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ORIGINAL ARTICLE

# Iron indices in adults with sickle cell nephropathy in Lagos, Nigeria

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## ABSTRACT

**Introduction:** Although several studies have explored iron indices in patients with sickle cell anaemia (SCA), there is a paucity of evidence regarding the iron status of patients with sickle cell nephropathy (SCN). This study evaluated the range of iron status of adult SCA patients with or without nephropathy in Lagos, Nigeria.

**Methods:** This was a cross-sectional study performed at the Sickle Cell Clinic of the Lagos University Teaching Hospital (LUTH). Patients who were aged 18–65 years were assessed for SCN by determining the albumin-to-creatinine ratio (UACR) on a spot urine sample, and determining the estimated glomerular filtration rate, using the CKD–EPI formula, on a steady-state serum creatinine concentration. Iron indices including serum ferritin, serum iron and total iron-binding capacity (TIBC) were measured, and percentage transferrin saturation (TSAT) was calculated. Data were analysed with the Statistical Package for the Social Sciences (SPSS) version 23.

**Results:** A total of 200 patients were included, of whom 119 had SCN. There were no statistically significant differences in iron indices in participants with or without SCN. The median serum ferritin and TSAT of patients with SCN were 265 ng/mL and 31.8%, respectively, while the values were 255 ng/mL and 33.5% in those without SCN, respectively. Few participants were noted to have iron overload based on ferritin and TSAT values, regardless of SCN diagnosis. Although not statistically significant, females tended to have higher ferritin and serum iron values compared to males, irrespective of the presence or absence of SCN; whereas females without SCN had statistically significant higher TSAT values compared to males without SCN (36.2 ± 15.0% and 28.8 ± 11.5%, P = 0.03).

**Conclusion:** Although iron overload is common in patients with SCA, our findings indicate that patients with SCN may require routine evaluation of iron indices because few were iron overloaded. For this reason, the evaluation of iron indices in patients with SCN should be individualised to guide the direction of care and improve clinical outcomes.

**Keywords:** iron; sickle cell anaemia; sickle cell nephropathy.

## INTRODUCTION

Over the years, several studies have extensively recorded the presence of anaemia in chronic kidney disease (CKD) and have reported a prevalence ranging between 26.7% and 75.5% among varying populations [1]. Additionally, studies have reported increasing prevalence with worsening disease [1]. This prevalence is estimated to be about 20% in patients with stage 1 CKD, and increases to as much as 80% in stage 5 CKD [1,2]. The impact of anaemia in CKD is associated with several complications and include impaired cognition, reduced exercise tolerance, left ventricular hypertrophy, reduced quality of life, increased cardiovascular risk, disease progression, and increased mortality [3].

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Following the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for managing individuals with CKD which recommend routine evaluation of the iron indices as part of the evaluation for anaemia, several controversies have ensued regarding iron-related issues in CKD [3]. This is because iron deficiency is common in patients with CKD and is a well-documented cause of erythropoietin (EPO) resistance [4]. Moreover, iron therapy in CKD patients improves anaemia and is associated with reduced EPO requirements [4].

In recent years, the improved care of patients with sickle cell anaemia (SCA), such as better education, adequate nutrition, avoidance of known precipitants of crises, better hydration, immunisation, compliance with routine drugs and improved management by healthcare professionals, has been associated with greater survival as well as the reduced need for red cell transfusions [7]. Consequently, over the last few decades, more patients with SCA are presenting with chronic disease complications, such as sickle cell nephropathy (SCN) [8]. Patients with SCN have certain peculiarities in symptomatology and management compared to other causes of CKD [9]. For one, the onset of nephropathy in patients with SCA is associated with worsening the underlying chronic anaemia [10]. Additionally, EPO requirements are greater in patients with SCN than in subjects with other CKD causes [11]. Therefore, the assessment of iron indices is even more vital to managing anaemia in CKD within this sub-population [12].

However, in the clinical management of patients with SCA, it is commonplace in low- and middle-income countries such as Nigeria to discount the need for iron therapy in SCN because of the generalised assumption of iron overload [13]. In the past, SCA patients were traditionally thought to be iron overloaded, or at least iron replete, due to the need for frequent blood transfusions related to acute crises [6,14]. It has been estimated that most patients with SCA would receive at least one transfusion in their lifetime [15]. These transfusions coupled with chronic haemolysis have resulted in iron overload in SCA patients [13,16]. As a result, iron supplementation is often discouraged and sometimes considered to be contraindicated in managing anaemia in SCA patients [13].

