Serum Transferrin Receptor Concentrations In Diagnosing And Differentiating Iron Deficiency Anemia From Anemia Of Chronic Diseases In Children.

1Manal A. Fathy, 2Hanan A Fathy, 3Manal M. Alkady, 1Nawal M. Khalifa, 1Amal A. El-Menshawy,
1Pediatric Department, Research Institute of Ophthalmology, Giza, Egypt.
2Pediatric Department and 3Clinical Pathology Department, National Center for Radiation Research and Technology, Cairo, Egypt.

**Abstract:** Iron deficiency anemia is the most common type of anemia. In children it can lead to lower growth rate, educational and behavioral problems and immune dysfunction. One of the main difficulties is to distinguish between the anemia of chronic diseases (ACD) with and without iron deficiency. There is an evident clinical need for non-invasive and sensitive means for the detection of iron deficiency.: This study was conducted to assess the diagnostic efficiency of serum transferrin receptor (sTfR) measurements, in diagnosis of iron deficiency in anemia of chronic disorders.

**Methods:** The patient population of our study consisted of 40 anemic children, 18 children were iron deficiency anemia (group1), 13 children suffered from iron deficiency anemia in presence of acute infection (group 1I) and 9 children had anemia of chronic disorders (group III). Twenty healthy children enrolled and studied as a control group. Complete blood count, serum iron, total iron binding capacity, serum ferritin and sTfR were assayed in all patient groups.

**Results:** The study showed that sTfR was very highly significantly elevated in all groups, when compared separately with the control group (p<0.001). sTfR level showed highest value in the iron deficiency anemia (IDA) group 1 (725.22± 228.65 u/ml), followed by the ACD group III (665.0±136.90 u/ml), then IDA with acute infection group II (466.14±97.86 u/ml). Moreover, TfR / ferritin ratio was also significantly elevated in the three groups when compared with the control (p<0.001).

**Conclusion:** We concluded that the increase in sTfR among patients with anemia of chronic disease reflects the increased demand for iron in the erythroid cells, thus we might rely on sTfR level in distinguishing the coexistence of iron deficiency anemia in anemia of chronic inflammatory diseases.

**Key words:** iron deficiency anemia, serum transferrin receptor, and anemia of chronic disorders, juvenile rheumatoid arthritis.

**INTRODUCTION**

Anemia is a worldwide health issue, which can have a profound effect on those affected and their quality of life. The most common cause is iron deficiency, estimated to be responsible for 50% of all anemia cases (WHO, 2001). Iron deficiency anemia (IDA) negatively impacts the cognitive and physical development of children as well as the work productivity of adults (Stoltzfus, 2001).

In most cases of (IDA) it can be treated simply with iron once the body’s iron status is ascertained. The standard tests for establishing (IDA) include measuring serum ferritin, serum iron and iron binding capacity. However these analytes are unreliable when there is inflammation present, as commonly occurs in chronic diseases. In fact, inflammation is a frequent confounder because chronic disease is the second most common cause of anemia (Weis &Goo 2005). Anemia of chronic disease (ACD), also known as anemia of chronic inflammation, occurs with infections, cancer, autoimmune diseases and chronic kidney disease and causes a state of ‘functional’ ID (Weis &Goo 2005). Recently, hepcidin (a liver-produced peptide) was found to be a link between the immune system and the movement of iron to and from the storage depots. Hepcidin binds to ferroportin, a transmembrane iron exporter present on macrophages, enterocytes and hepatocytes. It has been demonstrated that in vitro hepcidin induces the internalization and degradation of ferroportin. By regulating the number of iron exporters, hepcidin is involved in the control of iron uptake and release from enterocytes or macrophages. It is conceivable that processes that affect these regulatory mechanisms can result in defective iron mobilization without deficiency in the iron stores per se (Kemna et al., 2008).

**Corresponding Author:** Manal A. Fathy, Pediatric Department, Research Institute of Ophthalmology, Giza, Egypt.
The definitive method to distinguish between (IDA) and (ACD) is the assessment of stainable iron in bone marrow. However, bone marrow examination is an invasive procedure, cause discomfort to the patient and cannot be repeated often. Therefore, there is a clinical need for noninvasive and sensitive methods to determine the presence of concomitant (IDA) (Punnonen et al., 1997).

