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A Study of Serum Ferritin, Serum Iron and Total Iron Binding Capacity in Sickle Cell Disease

KEYWORDS: sickle cell disease, serum iron, ferritin, TIBC, iron overload.

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ABSTRACT

Background : *Sickle cell disease (SCD) patients can have iron deficiency or transfusional iron overload. It is important to know the pattern of iron parameters in different clinical states of SCD to decide when these patients require iron supplementation, blood transfusion or chelation therapy.*

Materials & Methods : *From 2009 to 2010, 60 patients with sickle cell disease and 40 patients with sickle cell trait who fulfilled inclusion criteria were included in the study. 50 age matched healthy controls were selected. History, general and systemic examination was recorded according to proforma. Serum iron, ferritin and TIBC and required routine investigations were done. Chi square test was used for statistical analysis.*

Results : *Out of 100 patients 60 were Sickle Cell Disease (35 males : 25 females) and 40 patients were Sickle Cell Trait (15 males : 25 females). 60% sickle cell disease patients had increased serum ferritin level, 36.6% had normal and 3.3% had decreased serum ferritin level. Serum iron level was normal in 58.3%, increased in 16.6% and decreased in 25% patients of sickle cell disease. Inadequate body iron store state was more frequently noted in non transfused sickle cell disease/trait patients as compared to the transfused (low serum ferritin 25.2% vs 2.2%). 75% of patients of sickle cell disease and sickle cell trait who received blood transfusion and 16% patients who did not receive blood transfusion were found to have increased serum ferritin with p value of < 0.0001. 73.6% patients of sickle cell disease were having raised serum ferritin during crisis with p value < 0.0028. Mean haemoglobin was lower in patients with sickle cell disease than in sickle cell trait (p value = 0.0018). None had features of end organ damage due to iron toxicity.*

Conclusion : *Adult SCD patients in steady state versus vaso-occlusive crisis (VOC) have significantly different iron status vis a vis serum iron, ferritin and TIBC. Correct interpretation of serum iron, ferritin and TIBC is difficult in the setting of sickle cell anemia as they are modified by the chronic inflammatory state and chronic haemolytic/ hyperhaemolytic process of SCD.*

Introduction :

A sickle cell disease (SCD) patient is prone to iron overload as an inevitable complication of episodic and/or chronic blood transfusion. Exogenous iron can accumulate, circulate as non-transferrin bound iron (NTBI), enter tissues, form reactive oxygen species (ROS) and finally result in organ damage. At the same time the patient is not immune to inherent and environmental factors that precipitate iron deficiency anemia (IDA). Such factors, especially in the tropics, include poor nutrition, parasitic infestations like hookworm and schistosomiasis as well as varying bacterial infections that may disturb iron metabolism.[1] A study in > 8000 individuals in India found that iron deficiency was more common in women with SCD (67%) than in those with sickle trait (26%) or healthy controls (22%).[2] Therefore, only when repeated blood transfusions are given does iron overload develop in SCD. Transfusion of red blood cells (RBCs) is a common practice in the treatment of patients with sickle cell disease (SCD) for two reasons: (1) the infusion of erythrocytes increases the oxygen-carrying capacity of the blood in the anemic patient and (2) the replacement of the abnormal RBCs with normal ones may alleviate the symptoms or prevent the complications of the disorder.[3] There are clear differences between SCD and other forms of transfusional iron overload with respect to extrahepatic iron distribution.[4] Thus when managing anemia in sickle cell disease patients, one can come across both aspects of the disease namely iron deficiency or iron sufficiency or at the extreme iron overload. The purpose of this report was to study iron status in SCD patients by measuring serum ferritin, iron and total iron binding capacity (TIBC) in different clinical states of SCD. Such an information can help in maintaining adequate iron stores, initiating iron supplementation in iron deficient states, initiating chelation therapy in iron overload states and planning blood transfusion as and when required in patients of SCD.

Aims and Objectives :

1. To study levels of serum ferritin, serum iron, and total iron binding capacity in patients of sickle cell disease and sickle cell trait.
2. To study levels of serum ferritin, serum iron and total iron binding capacity during sickle cell crisis.
3. To study levels of serum ferritin, serum iron and total iron binding capacity in transfused and non-transfused patients of sickle cell disease and sickle cell trait.