In West African countries, such as Nigeria, it is usual for patients with SCA, and even those with nephropathy, to be managed without iron supplementation [9]. Previous studies have yielded mixed results regarding the iron status of SCA patients. While many conclude that iron overload may be present due to repeated episodes of haemolysis, others have reported that iron deficiency may also occur, necessitating iron supplementation [18,19]. This study evaluated the range of iron status of adult SCA patients with or without nephropathy seen at a tertiary centre in Lagos, Nigeria.

## METHODS

We performed a cross-sectional study at the Sickle Cell Clinic of the Lagos University Teaching Hospital (LUTH), Idi-Araba, Lagos. LUTH is a federal government-owned, 761-bed, multidisciplinary, tertiary healthcare institution located in the Southwest area of Nigeria [20]. It functions as a referral centre for patients from Lagos and the neighbouring states [20]. The hospital runs two sickle cell clinics – a paediatric clinic, which is run by the paediatric haematology unit, and an adult clinic for patients aged 18 years and older, run by the Department of Medicine's Clinical Haematology/Haemato-Oncology unit. The latter was used for this study, which was conducted over six months between August 2015 and March 2016.

Study participants were previously diagnosed SCA patients aged between 18 and 65 years, diagnosed by haemoglobin electrophoresis. All stable SCA patients attending the adult sickle cell clinic were eligible for inclusion. Before obtaining consent, information was provided to each participant (verbally and written) about the nature of the study, its objectives, potential benefits and risks, as well as the voluntary nature of participation. After gaining informed consent to participate, patients were screened for SCN. Participants were recruited using a consecutive sampling method until the minimum sample size was reached. A minimum sample size of 111 was calculated using the Cochrane formula for prevalence studies and the prevalence from a similar study conducted in adults with SCA in Lagos [21,22]. Participants were excluded from the study if there was a history of transfusion within three months of data collection. Other exclusion criteria included a potential subject having had a sickle cell crisis within four weeks of data collection and the presence of diabetes mellitus, HIV, hepatitis B and C, or urinary tract infections. These patients were excluded to minimise the confounding effects of the comorbidities on the iron indices. Patients with SCA who were pregnant and those on iron therapy or erythropoietin therapy for any reason were also excluded to reduce the effect of confounding the iron indices. Patients with SCA but without evidence of nephropathy were recruited as controls.

Data were collected using a pre-designed and pre-tested data collection tool. SCN was defined as an eGFR <60 mL/min/1.73 $m^2$ (CKD-Epidemiological formula without correction for ethnicity) and/or spot urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g [23]. Iron indices

[serum ferritin, serum iron, and total iron-binding capacity (TIBC)] were determined for all participants. Serum ferritin was measured using ELISA-based kits (analytical sensitivity of 10 ng/mL) manufactured by Calbiotech Inc., USA. Serum iron was measured using an Automated Colorimetric Method with a Fortress Kit, using ferozoin as a chromogen and running on a Hitachi 902 auto analyser. The test kit had linearity of up to 125 µmol/L (698 µg/dL) and a sensitivity of 0.9 µmol/L (5 µg/dL).

TIBC direct was run by an immunoturbidimetric method with the Fortress kit on the Hitachi 902 auto analyser. The linear measurement range for this kit is 40–700 µg/dL. Percentage transferrin saturation was calculated from the serum iron and the TIBC [transferrin saturation (TSAT) (%) = (serum iron/TIBC) x 100]. In addition, haemoglobin, red cell indices, serum albumin and C-reactive protein (CRP) levels were also tested. A CRP level of <5 mg/L was regarded as normal and ≥5 mg/L as elevated [24]. All laboratory investigations were conducted at the APIN central research laboratory, LUTH.

### Statistical analysis

The data obtained were expressed as means and standard deviations, medians and interquartile ranges, and counts and percentages where appropriate. The statistical significance of observed differences between the groups of categorical variables was estimated using the chi-squared test or Fisher's exact test. Student's t-test was used for continuous variables that were normally distributed, and the Mann–Whitney U test was used when data were skewed. A P value of <0.05 was regarded as statistically significant, and 95% confidence intervals were used. Statistical Package for Social Sciences (SPSS) version 23 was used for statistical analysis.

