; MCV <80 fl); exclusion criteria were other types of anemia, associated chronic disease and previously administered anti-anemia therapy. For Subgroup II, inclusion criteria were anemia and MH, whereas the exclusion criteria were previously applied chemotherapy and transfusions of erythrocytes. In Subgroup I, there were 5 male and 41 female patients, aged 19-80 years, while the Subgroup II had 19 male and 21 female patients of 24-78 years of age. We used established diagnostic criteria for both subgroups.

All the patients were examined at the Clinic of Hematology, Clinical Center Niš, Serbia, and the laboratory tests were performed in the Immunology and Biochemical laboratories of the Clinical Center in Niš, from December 2012 to June 2013. These tests were done on the same blood samples that were taken for analyses in the ordinary diagnostic procedures. With regard to the World Medical Association Declaration of Helsinki, all the examined patients gave their personal consents related to the use of their blood samples for this research and to the publication of related results. All the mentioned investigations of biochemical parameters have been conducted in a serum by the standard procedures (IFCC recommended methods), on a Beckman Coulter AU680 biochemistry analyzer. Ferritin was determined by the immunoturbidimetric method, with Beckman Coulter reagents. UIBC was determined by the colorimetric method on the Beckman Coulter AU680 biochemical analyzer, with the reagents of the Beckman Coulter Company, while the TIBC was determined by calculation. sTfR levels were determined by nephelometry on Dade Behring BN II equipment with the original reagents (reference values ranging from 0.76 to 1.76 mg/l).

When including subjects in the study, apart from the clinical evaluation, the following laboratory tests were performed: complete blood count with red blood cell parameters on the automated counter, determination of the number of reticulocytes, peripheral blood smear test, serum iron determination, TIBC, UIBC, serum ferritin determination, determination of sTfR serum concentration by automated nephelometric method, bone marrow examination in the subgroup with malignant hemopathies. In order to eliminate other conditions and diseases, a com-

plete biochemical analysis, urine test and additional necessary examinations were carried out.

Statistical data processing: the data were presented in the form of arithmetic mean and standard deviation or as the median (the interquartile range), minimum and maximum values. Establishing a statistically significant difference between the mean values of several groups was performed by the ANOVA test in the Gaussian distribution (post hoc Tukey's test). Where the data were not normally distributed, the Kruskal-Wallis test was applied, while the Mann-Whitney test was used for the differences between two groups. The receiver operating characteristic (ROC) curve was applied in determining the best diagnostic marker. The data analysis was performed using the SPSS Program Package 16.0. Statistical significance was considered at $p<0.05$.

Results

The study covered the total number of 126 subjects, of which 46 patients were with IDA, 40 patients with MH and 40 healthy subjects.

In the group of healthy subjects, 36 (90%) of them had the sTfR concentration within the reference ranges. In the healthy population, the highest sTFR concentration was found in the subjects aged 61-70 years, while the lowest concentration appeared in the age group of 51-60 years. It was established that there was no statistically significant difference in sTfR values regarding the age of healthy subjects ($p=0.455$). Statistically significant higher concentrations were obtained in healthy female subjects as compared to the male subjects (1.22 ± 0.40 vs. 0.95 ± 0.16, $p=0.016$).

The ferritin values in the IDA group were reduced in 35 patients (76.1%), and reference values were recorded in 11 patients (23.9%). The sTfR values were increased in all IDA patients (100%). In the IDA patients with lower ferritin values, the sTFR/log ferritin ratio was statistically significantly higher as compared to the patients in whom the ferritin concentration was within the reference range ($z=3.786$, $p<0.001$). Lower levels of iron were found in 93.5% of IDA patients and in 35.0% of healthy subjects. Most of the IDA patients had TIBC values within the reference range (58.7%), while that percentage was 97.5% for healthy subjects. UIBC was increased in most of the IDA patients (73.9%), and this parameter was most often within the reference range in healthy subjects (92.5%). Decreased MCV values were found in 78.3% of the IDA group patients, and in 5% of healthy subjects.

It was found out that there is a statistically significant difference in the concentration of almost all the tested parameters between the studied groups (Table I). Statistically significant value reduction ($P<0.001$) appeared in the IDA patients compared to healthy subjects regarding the following parameters: erythrocytes, Hgb, hematocrit (Hct), MCV, mean hemoglobin value in erythrocytes (MCH), mean corpuscular hemoglobin concentration value (MCHC), iron, and ferritin. Statistically significantly increased values ($p<0.001$) in the IDA group as compared to the healthy subjects were found in the following parameters: sTfR, RDW, TIBC, UIBC.

