

Serum transferrin receptor levels in iron deficiency anemia and anemia of chronic disease

J. Kolsamma Nasrin^{1,*}, V. Aruna Padmavathi², Balamurugan M.³, CP Luck⁴, Revathy S⁵

^{1,2,5}Assistant Professor, ³Professor & HOD, ⁴Associate Professor, Dept. of Pathology, Tagore Medical College & Hospital, Chennai

***Corresponding Author:**

Email: nasrin.jkols@yahoo.com

Abstract

Introduction: Microcytic anemia in chronic disease patients, the commonest differential diagnosis are anemia of chronic disease (ACD) and iron deficiency anemia (IDA). Routine serum markers for body iron store are influenced by inflammatory mediators. Hence, STfr levels were used to identify the body iron status in chronic disease patients.

Material and Method: We have included 40 IDA in group A and 60 chronic patients in group B. Group B further sub grouped based on serum ferritin values, serum ferritin >200µg/L as group B1 and serum ferritin between 30-200µg/L as group B2. Serum STfr and serum ferritin levels were measured and compared among groups.

Results: In our study, mean STfr values of group A, B1 and B2 patients were 8.305, 2.660 and 5.927 respectively (normal range 5.0±1.0µg/L). Mean serum ferritin values of three groups A, B1 and B2 3.86, 562.30 and 58.20 respectively (normal range 30-200µg/L). Comparing between three groups showed statistical significance.

Conclusion: STfr levels were elevated in IDA and not affected in ACD group. In iron deficient group of chronic disease patients when serum ferritin levels did not confer the iron status of the body, STfr levels were elevated. In our study STfr correlated to iron status of the body. Suggesting STfr levels can be a valuable marker in ACD.

Keywords: ACD, IDA, STfr, Serum Ferritin.

Manuscript Received: 15th April, 2017

Manuscript Accepted: 2nd June 2017

Introduction

Anemia, contributes a major burden among the common clinical diagnosis all over the world irrespective of age, sex, race. With a large variety of etiologies the most common etiology is iron deficiency. It is necessary to identify the iron deficiency state in chronic disease patients not only because it is easily treatable but to avoid the iron overload and systemic adverse reactions of iron therapy.

Anemia in patients with chronic disease for more than 1 month is defined as anemia of chronic disease (ACD). Patients with chronic disease can also suffer iron deficiency in addition to ACD.⁽¹⁾ The standard method to determine the body iron status is grading of bone marrow iron store but it is an invasive and cumbersome technique increasing the morbidity to patient.⁽²⁾

Anemia of chronic disease occurs due to persistent immune activation and inflammation. There is an outpouring increase of cytokines like IL6, TNF. These inflammatory mediators upregulate the synthesis of iron regulator proteins like hepcidin.⁽³⁾ It is responsible for sequestration of iron within the reticuloendothelial cells.⁽⁴⁾ Thereby causes reduced availability of iron to erythroid precursors resulting in diminished erythropoiesis. ACD can present either as normocytic or microcytic anemia.

Iron is known for its potent pro-oxidant effect and systemic free radical generation as adverse effect. When administered during inflammatory conditions it

augments systemic inflammatory responses and cell injury.⁽⁵⁾ Ultimately increases the tissue damage in chronic diseased states.

The clinical diagnosis and etiology of anemia is routinely supported by hematological laboratory investigations of RBC parameters like Mean corpuscular volume (MCV), Hemoglobin (Hb), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW) and other biochemical parameters like serum ferritin.

Ferritin levels in serum generally correlate well with the body iron status.⁽⁶⁾ Currently it is the simplest procedure and investigation of choice to determine body iron store status. Serum ferritin levels less than 30µg/L implies iron deficiency. Similarly, levels greater than 200µg/L rules out iron deficiency. Serum ferritin levels get elevated during any type of inflammation, as it is a well known acute phase reactant.⁽⁷⁾ Therefore intermediate values of serum ferritin levels in chronic disease patients with low hemoglobin do not confer the body iron status.

STfr, a transmembrane protein involved in internalization of iron transferrin complex has two domains. Transferrin receptor gets cleaved and is shed into the circulation. The normal serum transferrin receptors level is 5.0±1.0µg/L. In iron deficiency state up regulation of transferrin receptor synthesis occurs. Standard tests like serum ferritin used to determine iron status are affected by inflammation⁽⁹⁾ and hinder clinical interpretation. Whereas STfr levels are not influenced

by inflammatory conditions. Hence transferrin receptor levels in serum is an indirect measure of iron status of the body and erythropoietic activity in the marrow.⁽⁸⁾

Materials and Method

Our study includes 100 cases with Hb< 12g/dl, they were further divided into groups.

Group A: 42patients with iron deficiency anemia. Hb< 12g/dl, MCV <70 fl, Serum ferritin <30µg/L

Group B: 58 chronic disease patients {Tuberculosis, SLE, RA, Chronic bacterial, fungal infections, suppurative lung infections, Asthma, Pneumonia, Osteomyelitis, Chronic urinary tract infections}. Hb <12g/dl, MCV <90 fl, Serum ferritin <30µg/L, C reactive protein> 20mg / L were included.

