Role Of Serum Soluble Transferrin Receptors (STFR) To Differentiate Iron Deficiency Anaemia And Anaemia Of Chronic Disease

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Abstract: Background: Iron deficiency is a common condition that is usually diagnosed using conventional laboratory tests of iron status, such as serum ferritin and transferrin saturation. However, both ferritin and transferrin proteins are markedly influenced by inflammation, behaving as acute-phase reactants and making it difficult to differentiate between iron-deficiency anemia (IDA) and anemia of chronic disease (ACD). Objectives: To evaluate the role of serum soluble transferrin receptors (STFR) to differentiate iron deficiency anaemia and anaemia of chronic disease. Material And Methods: A cross-sectional study was conducted in the Department of Medicine, Victoria hospital and Bowring and Lady Curzon hospital, Bangalore Medical College and Research institute, Bangalore. A total of 150 blood samples were evaluated, i.e., 50 samples from iron deficiency anaemia group and 50 samples from patients with anaemia of chronic disorders & 50 samples from healthy normal individual. Result: In present study, samples are age matched with mean age of control 45.66±10.23, ACD 50.68±18.03, IDA 48.14±18.47. Hb, MCV, MCHC & MCH were decreased in both the groups. However, the decrease in Hb & MCV was much more in IDA as compared to ACD. Microcytosis was seen in 92% cases of IDA while it was observed in only 11% cases of ACD. Serum soluble transferrin receptor levels is <3 µgm/ml in 90% of ACD group whereas >3 µgm/ml in 78% of IDA Group. STFR/ log ferritin index was >1.5 in 80% of IDA. 90% of ACD and control subjects had STFR/log ferritin index <1.5. STFR levels were significantly higher in IDA (7.7± 5.8) as compared to the ACD cases (1.6 ±0.89) (p<0.001). STFR/Log ferritin index is significantly higher in patients with Iron deficiency anemia (9.34±10.25) as compared to ACD (0.76±0.52) (p<0.001). Conclusion: The STFR levels along with the STFR/Log ferritin index indices is very useful in differentiating pure IDA, ACD and ACD with coexisting iron deficiency, thus providing a non invasive alternative to bone marrow iron. [Kumar M Natl J Integr Res Med, 2021; 12(3): 30-34]

Key Words: Anemia; Iron deficiency; Anemia of chronic disease; Transferrin receptor

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Introduction: Iron deficiency is the most common and widespread nutritional disorder in the world. As well as affecting a large number of children and women in developing countries[1]. Globally, 50% of anaemia is attributable to iron deficiency and accounts for approximately 841,000 deaths annually worldwide[2]. The anaemia that is often observed in patients with infections, inflammatory and neoplastic diseases that persist for more than 1 or 2 months is called Anaemia of chronic disease. It is characterised by hypoferremia in the presence of adequate reticuloendothelial iron stores[3].

Conventional laboratory indices of Iron status such as Serum iron, Total iron binding capacity (TIBC) and Serum ferritin do not always distinguish Anemia of chronic disease (ACD) from Iron deficiency anemia (IDA) as both Serum ferritin and transferrin are considerably influenced by acute phase responses in inflammation[4]. To interpret the actual iron status of the patient, a bone marrow examination is required which is the only reliable index of iron stores[4]. Bone marrow examination is invasive, expensive, painful and time consuming procedure and requires technical expertise. So it cannot be performed routinely in clinical practice[5].

There is an evident need for non invasive and sensitive means for detection of iron deficiency in hospitalized patients which is not influenced by acute or chronic inflammatory conditions. Soluble transferrin receptors (STFR) are the truncated form of the intact transferrin receptors found in the soluble form in human serum. Measurement of STFR is a new marker of iron metabolism that reflects body iron stores and total erythropoiesis[6].

Serum soluble transferrin receptor (STFR) levels are not influenced by inflammation. Therefore STFR determination can be used as a reliable differentiating marker in the diagnosis of iron deficiency anaemia and anaemia of chronic disorders. Thus providing a non-invasive alternative to bone marrow iron.

Material & Methods: The present cross sectional study will be conducted in the Department of Medicine, Victoria hospital and Bowring and Lady Curzon hospital, Bangalore Medical College and Research institute, Bangalore.