There was a significant statistical difference between the IDA patients and MH patients ($P<0.001$) with regard to the value reduction of MCV, MCH, MCHC, iron, ferritin and C-reactive protein (CRP), while in the IDA group statistically significant increased values were registered in the following parameters: sTfR, sTfR/log ferritin, erythrocytes, Hct, TIBC, UIBC.

Higher values of ferritin were found in 23 patients (57.5%), normal in 16 patients (40%), and lower ferritin values in one patient (2.5%) in the MH group. In MH patients, 11 (27.5%) had higher sTfR values, 18 (45%) were with normal sTfR values, and 11 patients had lower sTfR values (27.5%).

The sTfR values were increased in all patients

Table I. Demographic and hematological features in anemia patients and healthy persons.

	IDA X(SD)	MH X(SD)	Healthy X(SD)	p
Age (years)	49.57±20.46*	61.62±14.91#	43.40±13.07†	<0.001a
Gender (M/W)	5/41*#	19/21	18/22	<0.001b
sTfR (0.76 – 1.76 mg/l) rv	3.0 (2.85)*# 1.79-11.70	1.18 (1.23)# 0.14-10.40	1.02 (0.34)‡ 0.69-2.35	<0.001c
sTfR/log ferritin (0.63 – 1.8)	5.00 (6.31)*# 1.19-89.52	0.45 (0.89)# 0.04-5.35	0.52 (0.39) 0.26-2.10	<0.001 c
Erythrocytes (3.8 – 6.5 x10^{12}/l)	4.31±0.64*#	3.10±0.77#	4.88±0.46	<0.001 a
Hemoglobin (120 – 180 g/l)	91.94±20.84#	85.05±17.60#	142.58±14.29	<0.001 a
Hematocrit (37 – 54 %)	30.72±5.77*#	27.45±5.47#	42.53±3.59	<0.001 a
MCV (80 – 100 fl)	71.27±10.14*#	87.98±6.72	87.42±4.25	<0.001 a
MCH (27 - 32 pg)	21.42±4.45*#	27.86±2.95#	29.43±2.13	<0.001 a
MCHC (320 – 360 g/l)	296.83±20.68*#	310.38±14.99#	336.20±14.06	<0.001 a
RDW (11 - 16%)	16.00 (3.60)# 11.80-33.90	14.65 (3.55)# 11.90-22.50	12.00(1.17) 9.20-13.90	<0.001 c
Iron (10.7 – 32.2 µmol/l)	3.46 (3.26)*# 0.34-14.27	13.45 (18.04) 1.99-50.26	16.77 (10.84) 5.11-43.13	<0.001 c
TIBC (44 – 75 µmol/l)	71.48 (12.42)#* 51.19-100.99	42.42 (18.07)# 21.58-70.19	58.52 (4.49) 47.26-75.86	<0.001 c
UIBC (27.8 – 63.6 µmol/l)	69.82 (15.58)#* 44.15-99.24	29.81 (32.33)# 2.54-56.32	42.14 (10.03) 4.13-69.41	<0.001 c
Transferrin (2.0 – 3.6 g/l)	1.72 (0.47)#* 0.86-4.03	1.27 (1.30) 0.40-2.65`	1.11 (0.71) 0.72-2.50	<0.001 c
Ferritin (10 – 250 µg/ml)	6.40 (8.00)#* 1.30-66.80	44.96 (105.36)# 7.70-736.00	102.85 (176.95) 8.00-609.00	<0.001 c
CRP (0.0 – 5.0 mg/l)	1.40 (6.10)* 0.20-48.20	13.75 (71.88)# 0.60-138.70	1.50 (3.45) 0.20-20.60	<0.001 c

† Mean±SD, ‡ Median (Interquatile range), Min-Max, [a] ANOVA, [b] Chi-squared test, [c] Kruskal-Wallis test, * vs MH, # vs healthy, p<0.05
rv – reference values

with chronic lymphocytic leukemia (100%), in one patient with acute leukemia (9.1%), one patient with myelodysplastic syndrome (MDS) (25%), 3 patients with non Hodgkin lymphoma (NHL) (27.3%) and one with multiple myeloma (14.3%).

The ROC analysis was used in determining the best diagnostic marker in IDA patients. Table II shows the parameters of ROC analysis in IDA patients, and Table III presents these parameters in MH patients (AUC – area under the curve, 95% CI – 95% confidence interval, p= threshold level of significance).