This group was again subdivided based on ferritin values

Group B1: 47 patients with serum ferritin >200µg/L.

Group B2: 11 patients with serum ferritin 30µg/L - 200µg/L.

Patients with the following conditions were excluded:

- Macrocytic and hemolytic anemia.
- Acute blood loss.
- Plasma volume overloaded state
- Primary bone marrow disorders
- Hematopoietic malignancies.
- Recent blood transfusion.
- Already on iron therapy.
- Recent acute viral infections
- Endocrine disorders

Venous blood was used for study purpose.

- Routine complete blood counts were obtained using Sysmex k21 counter.
- CRP levels were determined using latex agglutination methods
- Peripheral smear stained with Leishman’s stain for morphological study.
- Sample centrifuged and serum separated for serum ferritin and STfr measurements.
- Serum ferritin was measured by chemiluminescence method using autoanalyser.
- The RD194011100 sTfr ELISA kit(Biovendor labs) for measurement of serum soluble transferrin receptor

Statistical analysis of results obtained were done using ANOVA test, Student *t* test. Statistical significance was studied using post hoc LSD. Pearson correlation was used to study relation between various parameters.

Results

In our study, mean ± SD values of Hb, MCV, MCH, MCHC, serum ferritin, serum soluble transferrin receptors of the three groups are shown in the (Table 1).

Table 1: Mean value of various study parameters

	Group A n = 42 Mean±SD	Group B1 n =47 Mean± SD	Group B2 n = 11 Mean±SD
Hb(g/dl)	5.05±2.22	9.2±2.692	9.8±1.24
MCV (fl)	70.13±5.21	75.3±3.38	73.2± 5.86
MCHC (g/dl)	29.4±2.75	34.3±2.46	31.8± 1.60
MCH (pg)	23.2± 2.18	25.9±2.63	23.4±0.99
Serum Ferritin(µg/L)	3.86± 1.385	562.30±159.2 70	58.20±6.261
STfr (µ/L)	8.305±4.169 9	2.660±1.6902	5.927±1.037 1

Inverse correlation was observed between STfr with Hb, and MCV in group A. In group B no such correlation existed between STfr with Hb and MCV. Serum ferritin and STfr had significant correlation in group A.

In group B patients with chronic disease the serum ferritin levels were significantly elevated. Serum soluble transferrin receptor levels were normal in group B1 patients. These patients though with a normal iron store had anemia (ACD).

Group B2 patients with chronic disease, the mean serum ferritin levels were 58.20±6.261. Serum soluble transferrin receptor levels were elevated and corresponded to the low iron stores. When compared among groups serum soluble transferrin receptor levels were increased and serum ferritin levels were decreased in iron deficiency patients with a statistical significance (Table 2).

Table 2: Statistical comparison of serum STfr and serum ferritin values in the three groups

	GroupA- B1	GroupB1- B2	Group A- B2
Serum ferritin	p < 0.001	p < 0.001	p < 0.001
STfr	p < 0.001	p < 0.001	p < 0.001

Thus group B2 chronic disease patient with low iron store had anemia due to iron deficiency later proved with bone marrow iron staining. These patients had an elevated serum ferritin as it is an acute phase reactant which normally gets elevated during any inflammation.

Anemia of inflammation (ACD) occurs in patients suffering from chronic infections, malignancy and inflammatory diseases. Unwarranted use of Iron therapy in ACD patients augments the systemic inflammatory responses.⁽¹⁾ Hence it becomes essential to identify the cause of anemia; thereby use of iron in patients with chronic inflammatory diseases can be avoided.⁽⁶⁾

Discussion

Patients with chronic disease can have anemia either due to iron deficiency or anemia of chronic inflammation (ACD). Bone marrow iron (perl's) staining, the standard method to evaluate the body iron status is an invasive technique.

STfr shed by the erythroid precursors in the bone marrow and reticulocytes reflects the rate of erythropoiesis. The STfr is upregulated and expressed on the cell surface of erythroid precursors in iron deficiency as a response to increased cellular demand for iron. Later it gets shed into the circulation. Therefore serum soluble transferrin receptor (STfr) level is influenced by intracellular iron levels of the erythroid cell series. Elevated soluble transferrin receptors (STfr) indicates iron deficiency as it is unaffected by inflammation.⁽⁵⁾ Hence STfr reflects the iron status more reliably.

Very high serum ferritin in chronic disease patients suggests iron overload.⁽²⁾ The increasing prevalence of anaemia in chronic disease patients has complicated the scenario of using serum ferritin for interpreting the body iron stores serum ferritin is an acute-phase reactant.