Study Period: October 2013 to September 2015**.**

Study Subjects: A total of 150 blood samples are evaluated, i.e., 50 samples from iron deficiency anaemia group and 50 samples from patients with anaemia of chronic disorders & 50 samples from healthy normal individual.

Inclusion Criteria: Patients aged >18 yrs, Iron deficiency anaemia, Anaemia of chronic disease and Healthy normal individuals

Exclusion Criteria: Patients aged <18 yrs, Hemolytic anemia, Vitamin B12 deficiency, Folate deficiency

Investigations Done: Complete blood picture and Peripheral smear**,** Iron Profile and Serum transferrin receptors (TfR)level.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significance is assessed at 5 % level of significance. The following assumptions on data are made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, and Cases of the samples should be independent.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. Significant figures: Suggestive significance (P value: 0.05<P<0.10) *Moderately significant (P value:0.01<P ≤ 0.05) **Strongly significant (P value : P≤0.01).

Statistical Software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results: The present study was done to differentiate IDA and ACD using STFR, STFR/ferritin index. Study included 150 patients with 50 control, 50 IDA , 50ACD. Detailed history, examination and investigation was done to all subjects.

In present study, samples are age matched with mean age of control 45.66±10.23, ACD 50.68±18.03, IDA 48.14±18.47 (Table 1).

Table 1: Hemoglobin % Levels In Three Groups Of Patients Studied

Hemoglobin %	Control		Anemia Of Chronic Disease		Iron Deficiency Anemia	
	No	%	No	%	No	%
<12	0	0.0	44	88.0	50	100.0
12-16	50	100.0	6	12.0	0	0.0
>16	0	0.0	0	0.0	0	0.0
Total	50	100.0	50	100.0	50	100.0

Hb, MCV, MCHC & MCH were decreased in both the groups. However, the decrease in Hb & MCV was much more in IDA as compared to ACD.

Microcytosis was seen in 92% cases of IDA while it was observed in only 11% cases of ACD(Table2). Serum Iron was reduced in both IDA and ACD group; decrease in Serum Iron was more in IDA compared to ACD. Serum ferritin was high in ACD whereas low in IDA group.

Transferrin saturation was decreased in both IDA and ACD group. Total iron bindingcapacity is increased in IDA group (Table3).

Table 2: Distribution Of Hematological Parameters In Three Groups Of Patients Studied

Hematological Variables	Control (N=50)		Anemia Of Chronic Disease (N=50)		Iron Deficiency Anemia (N=50)		P Value
	No	%	No	%	No	%	
Mean Cell Volume(fl)							
<79	0	0.0	11	22.0	46	92.0	<0.001**
79-93	50	100.0	34	68.0	4	8.0	
>93	0	0.5	5	10.0	0	0.0	
Mean Cell Hemoglobin Concentration %							
<32	27	54.0	7	14.0	44	88.0	<0.001**
32-36	23	46.0	43	86.0	6	12.0	
>36	0	0.0	0	0.0	0	0.0	
Mean Cell Hemoglobin(pg)							
<27	0	0.0	20	40.0	50	100.0	<0.001**
27-32	50	100.0	28	56.0	0	0.0	
>32	0	0.0	2	4.0	0	0.0	

Chi-Square test/Fisher Exact test

Table 3: Serum Iron Levels In Three Groups Of Patients Studied

Serum Iron	Control		Anemia Of Chronic Disease		Iron Deficiency Anemia	
	No	%	No	%	No	%
<50	0	0.0	41	82.0	44	88.0
50-100	44	88.0	9	18.0	4	8.0
>150	6	12.0	0	0.0	2	4.0
Total	50	100.0	50	100.0	50	100.0

Serum soluble transferrin receptor levels is <3 µgm/ml in 90% of ACD group whereas >3 µgm/ml in 78% of IDA Group (Table 4).

