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Serum iron Profile of Patients with Sickle Cell Disease and its Association with Socio-demographic Characteristics and Duration of Diagnosis

Sher Bahadur Kamar,[1] Hemraj Pandey,[2] Shurehraman Puri,[3] Ramesh Shahi,[4] Uttam Bhatta,[5] Sulochana Khadka,[6] Gopal Yadav,[7] Prativa Subedi,[8] Kapil Amgain[9]

[1]Department of Internal Medicine and COVID-19, Seti Provincial Hospital, [2]Department of Paediatrics, Seti Provincial Hospital, [3]Department of Emergency, Seti Provincial Hospital, [4]Department of Pathology, Seti Provincial Hospital, [5]Department of Internal Medicine, Seti Provincial Hospital, [6]Shree Birendra Sainik Hospital, Chhauni, Kathmandu, Nepal, [7]Department of Internal Medicine, Narayani Hospital, Birgunj, [8]Department of Internal Medicine, KIST Medical College and Teaching Hospital, [9]Department of Clinical Anatomy, Karnali Academy of Health Sciences.

ABSTRACT

Background : Sickle cell anemia is the most common hemoglobinopathy in the world. The study aimed to evaluate the iron profile and its association with socio-demographic characteristics in patients with sickle cell disease.

Methods: A hospital-based descriptive cross-sectional study was conducted to know the iron profile and its socio-demographic association in patients with sickle cell disease.

Results: The average serum iron, TIBC, and transferrin saturation were 16.75 ± 6.40 mcgMole/L, 69.46 ± 16.94 mcg/dl and 25.15 ± 12.51% respectively. The serum ferritin ranged from 10.00 to 3000.00 ng/ml. The proportion of participants with normal serum iron, TIBC, serum ferritin, and transferrin saturation were 86.10%, 0.00%, 33.90% and 36.40% respectively. All of the participants of this study had low TIBC (1005), and more than half of the participants had elevated serum ferritin (56.40%).

Conclusions: Iron overload is a common complication of sickle cell disease no association of iron profile with age. The TIBC variation between the Chaudhary ethnic group compared to other ethnic groups signifies the ethnic role in the iron profile.

Keywords: Ethnicity; iron overload; sickle cell disease; total iron binding capacity.

INTRODUCTION

Sickle cell anemia is a genetic blood disorder caused by point mutation in the globin gene of haemoglobin and is the most common inherited hemoglobinopathy worldwide.[1] It is highly prevalent in sub-Saharan Africa, south Asia, the middle east, and the Mediterranean and has spread globally due to rapid migration.[2,3] In Nepal, sickle cell disease(SCD) is mostly prevalent in Terai districts where the Tharu ethnic group predominantly reside.[4]

SCD is associated with altered iron metabolism and homeostasis.[5] While iron deficiency is common due to impaired absorption and hemolysis[6], iron overload is seen due to repeated transfusion.[7] Maintenance of iron balance is necessary to reduce infection and end-organ damage and promote well-being.[8] Iron chelation therapy may help prevent iron overload and its consequences.[9] The objective of our study is to assess the iron profile in patients with SCD and determine its socio-demographic associations.

METHODS

This is a cross sectional study conducted in Seti Provincial Hospital from Jan 1 2022 to 30 April 2022. Study population included registered patients of SCD visiting the inpatient and out-patient department of hospital. However, patients with other haematological disorders, pregnant women, critically ill patients from ICU and those refusing to give consent were excluded. There

Correspondence: Dr Kapil Amgain, Karnali Academy of Health Sciences, Jumla, Email: dr.kapilamgain@gmail.com, Phone: 9849081164.

were a total of 645 registered patients of SCD. Amongst them, 280 patients were included in the sample. The sample size was calculated using the formula

Written informed consent was taken from all the participants after explaining the purpose of the study. They were explained that their participation was entirely voluntarily and could withdraw at any point of time. IRC approval was taken from Nepal Health Research Council (NHRC) with Ref. No. 522. Socio-demographic information was obtained from the participants using self-administered questionnaire. Venous blood sample (3-5 ml) was obtained for the study of iron profile via NHPC registered lab technician and haematological indices were measured using an automated analyser.

