ORIGINAL ARTICLE

SERUM TRANSFERRIN RECEPTOR, SERUM FERRITIN AND SERUM TRANSFERRIN RECEPTOR-FERRITIN INDEX IN ADULTS WITH IRON DEFICIENCY ANAEMIA

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Background: Serum Ferritin (SF) and iron both show acute phase responses to inflammation, so iron may fall and ferritin rise independent of the marrow iron store. Bone marrow iron store has been considered the gold standard, but is invasive, painful and expensive and not suitable for everyone. Serum transferrin receptor (sTfR) which is the concentration of the soluble fragment of transferrin receptor in serum, is an important new haematological parameter. The ratio of sTfR to log SF is known as sTfR-SF index. This study was conducted to evaluate sTfR, Ferritin and sTfR-F Index in diagnosing and differentiating iron deficiency anaemia (IDA) from anaemia of chronic disease (ACD). **Methods:** One hundred and sixteen (116) adult subjects (80 anaemic and 36 controls) who already had their bone marrow examination done for various reasons were included in the study. sTfR, SF, and their index were measured and compared with bone marrow iron stores. Absence of iron stores denoted IDA whereas increased macrophage iron with decreased siderocytes and sideroblasts was diagnostic of ACD. **Results:** Out of 80 anaemic patients, 47 were diagnosed as IDA while 33 were diagnosed as ACD. In case of IDA the diagnostic accuracy of index was 91.57%, sTfR had accuracy of 85.54% while SF had accuracy of 75.90%. In case of ACD, the diagnostic accuracy of sTfR was 91.30%, index 89.86%, while SF had accuracy of 79.71%. **Conclusion:** sTfR-SF index is a better parameter than sTfR or ferritin alone but should only be used when the results of these parameters seem altered or a bone marrow aspiration is mandatory for diagnosis of ACD. The estimation of sTfR or index may offer a simple non invasive method that may enable more accurate assessments of iron status in such patients.

Keywords: Serum Transferrin Receptor, Index, Iron deficiency anaemia

INTRODUCTION

Serum Ferritin (SF) and iron both show acute phase responses to inflammation, so iron may fall and ferritin rise independent of the marrow iron store.[1] Bone marrow iron stores has been considered the gold standard[2] but is invasive, painful and expensive and not suitable for everyone[3]. Serum transferrin receptor (sTfR) which is the concentration of the soluble fragment of transferrin receptor in serum, is an important new haematological parameter.[4] The ratio of sTfR to log SF is known as sTfR-SF index.[5] Iron deficiency anaemia (IDA) affects more than 2 billion people worldwide. In developing countries nearly 70% of women especially pregnant and lactating, are estimated to be iron deficient.[6] It is defined as a disease of reduced erythrocyte production with low content of haemoglobin, due to lack of iron.[7] Classically it is described as a microcytic anaemia, other causes of this include anaemia of chronic diseases (ACD), thalassemias (a raised Hb A_2 >3.5%) and congenital sideroblastic anaemias (>15% of marrow erythroblasts are ring sideroblasts).[8] ACD is the commonest cause of anaemia in hospitalised population and is immune driven. ACD is defined as hypoproliferative anaemia of no apparent cause that occurs in association with an inflammatory, infectious or neoplastic disorder, and resolves when the underlying disorder is corrected.[9]

Aimone Gastin[10] described the traditional standard biochemical markers of iron status as serum iron, transferrin, transferrin saturation, ferritin and more recently, soluble transferrin receptor (sTfR). In several clinical conditions, the old parameters may not change rapid enough to reflect transient iron-deficient states, that develop during erythropoietin therapy.[11] Ferritin and iron concentrations both show acute phase responses to inflammation, so iron may fall and ferritin rise independent of iron stores. Bone marrow aspirates for iron granules has been considered gold standard but is invasive, painful and expensive and not suitable for everyone.

Transferrin receptor (TfR) is a disulphide-linked dimmer of two identical sub-units, 95 kDa each, found mostly on immature erythroid and malignant cells. Its function is to internalise absorbed iron into target cells. Most iron uptake occurs via a receptor-mediated endocytosis route with diferric transferrin, bound to the TfR located on the cell surface, forming a ligand complex. This is followed by internalisation of the complex with release of iron from transferrin into the cytosol; the apotransferrin-TfR complex is returned to the cell surface. When body iron stores are low, receptor expression increases, when iron stores become

replete, it decreases. TfR is susceptible to proteolysis producing a serum transferrin receptor (sTfR), a 75 kDa monomer that circulates in the plasma at a concentration which is proportional to the total cell mass of TfR.[12] Clinical significance of sTfR has been evaluated as an indicator of developing IDA and in monitoring changes in the rate of erythropoiesis.[13]

The ratio of serum transferrin receptor to the log ferritin is defined as sTfR-F index. Punnonem *et al*[14] postulated this ratio, i.e., sTfR/log SF. The results are calculated without converting units, i.e., µg/ml of sTfR divided by µg/l of SF and then its logarithmic conversion.[15] We concluded this study to evaluate the efficacy of sTfR, SF and sTfR-F index in diagnosing and differentiating IDA from ACD.