Materials and Methods :

The study was conducted in the Department of Medicine, Pt. Jawahar Lal Nehru Memorial Medical College and B.R. Ambedkar Memorial Hospital, Raipur from 2009 to 2010. 60 patients with sickle cell disease and 40 patients with sickle cell trait from the medicine OPD and ward who fulfilled inclusion criteria were included in the study. 50 age matched healthy controls were selected. History, general and systemic examination of selected patients of sickle cell

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disease and sickle cell trait was taken according to proforma. Serum iron and TIBC were measured by Ferrozine/ Magnesium Carbonate method using fully automated biochemisty I-Lab 650i autoanalyser. Serum ferritin was measured using ELISA Accubind (USA) test kit. The kit had a high specificity (with a cross reactivity <10%) and sensitivity of 0.75 µIU/ml at 95% confidence limit with CV of 0.9%. The statistical analysis of the results was done by students Chi square test. P value < 0.05 was taken as significant.

Inclusion criteria :
1. Patients > 14 years of age.
2. Patients of sickle cell disease and sickle cell trait with Hb electrophoresis - Hb SS and Hb AS respectively**.**

Exclusion criteria :
1. Patients < 14 years of age.
2. Patients with haemoglobinopathies other than sickle cell disease and sickle cell trait like sickle thalassaemia disorder.
3. Patients with acute or chronic blood loss e.g. bleeding piles, bleeding acid peptic ulcer disease.
4. Pregnancy

Blood sample was taken in morning with all usual precaution in plain tubes without any additives and anticoagulants; serum sample was collected after centrifugation. Samples were refrigerated at 2-8°C for a maximum period of five days. Those specimens which were not to be assayed within this time, were stored at temperatures of -20°C for up to 30 days. Repetitive freezing and thawing was avoided.

Normal reference ranges : [5]
Serum ferritin –
- Males – 16 – 220 ng/ml
- Females – 10 – 124 ng/ml
- Newborns – 22 – 220 ng/ml

Serum iron –
- Males – 60 – 160 µg/ml
- Females – 35 – 145 µg/ml
- Newborns – 150 – 220 µg/ml

TIBC – 250 – 400 µg/ml

Results :
In this study out of 100 patients 60 were Sickle Cell Disease (35 males : 25 females) and 40 patients were Sickle Cell Trait (15 males : 25 females). So in total there were 50 males patients and 50 female patients.

36 (60%) patients with sickle cell disease were found to have increased serum ferritin, 22 (36.6%) had normal serum ferritin and 2 (3.3%) patients had decreased ferritin. 5(12.5%) patients with sickle cell trait had increased serum ferritin, 31(77.5%) patients had normal ferritin level and 4(10%) patients had decreased serum ferritin level. The difference was statistically significant (p<0.0001). As compared to sickle cell trait patients, more number of sickle cell disease patients had increased serum ferritin level. (**Table no. 1**)

Table no. 1 - Levels of serum ferritin in sickle cell disease and sickle cell trait

	Increased Male>220 ng/ml Female>124 ng/ml		Normal Male 16-220 ng/ml Female 10-124 ng/ml		Decreased Male < 16 ng/ml Female < 10 ng/ml	
	No.	%	No.	%	No.	%
Sickle cell disease no. -60	36	60%	22	36.6%	2	3.3%
Sickle cell trait no. - 40	5	12.5%	31	77.5%	4	10%

P-<0.0001

10 (16.6%) patients with sickle cell disease had increased serum iron, 35 (58.3%) patients had normal serum iron and 15 (25%) patients had decreased serum iron level. 4 (10%) patients with sickle cell trait had increased serum iron, 29 (72.5%) patients had normal serum iron while 7 (20%) had decreased serum iron level. P value was > 0.05 therefore findings were statistically insignificant. (**Table 2**)

Table no. 2 - Levels of serum iron in sickle cell disease and sickle cell trait

	Increased Male >160 µg/dl Female > 145 µg/dl		Normal Male 60-160 µg/dl Female 35-145 µg/dl		Decreased Male < 60 Female < 35	
	No.	%	No.	%	No.	%
Sickle Cell Disease No-60	10	16.6%	35	58.3%	15	25%
Sickle Cell Trait No-40	4	10%	29	72.5%	7	17.5%
Total	14		64		22	