The data was entered into excel 2019 v16.0 (Microsoft, WA, USA) and exported to IBM SPSS® v29 (IBM, Armonk, NY) for the statistical calculations. The socio-demographic characteristics including duration of diagnosis of sickle cell disease and serum iron profile were presented with descriptive statistics like frequency, proportions (%), mean ± standard deviations (SD), or median ± interquartile range (IQR) wherever required. The normal distribution of data such as the components of serum iron profile was assessed using histogram, Q-Q plots, and tests like Kolmogorov-Smirnov and Shapiro-Wilk test. The P-value more than >0.05 in Kolmogorov-Smirnov and Shapiro-Wilk indicates normality. The association of socio-demographic characteristics with serum iron, serum ferritin, and transferrin saturation were assessed using Mann-Whitney U test owing to their non-parametric distribution. Similarly, the association of socio-demographic characteristics with TIBC was assessed using independent sample t test owing to its parametric distribution. The P-value less than 0.05 was considered statistically significant.

RESULTS

Out of 280 participants with SCD, the mean age was 25.84 ± 12.34 years. The maximum proportion of the participants belonged to age group 15-29 years (51.79%, 145) followed by 30-44 years (20.00%, 56). Half of the cases (53.93%, 151) were female. More than four-fifths of the participants belonged to the Chaudhary ethnicity (82.50%, 231) and Hindu religion (90.36%, 253). The median duration of diagnosis was 4 years with minimum and maximum being 1 and 34 years respectively. **(Table 1)**

Table 1. Socio-demographic characteristics, and duration of disease diagnosis of the study participants with sickle cell disease.

Characteristics		Frequency (%)
Age		
	Mean ± SD (Min-Max)	25.84 ± 12.34 (3-66)
	≤14	47 (16.79)
	15-29	145 (51.79)
	30-44	56 (20.00)
	≥45	32 (11.42)
Gender		
	Male	129 (46.07)
	Female	151 (53.93)
Ethnicity		
	Chaudhary	231 (82.50)
	Rana	37 (13.21)
	Others[1]	12 (4.29)
Religion		
	Hindu	253 (90.36)
	Christian	27 (9.64)
Duration of diagnosis (years)		
	Mean ± SD [Median ± IQR (Min-Max)]	6.49 ± 6.65 [4 ± 3-7 (1-34)]

[1]Others: Dangaura, and Kathariya

The average serum iron, TIBC, and transferrin saturation were 16.75 ± 6.40 mcgMole/L, 69.46 ± 16.94 mcg/dl and 25.15 ± 12.51% respectively. The serum ferritin ranged from 10.00 to 3000.00 ng/ml. The proportion of participants with normal serum iron, TIBC, serum ferritin, and transferrin saturation were 86.10%, 0.000%, 33.90% and 36.40% respectively. All of the participants of this study had low TIBC (1005), and more than half of the participants had elevated serum ferritin (56.40%). **(Table 2 and Figure 1)**

Table 2. Serum iron profile of the study participants with sickle cell disease.			
Characteristics	**Mean ± SD**	**Median ± IQR (Min-Max)**	**Reference values**
Serum iron (mcgMole/L)	16.75 ± 6.40	15.75 ± 12.53-20.03 (5.70-52.80)	10.0-30.0
TIBC[1] (mcg/dl)	69.46 ± 16.94	69.85 ± 57.80-80.68 (10.20-123.60)	300-360
Serum ferritin (ng/ml)	463.56 ± 655.05	233.95 ± 102.63-468.50 (10.00-3000.00)	50-200
TSAT[2] (%)	25.15 ± 12.51	22.76 ± 17.23-29.45 (8.60-109.00)	25-50