Red cell indices and iron parameters such as total iron binding capacity (TIBC) show considerable overlap. In general, IDA is associated with a serum ferritin value below 20 microg/L whereas a serum level above 100 microg/L excludes iron deficiency in majority of cases. Serum ferritin being an acute phase reactant increases nonspecifically in inflammatory conditions despite the presence of iron deficient stores (Punnonen et al., 1997).

The transferrin receptor mediates cellular uptake of iron by binding the iron carrier-protein transferrin (Tf). Following internalization of the iron-transferrin-TfR complex, iron is released from its binding sites in the acidic milieu of the endosomes (acidosomes), and the Tf-TfR complex is returned back to the cell surface, where apo-transferrin is released again (Kaup et al., 2002). The transferrin receptor is comprised of two identical subunits, each composed of 760 amino-acids with a molecular mass of 95 kDaltons. Each polypeptide subunit contains a trans-membrane segment with 21 amino acid residues, an N-terminal cytoplasmic domain with 61 residues, and a large C-terminal extracellular domain with 671 amino acids. The soluble form of TfR in serum was recognized since 1986 (Kohgo et al., 1986).

Humans use 80% of their body iron for erythropoiesis, and almost the same proportion of TfR in the body is found in erythroid progenitor cells. Erythrocytes entering the peripheral blood stream carry a high surface concentration of the receptor; as the cells mature the receptors are shed into the circulation (Shih et al., 1993). Release of TfR has been shown to be mediated by an integral membrane proteinase, and inhibited by a matrix metalloproteinase and the TNF-N protease inhibitor-2 (Kaup et al., 2002). Measurement of sTfR is a promising new tool of iron metabolism that reflects body iron stores and total erythropoiesis (Kohgo et al., 2002).

The objective of our study is to evaluate the predictive value of serum transferrin receptors measurements and serum transferrin receptors to ferritin ratios in the diagnosis of iron deficiency anemia, and to detect its diagnostic value in distinguishing iron deficiency in anemic patients with chronic inflammatory disorders.

Patients and Methods:
This work was conducted on 40 children with iron deficiency anemia attending the out–patient pediatric clinic of research institute of ophthalmology. The patients were divided into the following groups:

Group I: Included 18 children who fulfilled the criteria of iron deficiency anemia. They were 12 males and 6 females with a ratio of 2:1. Their ages ranged from 0.60-15 years with a mean of 6.32±5.21 years.

Group II: included 13 children with iron deficiency anemia in the presence of acute infectious disease. Five of them suffered from urinary tract infection, 4 had bronchopneumonia, 2 suffered from acute bronchitis and 2 from bronchiolitis. They were 7 males and 6 females with a ratio of 1.6:1 their ages ranged from 0.5-15 years with a mean of 4.5± 4.2years.

Group III: included 9 children suffered from juvenile rheumatoid arthritis as a model for anemia of chronic disorders (ACD). They were 5 males and 4 females with a ratio of 1.25:1. Their ages ranged from 4-16 years, with a mean of 11.24±5.32 years. All patient in this group met the American rheumatism association revised criteria (arnett et al., 1998) for the rheumatoid arthritis.

At the time of this study, all patients received non – steroidal anti –inflammatory drugs (NSAIDS). 7 of them were on steroids and 2 were on oral methotrexate in combination with NSAIDS.

Control group: twenty healthy normal children were chosen to serve as control group. They were 12 males and 8 females with a ratio 1.5: 1, their ages ranged from 0.75-15 years with a mean of 5.8± 4.38 years.

All groups of patients were subjected to the following:
- Full detailed history laying stress on nutritional habits, medication, growth as well as mental development.
- Through clinical examination laying stress on anthropometric measures.

