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Original Research Article

Utility of sTFR/Ferritin index 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 assess the utility of sTfR/ Log ferritin Index to differentiate Iron deficiency anaemia and Anaemia of chronic disease.

Materials 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.

Results: 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. 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: 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.

1. Introduction

Anaemia is a global public health problem; about 30% of the world's population is anemic.[1] Iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD) are two common forms of anaemia that have interesting interrelated characteristics, causing a diagnostic predicament.[2] 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.[3] Globally, 50% of anaemia is attributable to iron deficiency and accounts for approximately 841,000 deaths annually worldwide.[4] 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.[5]

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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.[2] To interpret the actual iron status of the patient, a bone marrow examination is required which is the only reliable index of iron stores.[2] Bone marrow examination is invasive, expensive, painful and time consuming procedure and requires technical expertise. So it cannot be performed routinely in clinical practice.[6]

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.[7]

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.

2. Materials and 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.

2.1. Study period

October 2013 to September 2015**.**

2.2. 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.

2.3. Inclusion criteria

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

2.4. Exclusion criteria

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

2.5. Investigations done

Complete blood picture and Peripheral smear**,** Iron Profileand Serum transferrin receptors (TfR)level.

2.6. 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 is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, 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.

2.7. Significant figures

Suggestive significance (P value: $0.05<P<0.10$) * Moderately significant (P value:$0.01<P \leq 0.05$) ** Strongly significant (P value: $P \leq 0.01$).

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.

3. 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

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. Table 2

4. Discussion

STfR levels are expected to be highest in IDA as reported earlier by Dimitriou H et al (2000),[8] by Malope B et al (2001)[9] and also by Angeles et al (2006)[10] and Hanif E et al (2005).[11] 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[12,13] 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 studies.[14–16]

Table 1: Age distribution of patients studied

Age in years	Control		Anemia of chronic disease		Iron deficiency anemia	
	No	%	No	%	No	%
<20	0	0.0	2	4.0	4	8.0
20-30	0	0.0	7	14.0	6	12.0
31-40	20	40.0	7	14.0	9	18.0
41-50	20	40.0	9	18.0	7	14.0
51-60	7	14.0	9	18.0	10	20.0
61-70	2	4.0	10	20.0	11	22.0
71-80	0	0.0	5	10.0	1	2.0
>80	1	2.0	1	2.0	2	4.0
Total	50	100.0	50	100.0	50	100.0
Mean ± SD	45.66±10.23		50.68±18.03		48.14±18.47	

Table 2: Transferrin saturation levels in three groups of patients studied

Transferrin saturation	Control		ACD		IDA	
	No	%	NO	%	No	%
<30	5	10.0	48	96.0	46	92.0
30-50	45	90.0	2	4.0	2	4.0
>50	0	0.0	0	0.0	2	4.0
Total	50	100.0	50	100.0	50	100.0

P<0.001**, Significant, Fisher Exact test.

Table 3: 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

P<0.001**, Significant, Fisher Exact test
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 6

Table 4: 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

P<0.001**, Significant, Fisher Exact test

Table 5: Comparison of hematological parameters in three groups of patients studied

Hematological variables	Control	Anemia of chronic	Iron deficiency	P value
Hemoglobin %	14.32±1.02	9.49±2.04	5.83±2.06	<0.001**
Mean cell volume (fl)	88.58±2.72	84.12±7.58	62.29±7.75	<0.001**
Mean cell hemoglobin concentration %	31.22±1.52	32.67±1.13	28.69±1.92	<0.001**
Mean cell hemoglobin (pg)	29.92±0.94	27.60±2.73	18.19±3.16	<0.001**
Serum Iron	127.36±26.2	30.24±29.06	28.40±50.32	<0.001**
Serum Ferritin	151.00±91.38	285.43±281.33	81.71±156.42	<0.001**

Table 6: Comparison of average values of concentration of soluble transferringreceptor (sTfR) and sTfR/logarithm of ferritin index (sTfR/logF index) in examined children

	IDA		IA		IA+ID		CG	
	sTFR (mg/l)	Stfr/logF Index	sTFR (mg/l)	Stfr/logF Index	sTFR (mg/l)	Stfr/logF Index	sTFR (mg/l)	Stfr/logF Index
Mean	4.56	9.98	1.89	0.63	3.71	4.57	1.87	1.22
SD	2.35	15.19	0.39	0.31	1.85	3.30	0.31	0.25
Min	2.33	2.07	1.26	-0.03	1.55	0.70	1.36	0.71
Max	13.3	75.5	2.63	1.10	8.82	13.7	2.48	1.76

Examined groups of children: IDA — iron deficiency anemia; IA — infectious anemia; IA + ID — infectious anemia with iron deficiency; CG — control group

Skikne et al[17] 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. Patients with uncomplicated IDA or a combination of ACD and IDA have significantly higher sTfR and sTfR Index values than subjects with ACD. sTfR values >1.55 mg/L, and sTfR Index values >1.03mg/L were predictive of iron deficiency anemia in the presence or absence of inflammation and chronic disease. Kamar et al[18] study showed following result which is similar to our study.

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. Similar differences were observed in examinations of 1–6 year old children by Malope[9] and of 1–10 year old children by Angeles Vazquez Lopez.[10]

Punnonen et al,[19] in turn, while examining adults with iron deficiency anemia, found that in 95% of cases lowered serum ferritin concentrations correctly identified iron deficiency, as confirmed by bone marrow biopsy. But among patients with chronic inflammatory disease, proper serum ferritin concentrations did not exclude iron deficiency.

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[20] 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. Akinsooto et al[21] proved sTfR levels to be a good test in hospitalised patients as compared to Serum Ferritin. Eun Jung Lee et al[22] evaluated sTfR in non haematological malignancy while Choi JW[23] found sTfR levels at different stages of iron deficiency to be a valuable diagnostic tool. Chen YC et al[24] proved sTfR-F index to be a new and surrogate marker to estimate body iron stores.

5. Conclusion

It was concluded that 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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7. Conflicts of Interest

All contributing authors declare no conflicts of interest.

8. Source of Funding

None.

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