19 (31.6%) patients with sickle cell disease had increased total iron binding capacity, 31 (51.6%) patients had normal TIBC and 10 (16.6%) patients had decreased TIBC level. 6 (15%) patients with sickle cell trait had increased TIBC, 26 (65%) patients had normal TIBC level while 8 (20%) patients were found to have decreased total iron binding capacity. TIBC level was high in patients of sickle cell disease as compared to sickle cell trait. (**Table 3**)

Table no. 3 - Levels of TIBC in sickle cell disease and sickle cell trait

	Increased > 400 µg/dl		Normal 250-400 µg/dl		Decreased < 250 µg/dl	
	No.	%	No.	%	No.	%
Sickle cell disease no. -60	19	31.6%	31	51.6%	10	16.6%
Sickle cell trait no. - 40	6	15%	26	65%	8	20%
Total	25		57		18	

Out of 43 transfused patients of sickle cell disease and sickle cell trait, 33 (75%) had increased, 9 (20.4%) had normal while 1 (2.2%) was found to have decreased serum fer-

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ritin level. Also 11 (25.6%) had increased, 27 (61.3%) had normal while 5 (11.6%) were found to have decreased serum iron level. Serum TIBC was found to be increased in 15(34%), normal in 19 (43.1%) and decreased in 9 (20.9%) . Among 57 non-transfused patients, 9(16%) had increased, 36 (64.2%) had normal while 12 (25.5%) were found to have decreased serum ferritin level. Also 8 (14.2%) had increased, 35 (62.5%) had normal while 14 (25.9%) were found to have decreased serum iron levels. Serum TIBC was found to be increased in 13 (23.2%), normal in 35 (62.5%) while decreased in 9 (16.6%). (**Tables 4, 5 & 6**)

Table no. 4 - Levels of serum ferritin in transfused and non-transfused patients of sickle cell disease and sickle cell trait (combined together)

	Increased Male>220 ng/ml Female>124 ng/ml		Normal Male 16-220 ng/ml Female 10-124 ng/ml		Decreased Male<16 ng/ml Female<10 ng/ml	
	No.	%	No.	%	No.	%
Transfused no. - 43	33	75%	9	20.4%	1	2.2%
Non-transfused no. - 57	9	16%	36	64.2%	12	25.5%
Total	42		45		13	

Table no. 5 - Levels of serum iron in transfused and non - transfused patients of sickle cell disease and sickle cell trait (combined together)

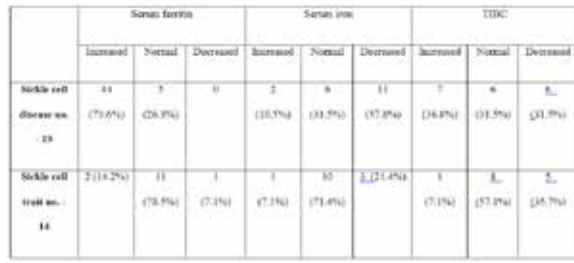
	Increased Male >160 µg/dl Female > 145 µg/dl		Normal Male 60-160 µg/dl Female 35-145 µg/dl		Decreased Male < 60 Female < 35	
	No.	%	No.	%	No.	%
Transfused no. - 43	11	25.6%	27	61.3%	5	11.6%
Non-transfused no. - 57	8	14.2%	35	62.5%	14	25.9%
Total	19		62		19	

Table no. 6 - Levels of TIBC in transfused and non - transfused patients of sickle cell disease and sickle cell trait (combined together)

	Increased > 400 µg/dl		Normal 250-400 µg/dl		Decreased < 250 µg/dl	
	No.	%	No.	%	No.	%
Transfused no. - 43	15	34%	19	43.1%	9	20.9%
Non-transfused no. - 57	13	23.2%	35	62.5%	9	16.6%
Total	28		54		18	