Investigations included
- Complete blood count using Coulter Counter.
- Serum iron using iron chromazurol B (iron CAB) from ELITECH diagnostic.
- Total iron binding capacity using (iron CAB) from ELITECH diagnostic.
- Serum ferritin level was determined by using enzyme linked Immunosorbent Assay (ELISA)
- Transferrin saturation was calculated by the following equation: (Lee, 1999)

Transferrin saturation = $\frac{\text{Serum iron} \times 100}{\text{TIBC}}$ %
- Erythrocytic sedimentation rate (ESR) and C-reactive protein (CRP) especially for group II and group III.
- Urine analysis and culture and sensitivity if needed.
- Serum transferrin receptor was measured using EUROGENETICS sTfR ELISA technique.

**Inclusion criteria**

The IDA children included in the present study were chosen with hemoglobin level <11 gm% according to WHO, (Walker, 1998), and mean corpuscular volume < 74fl, with a transferrin saturation < 16%.

**Exclusion criteria**

All blood samples were obtained before any blood transfusion, and any patient who received blood transfusion for the last two weeks was excluded. Patients on iron therapy were excluded from the study population. Patients with hematological diseases that might affect our data such as hemolytic anemia, hematological malignancies were also excluded from the study.

**Blood samples and analysis**

- Venous blood samples were obtained from the studied groups by venipuncture.
- Blood obtained was placed into clean vacutainer tubes, the blood was centrifuged to remove red cells at 3000 rpm for 10 min and serum was separated and divided into aliquots in multiple small plastic tubes and then was stored at -70°C until subsequent assay of sTfR.
- Briefly anti-sTfR monoclonal antibodies were incubated with patient's sera. The sTfR captured on the solid phase react in a second incubation step with a second sTfR specific monoclonal antibody conjugated to HRP. The microtiter plate readers were blanked and the absorbance of each well were determined at 450nm within 30 minutes.

**Statistical analysis:** statistical analysis of the results was carried out using the standard computer program SPSS (V.9.04, Echosoft corporation USA, 1998). Normally distributed results were compared using student's test. Pearson’s coefficient correlation test was used for correlations. Differences among groups were evaluated using one way Anova (group I, II, III). Results were expressed as mean ± SD. P values less than 0.05 were considered to be significant.

**Results:**

The characteristics of the groups will be illustrated in tables 1,2,3 and figures 1&2. Upon studying the male and female in all patients groups, the mean serum ferritin concentration was (29.02 ±17.40 ng/ml) and (26.47±17.86 ng/ml), respectively (t= 0.48, P> 0.05). While mean sTfR concentration was (659.20 ±217.68 U/ml) and (590.53 ± 194.29 U/ml), respectively (t = 1.08, P> 0.05). No significant differences were observed neither in serum ferritin nor TfR levels between male and female.

With regard to sTfR value we found a very highly significant increase in its mean value in IDA group I when compared with the control group (p<0.01), (table 1, figure 1).

Moreover, we observed a negative correlation between sTfR in IDA group I and serum hemoglobin concentration, serum iron as well as transferrin saturation. In the present study, the TIR/ferritin ratio was significantly increased when group I was compared with the control group (P<0.001), in addition to a negative correlation between its level and serum hemoglobin concentration and serum ferritin level (P<0.05).

With regard to group II (IDA in the presence of acute infection), we noticed no significant difference in the serum ferritin level when compared with the control group and neither with IDA group I nor ACD group III.

On the other hand, we observed a significant increase in the level of sTfR in group II when compared with the control group (P<0.001), (table 1). In addition to a significant decrease in its level in group II when compared with both IDA group I and ACD group III separately (P<0.001), (Table 2, figure 1). Moreover, TIR/ferritin was significantly higher in group II when compared with control group (P<0.01). (Table 1, figure 2).

On evaluating the sTfR and the sTfR /ferritin ratio in ACD group III, a very high significant increase in their levels were observed in ACD patient when compared with the control group (P<0.001), (Table 1, Figure 1&2).

However, sTfR was significantly higher in group I and III when compared to group II (P<0.001). Meanwhile, on comparing group I and III together, TIR was statistically insignificant (Table 2).