Table 4: Serum Soluble Transferrin Receptor Levels In Three Groups Of Patients Studied

Serum Soluble Transferrin Receptor(µgm/Ml)	Control		Anemia Of Chronic Disease		Iron Deficiency Anemia	
	No	%	No	%	No	%
<3	49	98.0	45	90.0	11	22.0
3-9	1	2.0	5	10.0	22	44.0
>9	0	0.0	0	0.0	17	34.0
Total	50	100.0	50	100.0	50	100.0

STFR/ log ferritin index was >1.5 in 80% of IDA . 90% of ACD and 100% control subjects had STFR/log ferritin index <1.5. Table 5

Table 5: STFR/Log Ferritin Index Levels In Three Groups Of Patients Studied

STFR/Log Ferritin Index	Control		Anemia Of Chronic Disease		Iron Deficiency Anemia	
	No	%	No	%	No	%
<1.5	50	100.0	45	90.0	10	20.0
>1.5	0	0.0	5	10.0	40	80.0
Total	50	100.0	50	100.0	50	100.0

Discussion: Iron deficiency is a common condition that is usually diagnosed using conventional laboratory tests of iron status, such as serum ferritin and transferrin saturation[7]. However, both ferritin and transferrin proteins are markedly influenced by inflammation,

behaving as acute phase reactants and making it difficult to differentiate between iron-deficiency anemia(IDA), which occurs when iron deficiency is severe enough to reduce erythropoiesis, and anemia of chronic disease (ACD) occurring with infection or malignancy[8]. The gold standard for assessing iron status is staining the bone marrow iron with Perl's stain. However, this procedure is invasive, expensive and painful[4].

Soluble transferrin receptor (STFR) has been shown to be an indicator of iron deficiency and is unaffected by concomitant chronic disease and inflammation[9]. The transferrin receptor is a transmembrane cellular protein primarily expressed in cells that require iron, and the soluble form is elevated in serum and plasma in cases of iron deficiency[10]. STFR levels are expected to be highest in IDA as reported earlier by Dimitriou H et al (2000)[11], by Malope B et al (2001)[12]. Present study showed similar result.

Serum ferritin levels reflect iron stores while STFR levels reflect the degree of availability of iron for cells. Calculating the STFR/log ferritin index (STFR Index) from these two measures provides an estimate of body iron over a wide range of normal and depleted iron stores[13]. In present study, patients of IDA had STFR/ log ferritin index of >1.5 while all pure ACD cases had STFR/ log ferritin index <1.5. Similar observations have been reported in previous study[14].

Skikne et al[15] prospective multicenter clinical trial further demonstrate the significant clinical utility for the STFR assay and the STFR/log ferritin index (STFR Index) as aids in the differential diagnosis of IDA & ACD. This study compared the efficacy of STFR and the STFR/Log ferritin Index in a representative patient population associated with IDA and ACD.

Kamar et al[16] study showed following result which is similar to our study. Soluble transferrin receptor values in children with IDA were 2.4 times higher, and in patients with infectious anemia and iron deficiency (IA + ID) two times higher, than STFR values in IA and CG children.

For STFR/logF, which was 8.2 times higher in children with IDA and 3.7 times higher among the subjects with IA + ID, the same differences were found, although more strongly expressed. However, no STFR differences were observed between IA and CG children. Also, it has to be remarked that STFR/logF values were lower in IA children than in those from the comparator group, as a consequence of increased serum ferritin concentration in children in the former group during the course of disease.

Burns et al[17] showed that among hospitalized patients, ferritin concentration gave the most effective estimation, with 90% of properly diagnosed iron deficiency cases, 84% for complete iron binding ability, 50% for the transferritin saturation index, and 41% for serum iron concentration vs. bone marrow bioptate evaluations.

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[18] 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. Alan et al[19] 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[20] and Joosten[21] suggested that the STFR as a single additional measurement to the existing methods.

Conclusion: When iron deficiency exists, the soluble transferrin receptor concentration in serum rises even before the haemoglobin concentration is significantly depressed. STFR concentration can therefore describe the functional iron status, while ferritin reflects the iron storage status.

Level of STFR is markedly elevated in Iron deficiency anaemia but remains normal in anemia due to chronic inflammation without iron deficiency. Thus levels of STFR may be of considerable help in differentiating between Iron deficiency anaemia and Anemia of chronic disease. In addition, use of the formula STFR/log ferritin ratio may increase the efficacy of STFR in identifying Iron deficiency anaemia and Anaemia of chronic disease.

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