### Ethical considerations

Ethical clearance was obtained from the LUTH Health Research Ethics Committee (HREC No.: ADM/DCST/HREC/1767).

## RESULTS

A total of 119 SCA patients with nephropathy and 81 SCA patients without nephropathy were included in the study. Of the 119 patients with SCN, 107 had UACR of ≥30 mg/g with a preserved eGFR ≥60 mL/min/1.73 $m^2$, whereas the remaining 12 patients had both a UACR ≥30 mg/g and an eGFR <60 mL/min/1.73 $m^2$.

Most participants with SCN and controls were in their third or fourth decade of life. The median age for participants with, versus without, SCN was 26 years (IQR 21–35 years) and 25 years (IQR 20–31 years), respectively (P = 0.18). Participants in both groups were predominantly female (60.5% vs 63.0%, respectively).

Most of the subjects (52%) reported no crises necessitating hospital admission in the previous two years, 29% reported one crisis per year, 7% reported two crises annually, and 13% reported three or more crises per year. Only four participants in the entire cohort reported hydroxyurea use. Regardless of nephropathy, about one-third of participants reported that they had never been transfused (Table 1).

**Table 1.** Sociodemographic, clinical and anthropometric characteristics of study participants.

| Variable | Patients with SCN (n = 119) | Patients without SCN (n = 81) | P value |
|---|---|---|---|
| Age (years), median (IQR) | 26 (21–35) | 25 (20–31) | 0.18[a] |
| Female, n (%) | 72 (60.5) | 51 (63.0) | 0.84[b] |
| Crises per year, median (IQR) | 0 (0–1) | 0 (0–1) | 0.50[a] |
| Total lifetime transfusions | | | 0.05[a] |
| Never transfused, n (%) | 39 (32.8) | 28 (34.6) | |
| Transfused <20 units, n (%) | 75 (63.0) | 53 (65.4) | |
| Transfused ≥20 units, n (%) | 5 (4.2) | 0 (0.0) | |
| Weight (kg), mean ± SD | 53.3 ± 8.5 | 52.6 ± 8.6 | 0.60[d] |
| Height (m), mean ± SD | 1.6 ± 0.1 | 1.6 ± 0.1 | 0.11[d] |
| BMI (kg/m2), mean ± SD | 19.2 ± 2.5 | 19.5 ± 2.8 | 0.53[d] |
| SBP (mmHg), mean ± SD | 111.0 ± 11.9 | 108.0 ± 12.0 | 0.52[d] |
| DBP (mmHg), mean ± SD | 67.0 ±7.8 | 66.0 ± 0.94 | 0.36[d] |

Abbreviations: BMI, body mass index; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; [a]Mann–Whitney U test; [b]chi-squared test; [c]Fisher's exact test; [d]Student's t-test.

Seventy-four subjects (62%) had normal iron status (serum ferritin 100–800 ng/mL and TSAT 20–50%) and nine subjects (8%) had elevated iron stores (serum ferritin >800 ng/mL or TSAT >50%). In the control group, 51 (63%) had normal iron status whereas 12 (15%) had elevated iron stores.

The median serum ferritin of participants with SCN was higher than in controls; however, this difference was not statistically significant (Figure 1). Conversely, the mean TSAT levels were lower in participants with SCN than in controls (Figure 2). There were also no statistically significant differences in the other iron or red cell indices between participants with or without SCN (Table 2).

Thirty-one participants with SCN (26%) had low serum ferritin values (<100 ng/mL), 79 (66%) had normal serum ferritin with values between 100–800ng/mL, and 9 (8%) subjects had high serum ferritin with values >800 ng/mL. A similar pattern of distribution was noted among participants without SCN (Table 2). There was no statistical difference in mean TSAT values between patients with and without SCN.

As shown in Table 3, male participants with SCN had lower serum ferritin and a lower TSAT compared to females with SCN; this pattern was also seen in the controls. However, these differences in ferritin in both groups were not statistically significant. Male participants without SCN had significantly lower TSAT levels than female participants without SCN (P = 0.03). The red cell indices were not different among the male and female subjects with SCN; however, the mean cell volume and mean corpuscular haemoglobin were significantly less in males than females in the control group.

