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 anemic 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 Hb, MCV and MCHC. sTFR was found to be an accurate diagnostic tool for the diagnosis of hypochromic microcytic anemia with 100% sensitivity and 98.2% specificity. **Conclusion:** sTfR is the less-invasive and a reliable differentiating marker with substantial clinical significance in hypochromic microcytic anemia for diagnose of iron deficiency anemia.

Keywords: Iron deficiency anemia, sTFR, Clinical significance.

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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, hypochromia and anisocytosis. The carriers of microcytic anemia exhibit less severe morphological variation in erythrocytes than affected patients.[2] 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. Hematinic 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 thalassaemia.[6,7] In β-thalassemia there are hypochromic levels of hemoglobin in RBCs with microcytic 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.[8] A raised serum TfR level is an excellent marker of deficiency of iron in tissue and despite iron stores.[9] The two key factors of the transferrin receptor (TfR) level are the iron status of body and the activity & expansion of bone marrow erythroid.[10] Thalassemia and hemolytic anemia also show a raised TfR level. Clinical studies show that there is lesser effect of inflammation on serum TfR 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 TfR 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

LUMHS Jamshoro / Hyderabad, in the perspective of the foregone.

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 and 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)

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

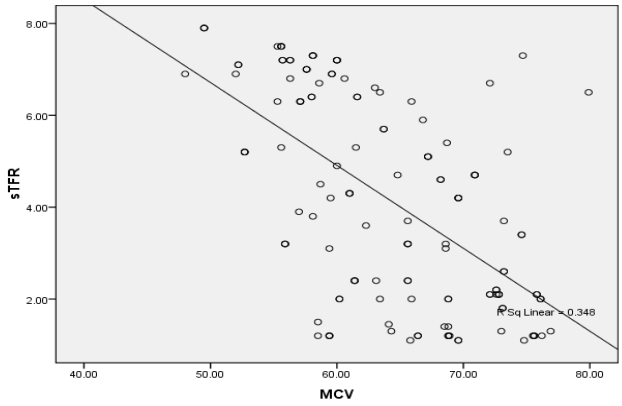

Fig 1: Correlation between sTfR and MCV level n=139
P-value 0.001 r=value 0.348

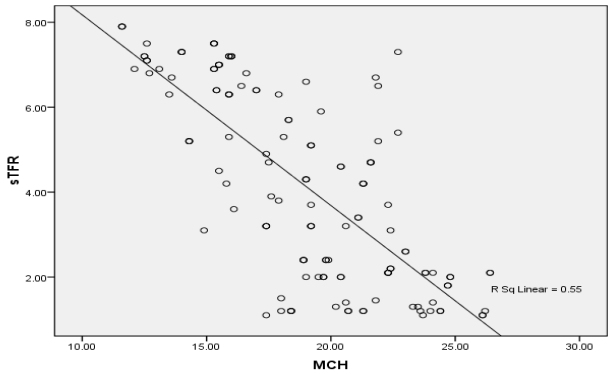

Fig 7: Correlation between sTfR and MCH level n=139
P-value 0.0001 r=value 0.55

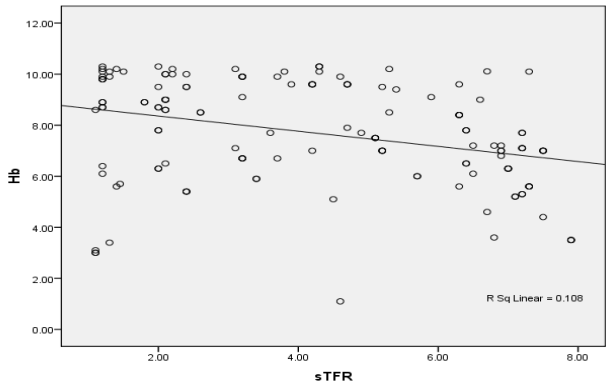

Fig 8: Correlation between sTfR and MCH level n=139
P-value 0.0001 r=value 0.108

DISCUSSION

In present study soluble transferrin receptors (sTFR) was observed with high concentrations among IDA patients and mean for Hb, RBC, MCV, MCH and 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. Similarly, Saboor M et al[13] reported comparable findings.

In present study mean for ferritin level, TIBC and sTFR level were found at 49.35±6.88, 40.55+96.26 and 4.17+2.25 respectively. Wians FH et al[14] and Saboor M et al[13] stated parallel findings.

The present study found negative correlation among ferritin level and sTFR (P-value and r-value as: 0.001 and 0.193 respectively), while perfect negative correlation was found between MCV and sTFR (p-value and r-value as: 0.001 and 0.348 respectively). Yokus O et al[15] reported a negative correlation between MCV and sTfR levels, (p-value <0.01; r-value 0.313), and similar correlation was found for ferritin and sTfR levels (p<0.001; r=−445). Jain S et al[16] observed strong correlation between MCV and sTfR (r-value = 0.714, p value <0.001). Baybeen K et al[17] also reported comparable findings.

Present study found sTFR as a precise diagnostic method for microcytic hypochromic anemia diagnosis with sensitivity and specificity of 100% and 98.2% respectively. Nadeem S et al[18] stated that in iron deficiency anemia (IDA), sTfR had a 100% sensitivity and 100% specificity. However, further studies[14,19] have also intended to prove sTfR F-index as a fresh and substitute marker in estimating body iron stores. Wians FH et al[14] likewise reported comparable findings. In contrast, Alan et al[20] observed 92% sensitivity and 84% specificity of sTfR, while SF was reported to have 92% sensitivity and 98% specificity. Worwood M et al in their study evaluated clinical significance of sTfR as a marker of IDA development as well as in monitoring variations in the rates of erythropoiesis.[21] The Iron stores assessment on aspiration of bone marrow is a benchmark for diagnosing the coexistence of IAD and chronic disorders associated anemia. As it is an expensive and invasive technique, therefore its routine application is challenging. Studies suggest that anemia of chronic disorders and IDA can be distinguished using STfr levels,[22] Generally, relatively limited 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[23] 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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AUTHORSHIP CONTRIBUTION

Fahmeena Qadri	Drafting the work or revising it critically for important intellectual content
Sadia Abbasi	Contribution in data collection
Maria Jawed	Contribution in manuscript writing
Ikram Din Ujjan	*Supervision and guideline*
Palvisha Altaf	Contribution in literature review and data analysis
Kulsoom Javed	Contribution in data analysis