Out of 19 patients of sickle cell disease with painful crisis, 14 (73.6%) had increased, 5 (26.3%) had normal while none of them were found to have decreased serum ferritin level. Also, 2 (10.5%) had increased serum iron, 6(31.5%) had normal while 11(57.8%) of them were found to have decreased serum iron level. It was also found that 7 (36.8%) had increased TIBC, 6 (31.5%) had normal while 6 (31.5%) of them were found to have decreased TIBC level. Whereas out of 14 patients of sickle cell trait with painful crisis, 2 (14.2%) had increased, 11 (78.5%) had normal while 1 (7.1%) had decreased serum ferritin level. 1 (7.1%) had increased serum iron, 10 (71.41%) had normal while 3 (21.4%) had decreased serum iron level. 1 (7.1%) had increased TIBC, 8 (57.1%) had normal while 5 (35.7%%) of them had decreased TIBC level. (**Table 7**)

Table no. 7 - Levels of serum ferritin, iron and TIBC patients of sickle cell disease and sickle cell trait during painful crisis.



	Serum ferritin			Serum iron			TIBC		
	Increased	Normal	Decreased	Increased	Normal	Decreased	Increased	Normal	Decreased
Sickle cell disease no. - 19	14 (73.6%)	5 (26.3%)	0	2 (10.5%)	6 (31.5%)	11 (57.8%)	7 (36.8%)	6 (31.5%)	6 (31.5%)
Sickle cell trait no. - 14	2 (14.2%)	11 (78.5%)	1 (7.1%)	1 (7.1%)	10 (71.4%)	3 (21.4%)	1 (7.1%)	8 (57.1%)	5 (35.7%)

Table no. 8 - Haematological picture in sickle cell disease and sickle cell trait.

	HB% Mean ± SD	MCV (fl) Mean ± SD	MCH (pgm) Mean ± SD	MCHC % Mean ± SD
Sickle Cell Disease No-60	6.72 ± 2.22	85.59 ± 15.09	28.72 ± 6.53	32.0 ± 4.38
Sickle Cell Trait No-40	8.55 ± 3.05	80.75 ± 13.87	25.56 ± 5.47	31.26 ± 2.03

In 60 patients of sickle cell disease, the haemoglobin (Hb), mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) values were 6.72 ± 2.22, 85.59 ± 15.09, 28.72 ± 6.53 and 32.0 ± 4.38 respectively. In 40 patients with sickle cell trait, the values were 8.55 ± 3.05, 80.75 ± 13.87, 25.56 ± 5.47 and 31.26 ± 2.03 respectively. The mean haemoglobin was lower in patients with sickle cell disease than in sickle cell trait (p value = 0.0018).

Discussion :

In our study, 60% sickle cell disease patients had increased serum ferritin level, 36.6% had normal and 3.3% had decreased serum ferritin level. Serum iron level was normal in 58.3%, increased in 16.6% and decreased in 25% patients of sickle cell disease. Iron deficiency is not expected to be present in hereditary anemias like thalassaemias and sickle cell anemia since there is a premature destruction of erythrocytes, iron released by haemolysis is available for reutilization which contributes towards iron stores. The increased gastrointestinal absorption of iron associated with hemolysis and the iron provided by red cell transfusions also provide a sufficient source of iron.[6,7] Aken'Ova et al[8] in their study had concluded that SCA patients have adequate levels of iron and ferritin in their serum. There are several reasons to believe that iron deficiency may occur in sickle cell disease patients. Factors such as (especially in the tropics) poor nutrition, parasitic infestations like hookworm and schistosomiasis as well as varying bacterial infections may disturb iron metabolism.[1] Iron deficiency anemia (IDA) is very common amongst indians due to several reasons like low dietary intake, malabsorption, excessive sweating and its prevalence varies from 75 per cent among children and women to 45 per cent among adult males.[9] Secondly, iron deficiency in patients with sickle cell anemia is most often due to excessive urinary losses of iron secondary to chronic intravascular hemolysis. The 24-hr urinary excretion of iron in sickle cell anemia may range from 0.5 to 3.5 mg.[10] In this study, the mean haemoglobin was lower in patients

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with sickle cell disease than in sickle cell trait (P value = 0.0018) which in our opinion was more due to sickling process than any nutritional deficiency.