[1]TIBC: Total Iron Binding Capacity

[2]TSAT: Transferrin saturation

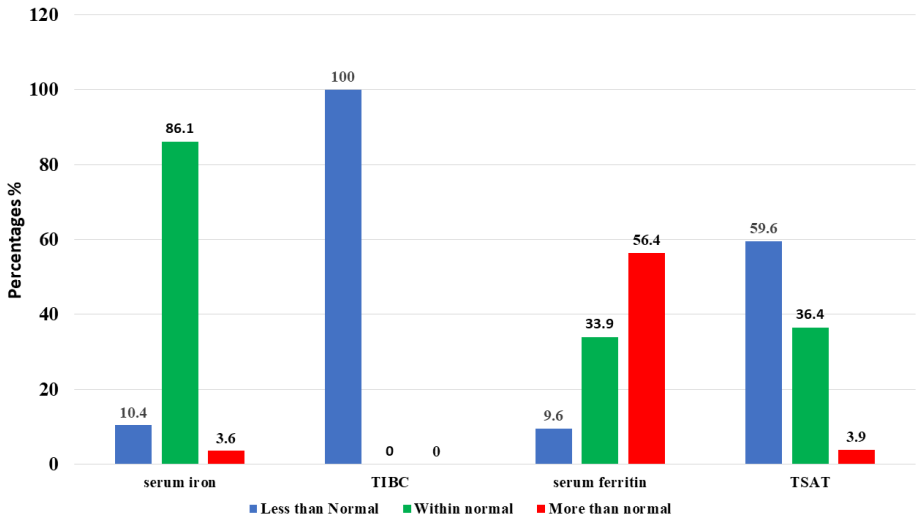

Figure 1. Distribution of serum iron profile among the patients with with sickle cell disease.

The Chaudhary ethnic group had significantly higher mean value of TIBC than *Rana* and other ethnic groups (70.40 ± 16.79 vs 65.03 ± 17.11 mcg/dl, P-value 0.044). The other socio-demographic characteristics did not show any significant association with different components of serum iron profile. **(Table 3)**

Table 3. Association of serum iron profile of the participants with sickle cell disease with socio-demographic characteristics and duration of diagnosis.								
Characteristics	Serum iron (mcgM/L)		TIBC (mcg/dl)		Serum ferritin (ng/ml)		TSAT (%)	
	Median ± IQR	P-value[1]	Mean ± SD	P-value[2]	Median ± IQR	P-value[1]	Median ± IQR	P-value[1]
Age								
<30	15.35 ± 47.10		70.62 ± 16.97		224.85 ± 2989.90		22.22 ± 85.00	
≥30	16.45 ± 28.4	0.124	66.93 ± 16.70	0.091	256.55 ± 2990	0.494	24.85 ± 100.40	0.050
Gender								

Table 3. Association of serum iron profile of the participants with sickle cell disease with socio-demographic characteristics and duration of diagnosis.

Characteristics	Serum iron (mcgM/L)		TIBC (mcg/dl)		Serum ferritin (ng/ml)		TSAT (%)	
	Median ± IQR	P-value[1]	Mean ± SD	P-value[2]	Median ± IQR	P-value[1]	Median ± IQR	P-value[1]
Male	15.80 ± 45.7	0.430	68.29 ± 15.44	0.285	235.80 ± 2990	0.481	24.10 ± 99.80	0.114
Female	15.70 ± 35.30		70.46 ± 18.12		233.10 ± 2989.90		21.90 ± 69.80	
Ethnicity								
Chaudhary	16.10 ± 47.10	0.027	70.40 ± 16.79	0.044	231.50 ± 2990	0.880	23.20 ± 100.4	0.156
Rana & others	14.30 ± 26.2		65.03 ± 17.11		258.70 ±2986.10		21.88 ± 45.60	
Religion								
Hindu	15.90 ± 47.1	0.103	69.55 ± 17.01	0.794	234.80 ± 2990	0.575	22.80 ± 100.40	0.342
Christian	12.60 ± 32.9		68.65 ± 16.57		215.60 ± 2142.30		21.90 ± 64.90	
Duration of diagnosis								
<5 years	15.70 ± 46.3	0.246	69.25 ± 17.08	0.802	225.90 ± 2990	0.448	22.72 ± 100.40	0.381
≥5 years	15.90 ± 29.8		69.77 ± 16.81		236.90 ± 2989.60		23.00 ± 69.80	

[1]P-value from Mann Whitney test

[2]P-value from independent sample ttest

TIBC: Total Iron Binding Capacity

DISCUSSION

The mean age of patients in our study was found to be 25 years with a range of 3 to 66 years Clinical features of SCD is rarely evident before the age of 6 months as the fetal haemoglobin is resistant to sickling .[10] Routine screening for sickle cell genes is not done among newborn in Nepal. There were almost equal proportion of males and females in our study. Sickle cell disease being an autosomal recessive disorder, does not bear any genetic gender predisposition. However, epidemiological data suggest male preponderance both in the diagnosis of sickle cell disease and the frequency and severity of sickle cell crises.[11,12] A study by Shrikhanda et al. showed that males predominate in pediatric population and females predominate in reproductive age group.[13] This has been linked to greater priority given to male child and recognition of clinical manifestations in pregnancy due to associated physiological changes and vulnerabilities.