Iron store is assessed by presence and absence of iron granules in the bone marrow. Serum STfr concentrations were elevated in majority of the IDA and chronic disease patients with iron deficiency anemia. In ACD patients, the STfr values were within normal ranges.⁽⁶⁾ Thus serum STfr measurement provided a reliable diagnosis of iron deficiency anemia.⁽⁹⁾ In patients of chronic disease there was an increase in mean serum ferritin levels. Serum soluble transferrin receptors levels were normal or low in group B1 patients. IDA patients had significantly elevated serum STfr levels.⁽³⁾ ACD patients with normal iron store had normal to low serum STfr.⁽¹⁰⁾ Chronic disease patients with low iron store had elevated STfr. This highlights the reliability of serum STfr levels, in differentiating iron deficiency state from ACD.

Our study results showed elevated soluble transferrin receptor levels in group A patients with pure IDA similar to other studies of Choi WJ *et al* and Markovic *et al*.^(11,12) Serum ferritin was decreased in iron deficiency group of patients. Serum soluble transferrin receptor values in IDA had significant correlation with other RBC indices like MCV, MCH, MCHC and RDW ($p < 0.001$). Serum soluble transferrin receptor levels and serum ferritin levels had an inverse relation. Serum soluble transferrin receptor levels and serum ferritin values had a statistical significant negative correlation.

STfr levels in group B1 were within normal range whereas B2 group were elevated correlating with study of Hanif *et al*.⁽¹³⁾ Serum ferritin levels were elevated in group B1 and normal in group B2 similar to study by Ferguson *et al*.⁽¹⁴⁾ This variation can be attributed by the fact that STfr correlates more to the bone marrow

iron stores in chronic inflammatory conditions.⁽¹⁵⁾ Group B2 chronic disease patients with a low iron store had combined anemia (ACD and iron deficiency anemia). Our study results imply that STfr as a useful marker for determining the iron status of chronic disease patients.

Conclusion

The serum STfr level increases in iron deficiency state in response to increasing cellular iron demand reflecting the tissue iron supply. STfr levels are not affected by inflammation in conditions and its elevated levels can be attributed to iron deficiency.

In our study, STfr levels were elevated in IDA and normal in ACD, which is in agreement with the literature. STfr levels were elevated in iron deficient state when it coexists with chronic disease. STfr values can be of great value in identifying iron deficiency state in patients with chronic disease.

Acknowledgement

The authors wish to thank senior professors and colleagues in the department of pathology, Tagore Medical College who supported the study.

References

1. Rahim F, Keikhaei B. Better Differential Diagnosis of Iron Deficiency Anaemia from Beta-Thalassaemia Trait. Turkish Journal of Hematology, 2009;26:138-145.
2. Amar DG, Alpina A. High Serum Transferrin Receptor Level in Anemia of Chronic Disorders Indicates Coexistent Iron Deficiency. American journal of hematology, 2003;72:3.
3. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. IL-6 mediates hypoferrremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J clinical investigations, 2004;113(9):1271-6.
4. Brady PG. Iron deficiency anemia a call for. Southern Medical Journal, 2007;100(10):966-967.
5. Andrews, C.N. Anaemia of Inflammation. The Cytokine-Hepcidin Link. The Journal of Clinical Investigation, 2004;113:1251-1253.
6. Zager RA. Parenteral iron compounds: potent oxidants but mainstays of anemia management in chronic renal disease. Clin J Am Soc Nephrol. 2006; vol 1 suppl 1: S24-31.
7. Lipschitz DA, Cook JD, Finch CA. A clinical evaluation of serum ferritin as an index of iron stores. New England Journal of Medicine, 1974;290:1213-1216.
8. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. Clin Chim Acta, 2003;329(1):9-22.
9. Jayarane S, Sthaneshwar P. Serum Soluble Transferrin Receptor in hypochromic Microcytic Anaemia. Singapore Medical Journal, 2006;47:138-142.
10. Mahdavi MR, Makhloogh A, Kosaryan M, RoshanP. Credibility of the measurement of serum ferritin and transferrin receptor as indicators of iron deficiency anemia in hemodialysis patients. Eur Rev Med Pharmacol Sci., 2011;15(10):1158-62.
11. Choi WJ, Pai, HS. Associations between Serum Transferrin Receptor Concentrations and Erythropoietic

- Activities According to Body Iron Status. *Annals of Clinical & Laboratory Science*, 2006;33:279-284.
12. Marković, M., Singh, M.N. and Subot Hanif E, Ayyub M, Anwar M, Ali W, Bashir M. Evaluation of serum transferrin receptor concentration in diagnosing and differentiating iron deficiency anemia from anemia of chronic disease. *J Pak Med Assoc.*2005 Jan;55(1):13-6.
 13. Ferguson BJ, Skikne BS, Simpson KM, Baynes RD, Cook JD. Serum transferrin receptor distinguishes the anemia of chronic disease from iron deficiency anemia. *J Lab Clin Med.*1992, Apr;119(4):385-90.
 14. Osman Yokus *et al.*, The Significance of Serum Transferrin Receptor Levels in the Diagnosis of the Coexistence of Anemia of Chronic Disease and Iron Deficiency Anemia. *EAJM*, 2011;43:9-12.