## DISCUSSION

We found no statistically significant difference in the iron status in patients with SCA with or without nephropathy. Additionally, only about 10% of participants in both categories were noted to have elevated iron stores. This finding challenges the commonly believed assumption of iron overload in patients with SCA [25], supporting the need for routine iron status testing to guide iron administration, as is recommended for other CKD patients, rather than the general avoidance of iron therapy in patients with SCA, as is common practice [3,13].

Although not statistically significant, the current study highlighted male participants with or without SCN had lower mean ferritin and TSAT levels than females. In healthy individuals, the inverse is usually reported and this is attributed to iron losses from menstrual bleeding and increased requirements during pregnancy [26]. Therefore, it was surprising to note that in this cohort, regardless of the presence or absence of SCN, iron indices were lower in males, though this difference was not statistically significant. This difference may be because males with SCA have more severe intravascular haemolysis, resulting in increased urinary iron losses compared to females [12,27]. It was not surprising that even among male participants, those with SCN in this study had lower iron indices than controls. This may be attributable to factors such as impaired iron absorption and chronic inflammation seen in patients with CKD, regardless of the cause [28].

It is noteworthy that the transfusion burden was generally low in the current study. Thus, the finding that a significant proportion of the population were iron deficient is in keeping with reports that SCA patients who have not received many blood transfusions tend to be iron deficient [12]. Additionally, the low transfusion burden seen in

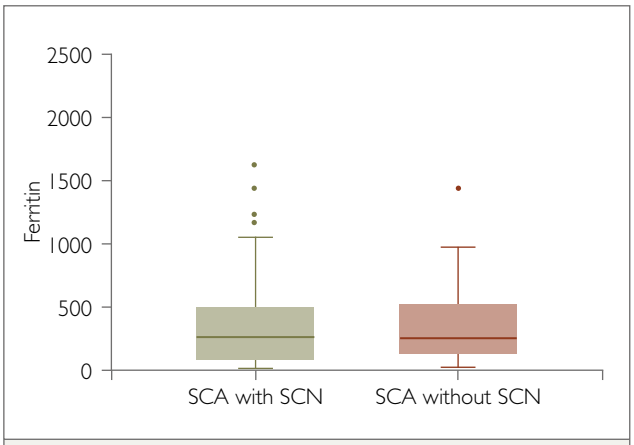


**Figure 1.** Serum ferritin (ng/mL) in sickle cell anaemia patients with or without nephropathy.
Abbreviations: SCA, sickle cell anaemia; SCN, sickle cell nephropathy.

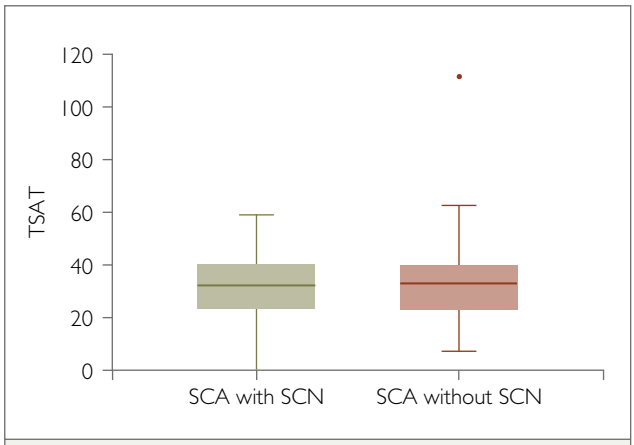


**Figure 2.** Comparison of percentage transferrin saturation in sickle cell anaemia patients with or without nephropathy.
Abbreviations: SCA, sickle cell anaemia; SCN, sickle cell nephropathy; TSAT, percentage transferrin saturation.

**Table 2.** Comparison of iron and red cell indices in study participants.

| Variable | Patients with SCN (n = 119) | Patients without SCN (n = 81) | P value |
|---|---|---|---|
| **Iron indices** | | | |
| Ferritin (ng/mL), median (IQR) | 265 (94.5–496.9) | 255 (134.5–468.9) | 0.07[a] |
| <100 | 31 (26%) | 16 (20%) | |
| 100–800 | 79 (66%) | 57 (70%) | 0.60[c] |
| >800 | 9 (8%) | 8 (10%) | |
| