Clinical Significance of Serum Soluble Transferrin Receptor in Hypochromic Microcytic Anemia

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ABSTRACT
Objective: To determine the clinical significance of soluble transferrin receptor (sTfR) in hypochromic microcytic anemia for diagnose of iron deficiency anemia. Study Design: Cross-sectional study. Settings: Department of pathology at Liaquat university of Medical and Health Sciences Jamshoro and Hyderabad Pakistan. Duration: From February 2015 to July 2015. Methodology: Patients of microcytic hypochromic anemias were included. Patients underwent serum ferritin level, serum iron, TIBC and soluble transferrin receptor tests. All the data was entered in the self-made proforma for the purpose of analysis. Results: Total of 139 patients were studied; their mean age was 26±15.62 years. Female gender was most common (75.5%). Mean ferritin level was 49.35±6.88, whereas TIBC value was 40.55±96.26. Mean of sTfR level was 4.17±2.25. sTfR was inversely proportional to ferritin concentration because of acute phase reaction to disease. Generally, the TfR level does not elevate with inflammation and iron deficiency can possibly be distinguished. Bone marrow investigations are generally considered definitive markers of iron deficiency specially when associated with chronic diseases. However, such examinations are uncomfortable, burdensome and unfeasible for routine practice. Therefore, sensitive and non-invasive means are clinically needed to detect iron deficiency and the assessment of soluble TfR is a feasible approach. In contrast to plasma ferritin, the plasma TfR level does not elevate with inflammation or infection. Measuring the plasma TfR level may therefore be particularly useful in distinguishing between anemia-related iron chronic inflammatory disorders and deficiency anemia. No findings on the contribution of serum soluble TfR among hypochromic microcytic anemia cases is currently present in Pakistan, this study was therefore executed at

Keywords: Iron deficiency anemia, sTfR, Clinical significance.

INTRODUCTION

Microcytic anemia usually results from conditions like chronic diseases, thalassemia’s and iron deficiency. Iron deficiency anemia (IDA) is a commonest hypochromic microcytic anemia globally. 1 The deficiency of iron modulates the Hb-A2 synthesis, causing diminished concentrations of Hb-A2 among IDA patients. Affected individuals exhibit morphological variations in erythrocytes such as microcytosis, poikilocytosis, hypochromy and anisocytosis. The carriers of microcytic anemia exhibit less severe morphological variation in erythrocytes than affected patients. The rates of hypochromic RBCs can possibly be high prior to the development of anemia. The decline in hemoglobin levels has been found to be a late characteristic of iron deficiency. Hematologic screening test directly demonstrates the reduced levels of serum ferritin in iron deficiency. 3 Worldwide, thalassemia is a commonest hereditary disorder. 4 Women and men are equally being affected by thalassemia which accounts for around 44 of every 100,000 live births. 5 So far, > 200 molecules-related causative defects in β-globin genes have been defined that result in beta thalassemia. 6 In β-thalassemia there are hypochromic levels of hemoglobin in RBCs with microcystic cells. The variations in the size of RBCs do not go beyond the limits. In the most hypochromic cells, there is a reduced concentration of hemoglobin or a thin layer of hemoglobin with a large region of central-pallors. Peripheral blood smear reveals distinct poikilocytosis in addition to some anisocytosis, however most are microcytes. 6 A raised serum TIR level is an excellent marker of deficiency of iron in tissue and despite iron stores. 9 The two key factors of the transferrin receptor (TIR) level are the iron status of body and the activity & expansion of bone marrow erythroid. 10 Thalassemia and hemolytic anemia also show a raised TIR level. Clinical studies show that there is lesser effect of inflammation on serum TIR as compared to serum ferritin. 11 However in the regions of epidemic infectious diseases, serum ferritin is an impractical marker because inflammatory response results in an increase in serum ferritin concentration because of acute phase reaction to disease. Generally, the TIR level does not elevate due to inflammatory response thus, in combination to serum ferritin level, inflammation and iron deficiency can possibly be distinguished. Bone marrow investigations are generally considered definitive markers of iron deficiency specially when associated with chronic diseases. However, such examinations are uncomfortable, burdensome and unfeasible for routine practice. Therefore, sensitive and non-invasive means are clinically needed to detect iron deficiency and the assessment of soluble TfR is a feasible approach. 12 In contrast to plasma ferritin, the plasma TfR level does not elevate with inflammation or infection. Measuring the plasma TfR level may therefore be particularly useful in distinguishing between anemia-related iron chronic inflammatory disorders and deficiency anemia. 12 No findings on the contribution of serum soluble TfR among hypochromic microcytic anemia cases is currently present in Pakistan, this study was therefore executed at

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**METHODOLOGY**

**Study Design:** Cross sectional study.

**Settings:** Pathology Department at Liaquat University of Medical and Health Sciences Jamshoro and Hyderabad Pakistan.

**Study duration:** Six month from February 2015 to July 2015.

**Study sampling:** Non probability consecutive sampling.

**Inclusion criteria:** All patients of hypochromic microcytic anemic patients having hemoglobin Levels < 11 g/dL, MCV < 76 fl or MCH < 27 pg were included.

**Exclusion criteria:** Patients with hemolytic anemia, folic acid and vitamin B12 deficiency, atypical renal function, and with recent blood transfusion history were excluded.

**Methods:** Study was conducted after taking ethical approval from ethical review committee of Liaquat University of medical and health Science. 10 cc of blood specimens were obtained and each specimen was split into two parts; 3ml blood sample was transferred to a tube containing an anticoagulant agent EDTA, whereas the remaining 7 ml was processed in a no anticoagulant containing glass tube to extract serum. An electronic hematology analyzer was used to calculate complete blood count (CBC) automatically. By using Automated Cell Counter, hematocrit was determined by multiplying MCV with RBC count. blood specimens obtained in EDTA tubes were processed at pH of 8.6 for the evaluation of hemoglobin variants through cellulose acetate Hb electrophoresis. Serum was split into 3 divisions, two of which were processed at -20 oC to determine soluble transferrin receptor (sTFR) and serum ferritin, whereas the 3rd aliquot was used in determining the serum iron and the total iron binding ability. ELISA approach was used to assess serum ferritin through Point Scientific, Inc Kit. TFR Elisa package was used for testing the TFR in Human serum specimen. All the data was entered in the proforma. Data analysis was done by SPSS version 20.

**RESULTS**

In this study the female gender was (75.5%); and for all patients mean age was 26+15.62 years, with 2 years minimum and 75 years maximum. TABLE: 1.

Mean for Hb, RBC, MCV, MCH, MCHC were found at 7.71+2.03, 4.22+0.99, 63.41+6.61, 18.77+3.51 and 29.38+3.4 respectively. TABLE: 2.

Perfect negative correlation was observed between MCV and sTFR; p-value and r-value = 0.001 and 0.348 respectively, FIG: 1

sTFR was inversely proportional to and MCH p-value 0.001 and, r=value 0.55 FIG: 2

MCHC and sTFR had a negative correlation (p-value and r-value as: 0.001 and 0.484 respectively) FIG: 3 sTFR showed sensitivity= 100% and specificity = 98.2% in hypochromic microcytic anemia diagnosis (95% CI; = (0.920 -0.995), AUC= 0.958)

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**Table 1: Patients distribution according to age and gender N=139**

| Age and Gender | Frequency | Percent |
|----------------|-----------|---------|
| Male           | 34        | 24.5    |
| Female         | 105       | 75.5    |
| Total          | 139       | 100.0   |
| Age(mean+SD)    | 26.0+15.62| years   |

**Table 2: Mean of Hb, RBC, MCV, MCH, MCHC, ferritin and TIBC n=139**

|            | Hb  | RBC | MCV  | MCH  | MCHC | sTFR | Ferritin | TIBC     |
|------------|-----|-----|------|------|------|------|----------|----------|
| Mean       | 7.71| 4.22| 63.41| 18.77| 29.38| 4.17 | 49.35    | 40.55    |
| SD         | 2.03| 0.99| 6.91 | 3.51 | 3.40 | 2.25 | 6.88     | 96.26    |
| Minimum    | 02.0| 1.15| 43.20| 11.60| 22.30| 1.10 | 0.74     | 189.00   |
| Maximum    | 10.30| 6.07| 73.50| 25.20| 45.00| 7.90 | 197.70   | 559.00   |

**Fig 1: Correlation between sTFR and MCV level n=139**
P-value 0.001 r=value 0.348

**Fig 7: Correlation between sTFR and MCH level n=139**
P-value 0.0001 r=value 0.55
studies exist with binary data for making reliable estimates regarding accuracy of sTfR diagnostic. The overall 86% sensitivity and 75% specificity of sTfR diagnostic accuracy indicates that it is nearly an ideal method, possibly suggesting sTfR as a reasonably good assay for screening IDA. In present study, the patients had a mean age of 26±15.62 years, and females were predominant (75.5%) in terms of gender as compared to males (24.5%). In contrast, Arnab Ghosh et al reported predominance of male gender and 4.9 years of mean age; however, the reported values for gender and mean age do not correlate with our findings.

CONCLUSION
It was concluded that sTfR is a reliable and a non-invasive differentiating indicator with significant clinical significance in microcytic hypochromic anemia for diagnosing iron deficiency Anemia. Further studies are, yet, necessary to outline the general diagnostic precision of sTfR assay and its potential status in the IDA diagnostic flowchart. When iron deficiency anemia and anemia of chronic disease cases are found to have high levels of sTfR, iron therapy intervention may be a suitable approach.

LIMITATIONS
This was a small sample size and single center study.

SUGGESTIONS / RECOMMENDATIONS
Further large sample size multicenter studies should be done to assess the more significance of this marker.

CONFLICT OF INTEREST / DISCLOSURE
There is no conflict of interest.

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- Drafting the work or revising it critically for important intellectual content

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Maria Jawed
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Ikram Din Ujjan
- Supervision and guideline

Palvisha Altaf
- Contribution in literature review and data analysis

Kulsoom Javed
- Contribution in data analysis