Using the analysis of variance (Anova), sTfR was able to discriminate between all studied groups (F ratio 8.88, P <0.001), followed by TIR / ferritin ratio (F = 3.19, P<0.05). On the other hand, serum ferritin level failed to discriminate between patient groups (F ratio = 0.89 P< 0.05), (Table 3).
Table 1: Comparison between control subjects and patients in all the three study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control N=20</th>
<th>Group 1</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys / girls</td>
<td>12/8</td>
<td>12/6</td>
<td>7/6</td>
<td>5/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5.8±4.39</td>
<td>5.32±5.21</td>
<td>4.5±4.2</td>
<td>11.24±5.32</td>
</tr>
<tr>
<td>Hgb (gm%)</td>
<td>12.1±0.65</td>
<td>9.13±1.4**</td>
<td>9.4±1.5**</td>
<td>9.82±0.92**</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>79.6±4.10</td>
<td>63.9±14.71**</td>
<td>68.80±3.9**</td>
<td>70.47±1.91**</td>
</tr>
<tr>
<td>S iron (ug/dl)</td>
<td>91.89±33.94</td>
<td>42.41±17.63**</td>
<td>53.8±10.6**</td>
<td>40.04±24.78**</td>
</tr>
<tr>
<td>TIBC (ug/dl)</td>
<td>298.28±56.78*</td>
<td>448.62±45.65**</td>
<td>366.2±47.78**</td>
<td>455.48±36.51**</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>31.28±11.54</td>
<td>10.5±4.2**</td>
<td>14.59±1.71**</td>
<td>11.6±4.8**</td>
</tr>
<tr>
<td>S ferritin (ng/ml)</td>
<td>34.43±21.63</td>
<td>24.68±16.12*</td>
<td>33.01±17.75</td>
<td>25.4±16.36</td>
</tr>
<tr>
<td>S . TfR (u/ml)</td>
<td>314.00±72.94</td>
<td>725.22±228.65**</td>
<td>466.14±97.86**</td>
<td>665.00±136.90**</td>
</tr>
<tr>
<td>TfR/ferritin</td>
<td>31.24±4.63</td>
<td>37.93±24.67**</td>
<td>20.12±15.33**</td>
<td>38.2±25.80**</td>
</tr>
</tbody>
</table>

*P <0.05 = significant  
** P< 0.001 = very highly significant

Table 2: Comparison of all measured parameters in the three study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb (gm%)</td>
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<td>53.8±10.6</td>
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</tr>
<tr>
<td>S . Ferritin (ng/ml)</td>
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<td>33.01±17.75</td>
<td>25.4±16.36</td>
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<tr>
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<td>TfR/ferritin</td>
<td>37.93±24.67</td>
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<td>38.2±25.80</td>
</tr>
</tbody>
</table>

Table 3: Comparison between all patient groups regarding the ferritin, Tsf/F using analysis of variance (ANOVA).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups</th>
<th>Mean</th>
<th>F ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Group I n= 18</td>
<td>24.68</td>
<td>0.89</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Group II n= 13</td>
<td>33.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group III n=9</td>
<td>25.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TsfR</td>
<td>Group I n= 18</td>
<td>725.22</td>
<td>8.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Group II n= 13</td>
<td>466.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group III n=9</td>
<td>665.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TsfR/Ferritin</td>
<td>Group I n= 18</td>
<td>37.93</td>
<td>3.21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Group II n= 13</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group III n=9</td>
<td>38.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P>0.05 = non significant, P<0.05 = significant, P<0.001 = very highly significant.

Fig. 1: The means TRF level (U/ml) in control, group I, II and III.
The prevalence of iron deficiency anemia (IDA) has decreased sharply during the past two decades, however, IDA still remains the most common single nutrient deficiency disorder in the world and the highest rates occur in the less developed regions of the world (Kim et al., 1996). Evaluation of anemia in patients with inflammation may be difficult because conventional laboratory measurements of iron status are often unable to differentiate between iron deficiency and anemia of chronic disorders, making it necessary to do a bone marrow examination to evaluate iron stores and to establish a definitive diagnosis. Nevertheless, this examination cannot be routinely performed since it is invasive, painful, expensive and time consuming. Studies have shown sTfR to be a better indicator of iron deficiency when associated with inflammation (Chijiwa et al., 2001). Circulating transferrin receptor concentrations do not increase in anemia secondary to inflammatory disorders. In situations where iron deficiency anemia co-exists with anemia of chronic disease, transferrin receptor concentrations increase secondary to the underlying iron deficiency (Ferguson et al., 1992).

With regard to sTfR value, we found a very highly significant increase in its mean value in IDA group I when compared with the control group (P< 0.001). This significant increase in sTfR level in the IDA group accords with many studies Goodnough et al., 2000, Beguin et al., 2003, Jayaranee & Sthanashwar (2006) & Skikne (2008). The increased sTfR in IDA patients was attributed to the erythroid marrow hyperplasia (Huebers et al., 1990). Where concentration of sTfR correlates directly with erythropoietic activity and inversely with the amount of iron available for erythropoiesis (Ferguson et al., 1992). Furthermore, sTfR present in human plasma is a truncated form of tissue receptor and the sTfR numbers on the cell surface reflect the iron requirement, and logically, iron deprivation results in the prompt induction of transferrin receptor synthesis (Punnonen et al., 1997).

Moreover, we observed a negative correlation between sTfR in IDA group I and serum hemoglobin concentration, serum iron as well as transferrin saturation. This was in agreement with Ianzkowski, (2000) who observed the negative correlation between sTfR and iron indices.

Suominen et al., (1998) Simek et al., (2002) & Skikne (2008) reported that sTfR is a sensitive marker of IDA and it offers a particular advantage over serum ferritin in assessing iron status in segments of population where prevalence of iron deficiency is high, as in infants, children, and women during pregnancy. In these populations, the serum ferritin is usually close to the iron deficient range and does not accurately portray differences in functional iron.

In the present study, the sTfR /ferritin ratio was significantly increased when group I was compared with the control group (P<0.001), in addition to a negative correlation between its level and serum hemoglobin concentration and serum ferritin level (P<0.05). This was in accordance with Rimon et al., (2002) goyal et al., (2006) Jayaranee & Sthanashwar (2006) & Skikne (2008) who suggested that TIR /ferritin ratio and TIR/log ferritin index are a good estimate of body iron. The usage of this ratio provides the advantage of the combining of two phenomena i.e., increase in TIR and a decrease in the ferritin concentration. These two variables, in general, are influenced by the body iron stores, the availability of iron for erythropoiesis, and total mass of erythroid marrow.
In our attempts to distinguish the possible coexistence of IDA in anemia of chronic disease (ACD). Juvenile rheumatoid arthritis (JRA) patients were studied as ACD group III. We observed that 70% of the ACD patients had serum iron level <50 ug/dl (below the lower reference limit) and when its mean iron level was compared with the control group, a significant lower mean level was found (P<0.001). It is known that serum iron level may be decreased in the presence of inflammatory diseases irrespective of their true iron status. The determination of conventional hematological iron indices as well as biochemical variables are of little help in demonstration iron deficiency with chronic inflammatory diseases (Peterson et al., 1994).

With regard to sTfR, we expected that its level in the ACD group to be unchanged in comparison to the control group. On the contrary, a very high significant increase in its level was observed in ACD patients when compared with the control group (P<0.001). sTfR was observed to be a sensitive and reliable index of early tissue iron deficiency and its increased level could estimate even mild ID (Skikne, 2008). This raises the possibility of coexistence of IDA in our ACD group of patients. This possibility could be emphasized by our previous observation of increased sTfR in the IDA patients (group I), as well as, the insignificant difference in its mean level when the IDA (group I) was compared with the ACD (group III) (P>0.05). This, in addition to the other laboratory criteria of iron status, where we observed that 90% of our ACD patients had transferrin saturation below 16%, 20% of these patients had serum ferritin below 12 ng/ml as well as, a significant decrease in the MCV value in this group when compared with control group (P<0.001). Skikne (2008) stated that the combined use of MCV and ferritin helps to predict iron deficiency in patients with JRA but he pressed on the need for a single laboratory test that reliably identifies iron deficiency in patients with inflammation.

