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# The Importance of Serum Transferrin Receptor and TfR-F Index in the Diagnosis of Iron Deficiency Accompanied by Acute and Chronic Infections

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## ABSTRACT

This study evaluated the diagnostic superiority of serum transferrin receptor (sTfR) measurement to other laboratory tests performed for the determination of iron deficiency caused by chronic disease (CD). Study group consisted of 114 anemic patients allocated into 3 groups at the pediatrics clinic of Ankara University, Faculty of Medicine and 32 healthy pediatric subjects as the control group.

sTfR value ranged between 11.00 nmol/L and 26.20 nmol/L for the control group. However, it was  $61.29 \pm 39.33$  nmol/L in iron deficiency anemia (IDEA) group, consisting of 51 patients. While there was a significant positive correlation between sTfR and Hb, MCV, serum iron, ferritin levels, there was a significantly inverse correlation between sTfR with RDW in the IDEA group.

Mean sTfR value was found  $47.05 \pm 28.07$  nmol/L in the acute infection (AI) group consisting of 22 patients,  $39.31 \pm 26.16$  nmol/L in the CD group with 41 patients. Statistically significant difference was found between sTfR of IDEA group and sTfR of the AI group, though accompanied by iron deficiency. These findings showed that sTfR levels were suppressed.

That all hematologic parameters including ferritin and sTfR of all patients in the CD group were heterogenous and revealed both normal and abnormal values was noteworthy. To determine the existence of accompanying iron deficiency, sTfR values above 28.10 nmol/L were chosen. It was concluded that the diagnosis of these patients was not possible without sTfR measurement.

TfR-F index (sTfR/log ferritin) was found  $97.72 \pm 108.81$  in the IDEA group,  $52.16 \pm 66.25$  in the AI group, and  $24.36 \pm 43.00$  in the CD group ( $p < 0.001$ ). TfR-F index values of the chronic disease anemia group (ACD) and the iron deficiency anemia group accompanied by chronic disease (COMBI) were compared. The difference between these two groups was statistically significant ( $p < 0.001$ ). Thus, TfR-F index proved useful in evaluating the changes of iron metabolism and reducing iron necessities in patients.

Key Words: Iron deficiency anemia, Serum transferrin receptor.

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## INTRODUCTION

Iron deficiency has been identified as one of the most prevalent nutritional problems in the world. As the nutritional habits of the people are dependent mostly on grain cereals and vegetable originated proteins, iron deficiency constitutes a significant health problem in our country as well<sup>[1,2]</sup>.

When accompanied by infections, inflammations, or malignancies, differential diagnosis of iron deficiency anemia is difficult to establish with the routine laboratory tests. Unlike serum iron transferrin and ferritin values, serum transferrin receptor (sTfR) concentration, which has recently been identified, is unaffected by acute phase reactions; thus, providing superiority and more advantages over other methods of testing. In addition, it proves to be as beneficial as the iron stained bone marrow examination in the diagnosis of iron deficiency in the existence of chronic disease<sup>[3-7]</sup>.

The parameter defined as TfR-F index is calculated in terms of sTfR/log ferritin. Compared to only sTfR, the combination of two parameters reflecting iron status and infection is regarded more valuable<sup>[7,8]</sup>.

This study aimed at investigating the contribution of sTfR levels, the sTfR correlation with other parameters in iron deficiency, the role of TfR-F index (defined as sTfR/log ferritin) in the diagnosis of simple iron deficiency when accompanied by infections or chronic diseases.

## MATERIALS and METHODS

The subjects of this study comprised of 114 patients with iron deficiency (iron deficiency without infection) (IDEA), iron deficiency with acute infection (AI), and chronic disease (CD), who were admitted for anemia to the pediatrics clinic of Ankara University, Faculty of Medicine. The ages of the patients ranged between 0.3 and 18 years, and 47 patients were girls while 67 were boys.

Fifty-one patients, complaining of paleness and diagnosed as iron deficiency anemia with sedimentation rate of less than 20 mm/hr, were grouped as iron deficiency anemia (IDEA). Mean age of the patients of this group was  $3.74 \pm 3.88$  (0.50-15.00-years-old). There were 26 boys and 25 girls.

Acute infection group, which consisted of 22 pati-

ents, were previously admitted for fever and diagnosed as having upper respiratory tract infection, otitis, pneumonia, stomatitis, urinary tract infection accompanied by anemia and had sedimentation rates over 20 mm/hr. Mean age of the patients were  $3.40 \pm 3.77$  (0.50-14)-years-old. There were 7 girls and 15 boys.

Patients followed by pediatric cardiology and nephrology for juvenile rheumatoid arthritis and FMF, and patients with recurrent infections, all with anemia and sedimentation rate over 20 mm/hr constituted the CD group. There were 41 patients (15 girls and 26 boys), mean age of whom was  $8.08 \pm 4.61$  (0.30-18-years-old).

Control group consisted of 32 healthy subjects (20 girls and 12 boys) with no complaints and anemia, and presenting normal physical examinations. Mean age was  $7.15 \pm 5.37$  (0.80-17)-years-old.

Blood samples of patients were received for complete blood count, peripheral smear examination, serum iron (SI), total iron binding capacity (TIBC), ferritin level, sedimentation rate and sTfR. All venous blood samples were collected simultaneously, i.e. in the morning, and during fasting. Blood serums were separated and stored at -70°C for serum transferrin receptors while all the other results were obtained within the same day.

## Sample Analysis

Blood counts of the patients were automatically conducted with Coulter Counter CT (Table 1). SI, transferrin, TIBC were analyzed manually in line with the measurement methods. TS was calculated as serum iron/TIBC x 100. Serum ferritin level was measured as immulite ferritin with immulite automatic anal apparatus (Immulite Ferritin Euro/DPC Ltd, United Kingdom), and sTfR levels were measured by (ELISA) "Enzyme Linked Immunosorbent Assay" using Quantikine In Vitro Diagnostic Kits (R&D System Inc, Minneapolis, MD, USA).

## Statistical Analysis

The analyses of the data were conducted at the biostatistical department of Ankara University, Faculty of Medicine through "SPSS for Windows". Student t-test was used to compare means of groups while Mann-Whitney U test was used in the comparison of ferritin levels.

Table 1. Blood count results of subjects (mean ± SD) and ranges showing iron deficiency in children

	Iron deficiency anemia	Acute infection	Chronic disease	Control	Ranges of iron deficiency anemia
Hb	9.26 ± 11.23	8.93 ± 1.93	9.59 ± 11.21	12.02 ± 1.31	< 10.7
MCV	64.81 ± 7.05	68.39 ± 9.33	71.18 ± 7.74	79.10 ± 6.68	< 70
RDW	18.35 ± 3.19	18.37 ± 3.80	15.86 ± 2.72	13.50 ± 2.08	> 14.5

## RESULTS

In infections with acute phase response (sedimentation rate over 20 mm/hr), while ferritin levels increase, its diagnostic value decreases. Therefore, diagnosis of iron deficiency in the presence of chronic infections through these parameters is highly difficult. In such cases, the wide distribution (9.40-145.00 nmol/L) and increased mean ( $39.31 \pm 26.16$  nmol/L -median 29.60) of sTfR indicate association of iron deficiency in some cases (Table 2).

The correlation of sTfR with the parameters used to date in the diagnosis of iron deficiency anemia is presented in Table 3. The findings revealed a negative correlation between sTfR and hemoglobin, MCV, and serum iron and a positive correlation with RDW in simple iron deficiency anemia. RDW is higher in IDA. sTfR, considered as the best indicator of functional iron deficiency, was also at higher levels. The positive correlation between sTfR levels and RDW ( $p < 0.001$ ) is statistically significant. However, there was a negative correlation between sTfR and ferritin ( $p < 0.01$ ).

Mean sTfR of acute infection group with 22 patients is  $47.05 \pm 27.08$  nmol/mL while 41 patients of chronic disease group have a mean sTfR value of 39.31

$\pm 26.16$  nmol/L (Table 2, Figure 1). In infection and inflammation groups, though accompanied by iron deficiency, there is a suppression of sTfR levels (Figure 1). The difference of sTfR values between iron deficiency anemia and two infection groups is statistically significant ( $p < 0.05$  for AI with IDEA, and  $p < 0.001$  for CD with IDEA).

Of the 41 chronic disease patients (sedimentation rate over 20 mm/hr), those with sTfR over 28.10 nmol/L were separated in order to detect those with chronic diseases accompanied by iron deficiency, which are difficult to diagnose. Thus, two groups, chronic disease anemia (CDA) group consisting of 16 patients and chronic disease with iron deficiency (CD + IDEA) group with 25 patients, were formed.