It was shown that sTfR/log ferritin and sTfR occupy the largest area under the curve. These

Table II. ROC analysis parameters in patients with IDA

	AUC	95%CI	p
sTfR	0.931	0.886-0,975	<0,001
sTfR/log ferritin	0.977	0.956-0.998	<0,001
Transferrin	0.739	0.652-0.826	<0,001
Ferritin	0.920	0.872-0.968	<0,001

Table III. ROC analysis parameters in patients with MH

	AUC	95%CI	p
sTfR	0.661	0.557-0.765	0,004
sTfR/log ferritin	0.770	0.684-0.855	<0,001
Transferrin	0.642	0.524-0.759	0,011
Ferritin	0.685	0.586-0.785	0,001

two biochemical parameters represent the best diagnostic markers in IDA patients (Fig. 1).

In patients with malignant diseases, the best diagnostic marker for associated iron deficiency proved to be sTfR/log ferritin (Fig. 2).

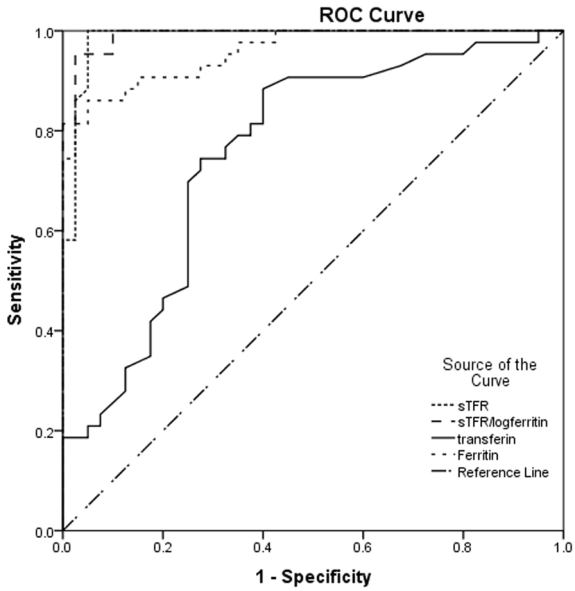

Figure 1. ROC curves for Iron Deficiency Anemia group

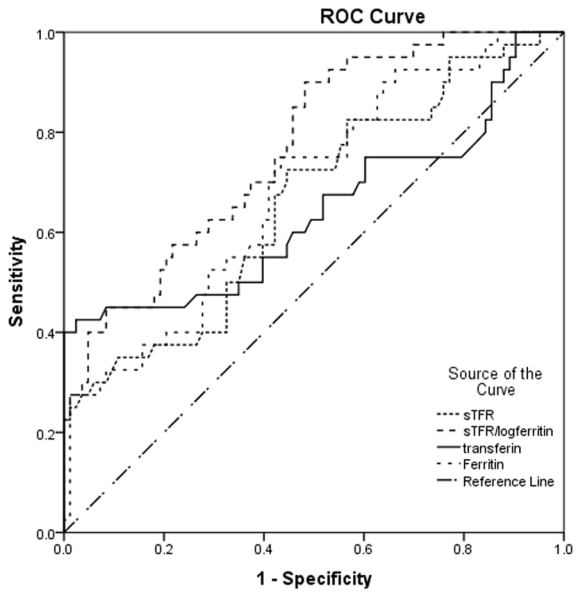

Figure 2. ROC curves for Malignant Hemopathies group

Discussion

The reference values of sTfR concentrations, given for the nephelometric method, are appropriate for our healthy population, as well. In our healthy subjects, 90% of the results were within the given reference range values. The age of subjects in our group did not affect the sTfR concentration, which is known from a number of works [15], but a statistically significant higher sTfR concentration was registered in the healthy female as compared to the male subjects. Although numerous authors argue that there is no statistically significant difference between the sexes in view of sTfR concentration [16], there are also those who have established the difference [17], like we did. However, the verification on a bigger number of subjects would certainly be more valid.