MATERIAL AND METHODS

It was a cross-sectional comparative conducted at Department of Haematology, Sheikh Zayed Medical Complex, Lahore from 2007–09. One hundred and sixteen (116) subjects (80 anaemic patients and 36 controls) who already have had their bone marrow examination done for various reasons were included. Inclusion criteria consisted of Hb <12 g/dl in males and <10 g/dl in females, MCV <80 fl while MCH was <27 ρg. Cases excluded were previous iron therapy or blood transfusions, haematological malignancies, haemolytic anaemia, deficiency of Vitamin B_{12} or folic acid , chronic liver disease. Five ml of whole blood collected from each patient was used for full blood counts, while the rest was used to estimate serum iron, TIBC, SF, sTfR and sTfR-F index. SF was estimated by Ferritin Enzyme immunoassay (Biocheck) while sTfR were measured by immuno-enzymometric assay which was based on a non-competitive sandwich type assay technique (Biovendor Labs, Czech Republic). Absorbance values were recorded at 450 nm using a microplate spectrophotometer. sTfR-F index was calculated as ratio of sTfR to log ferritin values. Assessment of bone marrow iron stores was done by staining the already available marrow slides with Perl's stain which served as a gold standard. Absence of these stores denoted IDA whereas increased macrophage iron with decreased siderocytes and sideroblasts was diagnostic of ACD. Statistical analysis was done using SPSS-16. Methods as *t*-test and ANOVA were used for data analyses.

RESULTS

In IDA cases, the sensitivity of index was the most being 100%, sTfR was 89% and SF was of 85%. The specificity of sTfR and Index were 80.60% which was greater than SF which had a low specificity of 63.90%. In case of ACD, the sensitivity of index and sTfR was equal 84.80% each while SF had a low value of 81.80%. The specificity of sTfR was the most which was 100%, index had a value of 97.20% while SF had lowest specificity of 77.80%, (p<0.001).

Table-1: Sensitivities of Markers for IDA

	Serum ferritin	sTfR	Index
Sensitivity	85%	89%	100.00%
Specificity	63.90%	80.60%	80.60%
Positive predictive	75.50%	85.70%	87.00%
Negative predictive	76.70%	85.30%	100.00%
False Positive	36.10%	19.40%	19.40%
False Negative	14.90%	10.60%	0.00%
Accuracy	75.90%	85.54%	91.57%

Table-2: Sensitivities of Markers for ACD

	Serum Ferritin	sTfR	Index
Sensitivity	81.80%	84.80%	84.80%
Specificity	77.80%	100.00%	97.20%
Positive predictive	77.10%	100.00%	96.60%
Negative predictive	82.40%	87.80%	88%
False Positive	22.20%	0.00%	2.80%
False Negative	18.20%	15.20%	15.20%
Accuracy	79.71%	91.30%	89.86%

DISCUSSION

In this study, evaluation of sTfR, SF and sTfR-F Index in diagnosing and differentiating IDA from ACD was conducted. In case of IDA, the sensitivity of index was the most being 100%, the specificity of sTfR and Index was the most being 80.60% while the diagnostic accuracy of index was the most with a value of 91.57%. In case of ACD, the sensitivity of index and sTfR was equal 84.80% and more compared to SF. The specificity of sTfR was the most which was 100% while the diagnostic accuracy of sTfR was the most with a value of 91.30%. For diagnosis of IDA, the cut-off values were SF <150, sTfR >1.44 and Index >0.70. For diagnosis of ACD, values were SF >200, sTfR <1.0 while Index <0.50. When compared to each other, Index is a better parameter than sTfR and sTfR is better than SF in diagnosing and distinguishing IDA from ACD.

Many studies have been done to evaluate sTfR over SF and prove that SF is affected by the acute phase response to inflammation in chronic disorders. Kari Punnonen *et al*[5] evaluated sTfR and sTfR-F index and concluded that SF may provide a rational basis for identifying IDA but all factors affecting ferritin levels have to be considered. Some workers contradicted this view. Alan *et al*[16] concluded that sTfR levels did not provide sufficient additional information to ferritin to warrant routine use. His study gave sensitivity of sTfR to be 92% and specificity 84% while sensitivity of SF 92% and specificity 98%. Fernandez-Rodriguez *et al*[17] and Joosten[18] suggested that the sTfR as a single additional measurement to the existing methods does not provide more substantial information on iron status than SF. Further studies were conducted on these parameters. Akinsooto[19] proved sTfR levels to be a good test in hospitalised patients as compared to SF. Eun Jung Lee *et al*[20] evaluated sTfR in non

haematological malignancy while Choi JW[21] found sTfR levels at different stages of iron deficiency to be a valuable diagnostic tool. In Pakistan, Hanif E[22] evaluated the diagnostic efficacy of sTfR. Out of 176 anaemic patients, 51.1% were diagnosed as ACD whereas 48.8% as IDA on the basis of marrow iron stores. Both sensitivity and specificity of sTfR in IDA was found to be 100% while in ACD, these were 66.6% and 100% respectively. Other studies[23–25] have also been done to prove sTfR-F index to be a new and surrogate marker to estimate body iron stores.

CONCLUSION & RECOMMENDATIONS

The sTfR and sTfR-F index have a more diagnostic efficacy than SF and other conventional laboratory iron parameters in diagnosing and distinguishing IDA from ACD and is also as reliable as bone marrow aspirate in detecting iron stores in patients with IDA. For estimation of body iron stores in anaemic patients with chronic inflammatory diseases, diagnostic tests like sTfR and sTfR-F index should be considered.

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