Even though there is no significant difference when Hb, MCV, RDW of these groups are compared, in a general evaluation, these values do not facilitate interpretation. In chronic disease anemia with higher sedimentation rate and already high ferritin, the absence of difference in SI, TIBC, and TS levels ( $p > 0.05$ ) among the groups with normal or higher sTfR levels demonstrates that sTfR is the only parameter in differential diagnosis of iron deficiency existence in chronic diseases. The other parameters, on the other hand, re-

Table 2. Iron status and sTfR averages of subjects

Parameters of iron status	IDEA	Acute infection	Chronic disease	Control	Ranges of iron deficiency anemia
SI	33.27 ± 11.85	36.55 ± 15.86	55.07 ± 33.98	106.53 ± 34.46	< 71
TIBC	673.59 ± 125.86	623.00 ± 121.69	440.85 ± 126.17	426.56 ± 78.11	> 360
TS	5.00 ± 2.44	6.23 ± 3.36	14.35 ± 15.46	25.48 ± 8.25	< 16
Ferritin	3.53 ± 2.39	14.28 ± 12.80	41.39 ± 44.93	28.53 ± 21.38	< 10
sTfR	61.29 ± 39.33	47.05 ± 27.08	39.31 ± 26.16	20.58 ± 3.51	> 28.1*

\* Values are mean ± standard deviation.

\*\* Upper values of normal ranges for commercial kits.

Table 3. Correlation between sTfR and other hematologic parameters in iron deficiency anemia (IDEA) group

IDEA group	Median	r	p
Hb (g/dL)	9.50	-0.5534	< 0.001
MCV (fl)	65.20	-0.4492	< 0.001
RDW (%)	17.60	0.6098	< 0.001
SI (µg/dL)	38.00	-0.5028	< 0.001
Ferritin (ng/mL)	2.90	-0.4302	< 0.01

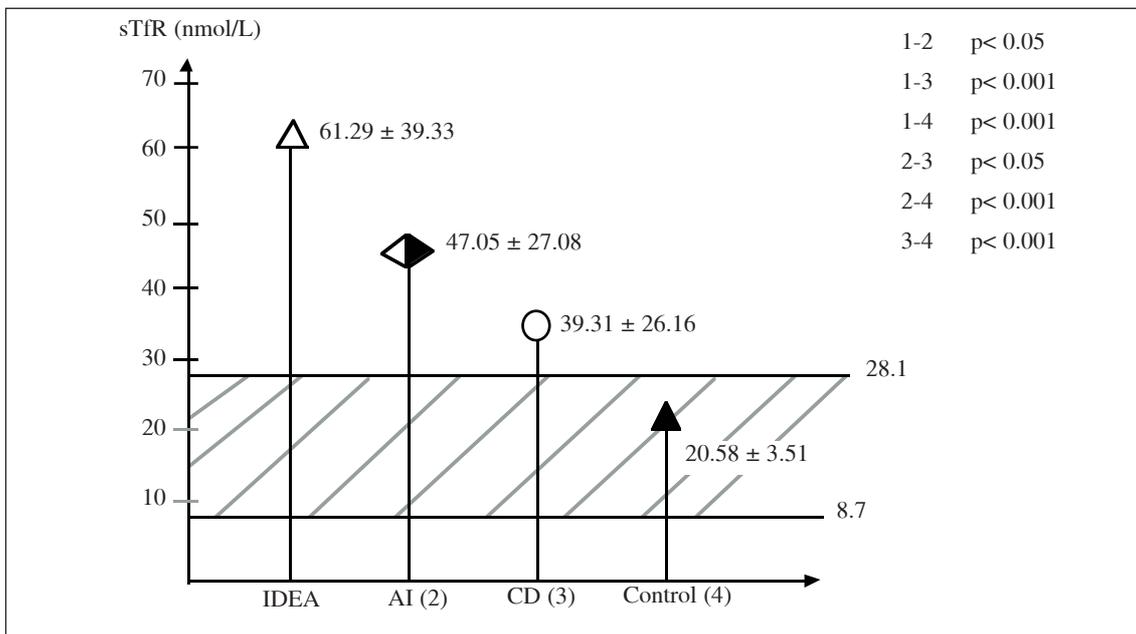


Figure 1. sTfR concentrations in patient groups and correlation of sTfR between groups.

main nonbeneficial in diagnosis. In Table 4, Hb, MCV, serum iron, TIBC, TS, and ferritin levels of CDA and CD + IDEA groups are compared.