In the procedure of IDA diagnosing, we use the standard analyses which include the complete blood count on automated counters, as well as additional biochemical analyses. As we had expected, we obtained significantly lower values of erythrocytes, Hgb, Hct, MCV, MCH, MCHC, iron, ferritin in the IDA group of patients compared to the healthy subjects, and significantly higher values of RDW, TIBC, UIBC, respectively. All these parameters have not been sufficient to establish an IDA diagnosis in each individual case. Even with the added ferritin, which was lower in 76.1% of patients, there is almost a quarter of patients left without a reliable diagnosis. The sTfR were useful in this case, since higher values were found in all IDA patients, which proved an excellent sensitivity of this test. This is in line with up-to-date literature [18]. By applying the ROC analysis with IDA patients, it was shown that sTfR/log ferritin (AUC 0.977) and sTfR (AUC 0.931) occupied the largest area under the curve, having thus confirmed that they represent the best diagnostic markers for these patients. These findings are fully conformant

with the findings in several recent studies [19, 20].

In MH patients, the process of associated IDA diagnosing is much more complicated, owing to the presence of primary disease. Ferritin by itself is of little help, because it behaves as an acute phase reactant. Our results have shown a statistically significant increase of ferritin value in this group of patients, compared to IDA group of patients, as well as to the group of healthy subjects ($p<0.001$). In MH patients, 57.5% had higher ferritin values, while 40% had the ferritin value in the reference range. In these patients, CRP was statistically significantly higher than in the IDA group of patients, as well as in the healthy subjects. There was no statistically significant difference in hemoglobin value between the IDA and MH groups, respectively [21].

The investigations to date have shown that the level of sTfR is not increasing in case of inflammatory conditions [22], or in anemia of chronic diseases [23]. In our MH patients, 72.5% had normal or lower values of sTfR, so it may be considered a reliable diagnostic parameter of associated iron deficiency in most patients with malignant hematologic diseases. The only exception is registered in the patients with chronic lymphocytic leukemia, since our results have shown the increase of sTfR levels in all the patients with this diagnosis. Of course, it refers to the patients with advanced CLL or relapse, as shown by recent studies [14]. For that reason, it may be considered as the marker of the disease progression in CLL patients. In patients with acute leukemia types, sTfR values are generally lower or normal according to the literature data [24], so that higher sTfR values could indicate the associated IDA. We found lower or normal values of sTfR in 90.9% patients with acute leukemia. In patients with MDS, 25% of patients had higher sTfR values. The data found in literature also indicate that higher, normal or lower values of sTfR level may be registered in MDS patients, reflecting various models of erythropoiesis that may be found in these patients [25]. In 14.3% of patients with multiple myeloma we found higher sTfR levels, while 85.7% had the normal values, that being in accordance with the literature [24]. The NHL patients had higher sTfR levels in 27.3% of cases, although all of them suffered from the active disease. According to some studies, the increased levels of sTfR values correlate with the disease progression in patients with aggressive NHL [26], while some others imply similar conclusions but with the recommendation that it is necessary to do further research [27], and we agree to that.

In order to establish the best diagnostic parameter for the associated iron deficiency in MH patients, we used the ROC analysis and found out that it was sTfR/log ferritin. Recent works also contain the recommendation to use this parameter in diagnosing MH with the associated iron deficit, which entails sTfR and ferritin in the serum [28]. They have also been recommended as the latest standard for determining the iron status among healthy persons [29].

Conclusion

The nephelometric method of determining sTfR levels is safe, and the reference values are adequate for our healthy population. sTfR levels are useful in IDA diagnosing, and particularly when ferritin values are not lowered. The calculation of the sTfR/log ferritin index is even more reliable. In patients with CLL, this method might not be reliable for iron deficiency determining, but it could rather serve as the marker of the disease activity. Our group of CLL patients was too small (only 4 patients) to make any firm statement in this respect. In patients with MH the associated iron deficiency may be best indicated by the sTfR/log ferritin index, but this would also have to be investigated on a bigger and more homogenous sample in order to be proved.

Conflict of interest

All authors declare that there is no conflict of interests.

Abbreviations

IDA – Iron Deficiency Anemia
Hgb – Hemoglobin
MCV – Mean Corpuscular Volume
Hct – Hematocrit
MCH - Mean Corpuscular Hemoglobin
MCHC - Mean Corpuscular Hemoglobin Concentration
MH - Malignant Hemopathies
RDW – Red Cell Distribution Width
TIBC – Total Iron Binding Capacity
UIBC – Unsaturated Iron Binding Capacity
sTfR – Soluble Transferrin Receptor
ACD – Anemia of Chronic Disease
CLL - Chronic Lymphocytic Leukemia
ROC – Receiver Operating Characteristic
MDS – Myelodysplastic Syndrome
NHL – Non Hodgkin Lymphoma
CRP – C-Reactive protein

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