Vichinsky et al[11] in their study, which included 50 homozygous sickle cell anemia (HbSS) and 20 doubly heterozygote for HbS and HbC (HbSC) patients, detected iron deficiency anemia in 9% of their study group. None of the 32 patients who had a history of red cell transfusion were iron deficient. In contrast, among the 38 patients who were not transfused, 6 iron deficient patients were identified. We observed almost similar findings in our study. Inadequate body iron store state was more frequently noted in non transfused sickle cell disease/trait patients as compared to the transfused (low serum ferritin 25.2% vs 2.2%). 75% of patients of sickle cell disease and sickle cell trait who received blood transfusion and 16% patients who did not receive blood transfusion were found to have increased serum ferritin with p value of < 0.0001 and was statistically highly significant. The practice of transfusion is so common that most adult patients with sickle cell disease have been transfused at one time or another, many with a great number of units of blood. Thus transfused sickle cell disease/trait patients fared well because blood transfusion was the source of additional elemental iron. SK Ballas[12] in his study found that multiple blood transfusions on a chronic basis led to excessive accumulation of iron especially in adults with sickle cell anemia (SS) with progressive increase in serum ferritin. Radha Raghupathy et al[13] in their review article have elaborated the mechanism of transfusion mediated iron overload state. Transfusion of packed red blood cells (RBCs) provides 1mg per mL transfused of additional elemental iron. Long term transfusion therapy of, for instance, 20-units RBCs/ year is associated with significant iron overload (20 units ×220mL per unit × 1mg per mL = 4400 mg exogenous iron/ year). With repeated transfusions, serum transferring becomes saturated and the excess circulating iron is transported as Non Transferrin Bound Iron (NTBI). NTBI enters cells in a dysregulated fashion; a subset of NTBI, called Labile Plasma Iron (LPI), may cause end organ damage secondary to its high redox potential. In our study, despite there being an iron overload state in some of the patients, none had features of end organ damage due to iron toxicity.

In our study 73.6% patients of sickle cell disease were having raised serum ferritin during crisis which was statiscally highly significant with p value < 0.0028. In a study by OA Oluboyede et al[14] the mean serum ferritin was 296.3 ng/ ml in the sickle cell disease patients and was significantly higher (p < 0.01) than the steady state participants. JB Porter et al[15] found that the serum ferritin done within 7 days of a painful crisis was significantly greater than the serum ferritin from the same patients in the steady state (p < 0.025).

changes were nonlinear compared with increasing iron load measured by transfusion iron load (TIL) or liver iron concentration (LIC). In their study, after an initial rapid rise, serum ferritin rate of change slowed down after reaching approximately 1500 to 2500 ng/mL, despite evidence of increasing iron load. After further iron overload, patients developed high levels of serum ferritin (≥ 3000 ng/mL).[16] Serum ferritin is an acute phase reactant that is affected by both inflammation and infection. Sickle cell pain crisis may cause a rise in the serum ferritin that may persist for 1–3 weeks. Thus, serum ferritin is a measure of available stores of body iron only if drawn in the steady-state.[16]

Conclusion :

Iron deficiency is common in sickle cell disease patients. Iron supplementation should be given in proven cases of iron deficiency anaemia to improve their general condition and work efficiency. Peterson et al[17] demonstrated that patients who received iron supplementation had a significant rise in haemoglobin concentration. While conventionally diagnosis of iron deficiency in anemia patients can be based on the measurement of a low serum iron and low serum ferritin with an elevated TIBC, interpreting iron parameters in sickle cell disease patients remain complex as they are highly modified by the chronic inflammatory state and chronic haemolytic/ hyperhaemolytic process. Increasing number of patients with sickle cell disease are receiving chronic blood transfusions for the prevention or management of disease-related complications. Iron overload is a feared complication of long-term transfusion in sickle cell disease. While the indications for transfusion in sickle cell disease continue to broaden and unnecessary transfusions should be minimized as much as possible. Sickle cell disease is a condition with a strong inflammatory component and ferritin, which is an acute-phase reactant, may not accurately predict body iron stores. Chelation therapy (adapted from Radha Raghupathy et al[13]) should be considered when:

1. adult patients with SCD have received 20–30 units of RBC transfusion,
2. pediatric patients with SCD are approaching a transfusion iron load (TIL) ≥ 100 mg/Kg,
3. and/or hepatic iron content (HIC) in any age group exceeds 7–9 mg/g

(Excessive HIC is likely when the serum ferritin is >3000 ng/mL, less clear at 1500–3000 ng/mL).

Ethical approval :

All authors hereby declare that the study was undertaken after the study protocol was approved by the local ethical committee.

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