As shown in Figure 1, sTfR is statistically significant in iron deficiency anemia and acute infection group ( $p < 0.05$ ) while TfR-F index is more significant in differentiation of these two groups ( $p < 0.001$ ) (Figure 2). This finding confirms that TfR-F index, calculated by the combination of two parameters revealing iron deficiency and infections, is more sensitive than sTfR in diagnosis of iron deficiency anemia during infections.

## DISCUSSION

The failure to detect iron stores on a Prussian blue

stained bone marrow aspirate provides the key defined as the “golden standard” to the differential diagnosis of iron deficiency anemia<sup>9,10</sup>. Nevertheless, this examination can not be routinely performed since it is invasive, painful, expensive and time consuming. Recent studies have confirmed sTfR to be a better indicator for iron deficiency diagnosis.

In a study conducted on a group of 77 randomly selected patients, sTfR detection has been found inappropriate as a first test in diagnosis of iron deficiency<sup>9</sup>. Another study from Canada involving 485 healthy subjects, between the ages of 9 to 15 months, is the first study to present percentile estimates of sTfR and log TfR<sup>11</sup>. In our study, high sTfR levels ( $61.29 \pm 39.33$  nmol/L) of 51 iron deficient patients have been consi-

Table 4. Hematologic parameters comparing chronic disease anemia and chronic disease with iron deficiency (Classified according to sTfR)

Parameter	CDA (n= 16)	CD + IDEA (n= 25)	P
Hb (g/dL)	10.23 ± 0.97	9.19 ± 1.20	< 0.05
MCV (fl)	75.13 ± 7.33	68.66 ± 7.04	< 0.05
RDW (%)	14.42 ± 2.03	16.78 ± 2.74	< 0.05
SI (µg/dL)	69.13 ± 45.08	46.08 ± 20.96	> 0.05
TIBC (µg/dL)	416.56 ± 139.00	456.40 ± 117.54	> 0.05
TS (µg/dL)	16.01 ± 11.90	13.29 ± 17.52	> 0.05
Ferritin (ng/mL)	53.24 ± 51.77	33.82 ± 39.20	< 0.05
sTfR (nmol/L)	21.02 ± 4.43	51.03 ± 27.61	< 0.001

dered as a superior indicator of iron deficiency.

Furthermore, sTfR range (11.00-26.20 nmol/L) of the control group has been found at nearly the same levels as that of commercial kits.

When the correlation between sTfR and other hematologic parameters is investigated, our results are in conformity with the literature and expected values. While sTfR is found to be negatively correlated with MCV, TS and ferritin, it presents no significant correlation with serum iron in a randomized study of 77 pa-

tients<sup>[19]</sup>. Likewise, sTfR did not have correlation with Hb, Htc, MCV, serum iron, TS and ferritin in 62 prepubertal and early pubertal boys and the correlation between sTfR and Hb ferritin was not significant in 485 infants<sup>[11,12]</sup>. In our study, sTfR is correlated with ferritin in IDEA group (p< 0.01). As ferritin decreases, sTfR increases. Thus, sTfR constitutes a valuable parameter in reflecting even slight tissue iron deficiencies as was reported in our earlier study<sup>[8]</sup>. In addition, a significant inverse correlation of sTfR with Hb, MCV and serum iron (p< 0.001).