Around four fifth of the study participants belonged to Chaudhary ethnicity. A study by Shrestha et. al on analysis of sickle hemoglobin showed that the Chaudhary ethnic group had the highest prevalence (82.8%) of the disease followed by Rana (8.5%).[14] A study done in Western Nepal showed an estimated Hb S prevalence of 9.3% suggesting a high burden of disease in Tharu communities.[15] In Nepal, SCD is mostly prevalent in provinces Lumbini , Karnali and Sudurpaschim where Tharu communities mostly reside with highest prevalence in Province number Karnali which is our study location.[16] A study done in Bardiya, the western district of Nepal by Pandey et. al, showed that the prevalence of sickle cell disease among the Tharu population was 14.67%. whereas

another study was done in five different centers of Nepal which showed a prevalence of 58.3% in the Tharu population.[14,16] However, the lack of health education, screening, and utilization of health services in the prevalent areas has led to a lack of proper estimation of the actual diseased population in our country.[15]

The sickled RBCs have decreased life span and increased turn over. [17]As the red blood cells are destroyed, the iron they contained is released into the bloodstream and can lead to elevated serum iron levels and ferritin levels.[18] In our study, more than half of the patients (56.40%) had elevated serum ferritin with a mean serum ferritin of (463.56 ± 655.05). It is in contrast to a study performed in Nigeria where only 2% of participants had elevated ferritin levels.[19] One of the most crucial instruments for measuring iron balance in stable sickle cell disease is serum ferritin.[20] It may be due to repeated blood transfusions which are often required in sickle cell crisis and severe anemia or gastrointestinal absorption of iron due to sickle cell-associated chronic hemolysis. [19] However, the transfusion status of the patients was not known in our study.

This study showed that the mean total iron binding capacity (TIBC) of patients with SCD was markedly below the normal range (69.46 ± 16.94) and none of the patients had normal or high TIBC. This is in contrast with the study by Peterson et al. where the TIBC is within low-normal range. [21]TIBC values are important in diagnosing iron deficient and overload status. [22] In a study done in Yemen, the mean TIBC was significantly higher median values in iron deficient than in non-iron-deficient patients (P<0.001).[23] The TIBC values are low in the state of iron overload, multifactorial anemias, or anemia of chronic disease. Thus, This study findings suggest that iron overload is common in SCD. In this study, the TIBC of the Chaudhary caste was higher compared to another ethnic group which was statistically significant (P<0.044). It may be related to the low mean values of serum Iron in the Chaudhary group. However, our study also showed that the mean iron levels were within the normal limit but were significantly different among the Chaudhary ethnic group compared to other ethnic groups like Rana, Dangaura, and Kathariya. Thus, ethnicity could have its independent implication over the iron profile in patients.

Treatment modalities aimed to counteract the pathogenesis of SCD include stem cell transplant and hydroxyurea therapy. Blood transfusions are useful in the management of acute complications like vaso-occlusive crisis and acute chest syndrome. [24] Majority of individuals with SCD require chronic episodic blood transfusions, which puts them at risk for iron overload.[18] According to recent findings, individuals who get continuous transfusions may be at risk for organ failure due to iron excess.[25] Blood transfusions can save lives, however, patients with SCD should continuously be cautioned against iron overload.[26]

While the screening and diagnostic tests being expensive or unavailable is a challenge, the need to monitor the iron levels to know the iron deficiency or overload status is important to treat the patients and prevent complications. Monitoring serum iron levels, transferrin saturation, and ferritin levels as well as performing liver function tests and iron overload imaging studies is important to monitor and treat the iron overload.[26] Increasing the testing centers and raising awareness for genetic counseling is required.[27]

This study has few limitations. Due to the nature of the cross-sectional study, could not understand this. We have not taken into account the frequency of blood transfusions and co-morbid conditions.

CONCLUSIONS

Sickle cell disease can be associated with iron overload along with iron deficiency. There is no association of iron profile with age and sex with SCD. The TIBC variation between the Chaudhary ethnic group compared to other ethnic groups signifies the ethnic role in the iron profile. Continuous monitoring of the iron profile is required to prevent complications that can arise from iron overload.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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