Numerous authors, who studied possibility of the coexistence of IDA with ACD, agree with our findings, in that sTfR increased in ACD patients in the presence of IDA with no iron stain in the bone marrow; Simek et al., 2002; Das Gupta and Abbi 2003 Koulaovazidis et al., 2009 & Jain et al., 2010. Moreover, they elucidated the capability of sTfR to differentiate between iron deplete and iron replete patient groups.

Our findings of increased sTfR and sTfR/ferritin ratio in ACD patients could be attributed to the accepted explanation of the possibility of the presence of IDA with ACD.

On the other hand, Diaz et al., (2001) and Van Tellingen et al., (2001) disagreed with our results and concluded that sTfR cannot be considered a good parameter for making a diagnosis of iron deficiency in chronic diseases.

However, it has been reported that treatment with NSAIDs and corticosteroids may cause gastrointestinal bleeding that leads to IDA in patients with chronic inflammatory diseases (Peterson et al., 1994). This could explain the presence of IDA in our patients ACD group. Where all the patients in this group received NSAIDS, in addition, seven of them were on steroids and two on methotrexate. Dietary factors may also contribute to the development of iron deficiency in patients with rheumatoid arthritis. Cazzola et al., 1996, stated that the defective supply of iron to developing erythroid cells, responsible for the anemia associated with systemic onset juvenile rheumatoid arthritis (soJRA), may be the consequence of both severe reticulo–endothelial iron block and true iron deficiency.

Cazzola et al., 1996, also observed that excessive production of interleukin – 6(IL -6) in JRA, might directly be responsible for the abnormalities in iron metabolism. Moreover, this cytokine may enhance ferritin synthesis and increase hepatic uptake of serum iron (Kobune et al., 1994). In turn, increased ferritin expression results in reticulo-endothelial iron block and impairs iron absorption. Therefore, the chronic anemia associated with high IL – 6 appears to be peculiar in that it is associated with adequate endogenous erythropoietin (EPO) production and is mainly caused by a defective iron supply for erythropoiesis (Cazzola et al., 1996).

In addition, there are increased levels of tumor necrosis factor-a (TNFa) and interleukin – 1(IL -1) in active rheumatoid arthritis which inhibit erythroid progenitor proliferation and may blunt erythropoietin response to anemia. These cytokines are also responsible for the alterations in iron metabolism that result in reduced iron supply to the erythroid marrow (Means et al., 1992).

Thus, a true body iron deficiency caused by decreased iron absorption likely complicates long lasting inflammation and in most anemic children, as those with our JRA patients, and can be recognized by high serum transferrin receptor levels, as stated by Cazzola et al., (1996); Das Gupta and Abbi (2003).

In our ACD study group, sTfR did not correlate with any of the conventional hematological indices of iron status (S. iron, TIBC and serum ferritin). This was in accordance to Peterson et al., (1994). Who observed that in their patients group with both inflammation and iron deficiency, there was a weak insignificant correlation between sTfR and serum hemoglobin level.

We observed a significant increase in the level of sTfR in group II as well as TIR/ Ferritin ratio when compared with the control group (P<0.001). In addition to a significant decrease in its level in group II when
compared with both IDA group I and ACD group III separately (P<0.001). Thus, the increased sTfR measurements can effectively identify iron deficiency even in the presence of accompanying inflammatory or acute infectious conditions. As it was previously suggested, the quantification of sTfR has been shown to differentiate effectively between iron replete and iron deplete anemic states, irrespective of the presence of acute or chronic inflammatory conditions (Das Gupta and Abbi, 2003; Pavai et al., 2008; Koulaouzidis et al., 2009 & Jain et al., 2010.)

So we concluded that sTfR is assumed to reflect reliably the degree of tissue iron supply. sTfR is more reliable as an index of iron status than other iron indices, therefore, its measurements could be very useful in differentiating pure IDA, ACD and ACD coexisting with iron deficiency. Moreover, we also concluded that the increase in sTfR among patients with anemia of chronic disease reflects, the increased demand for iron in the erythroid cells. In light of these observations, we would be prudent to treat ACD patients with high sTfR levels with iron replacement therapy.

REFERENCES