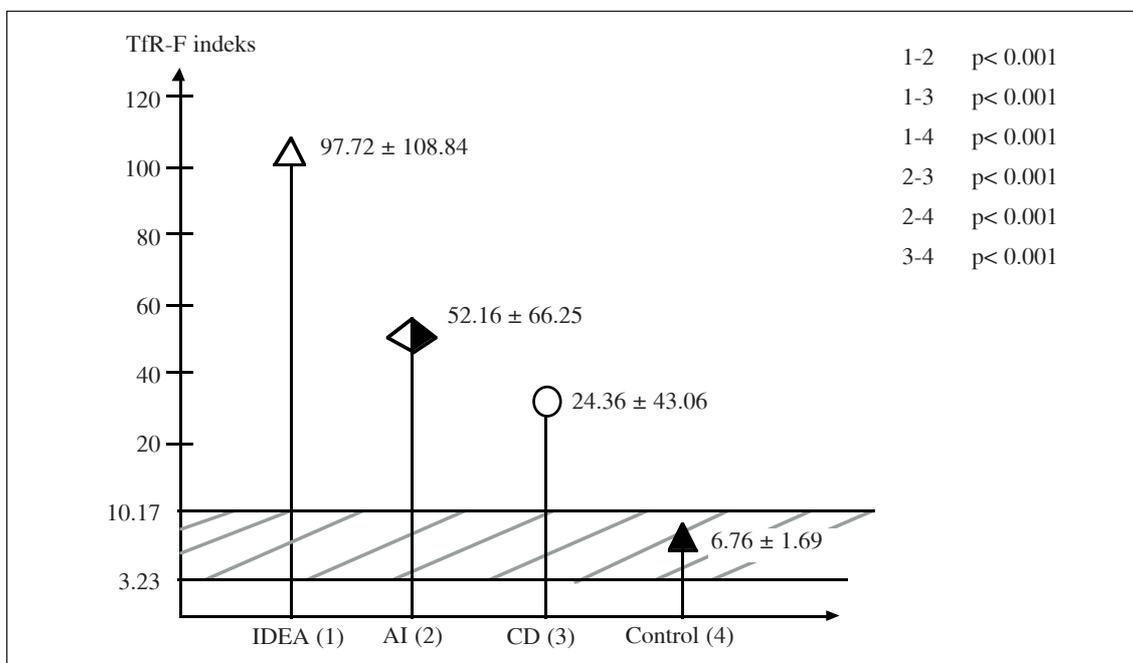


Figure 2. TfR-F index averages between patient groups and correlation of TfR-F index between groups.

In our study high sTfR values have provided evidence for iron deficiency accompanied by acute infection. However, relatively considerable decline in sTfR concentrations with respect to noninfectious iron deficiencies, ( $p < 0.05$  for AI and IDEA,  $p < 0.001$  for CD with IDEA) is thought provoking as to sTfR's being affected by the infection. Contrary to the relevant literature asserting that sTfR is not affected by infection, this finding may be of great importance<sup>[10,11,13,14]</sup>.

sTfR concentration has been a guide particularly in infection and inflammation. The differentiation of chronic inflammation anemia and iron deficiency has always been challenging. In anemia of chronic infections, sTfR does not increase in the absence of iron deficiency. In a series of 129 adult patients (48 with IDEA, 64 with CDA, 17 with CD + IDEA), sTfR was found to have increased in most of IDEA and CD + IDEA patients while it was within normal limits for those with CDA (17). In another study of 104 patients (45 with IDEA, 36 with CDA, 23 with CD + IDEA) sTfR markedly differentiated the iron deficient group<sup>[14]</sup>.

Our results are compatible with these data and all other hematologic parameters, except for sTfR, appears to be nonspecific and insensitive in determining iron deficiency accompanied by chronic disease. Although sTfR clearly reflects iron deficiency, in the cases with elevated sedimentation rate, such as those with infection or inflammation, it does not reach at as high values as detected in simple iron deficiency.

Results of this study confirm the reports of earlier studies in that the TfR-F index, calculated in terms of sTfR/log ferritin is more sensitive and specific in diagnosis of iron deficiency in early stages and in the presence of infection<sup>[7,8,10,15]</sup>. In a study of 10 patients, especially with acute phase responses, the increase in TfR-F index has been regarded as an early sign of decrease in iron stores<sup>[5]</sup>. Similarly in our study, TfR-F index shows significant difference in CDA and CD + IDEA group ( $p < 0.001$ ). That there is a more significant difference between acute infection and CD groups than in sTfR is suggestive of TfR-F index to be more sensitive in the diagnosis of iron deficiency and more importantly in defining the iron necessity of organism. Even if sTfR is high and TfR-F index is low, organism does not need much iron and iron treatment after the resolution of the infection, when suitable for use in

erythropoiesis, proves to be the appropriate approach. The higher degree of TfR-F index suppression compared to that of sTfR depression in acute infection group ( $p < 0.001$ ) shows that this parameter is a better indicator of iron need of the organisms.

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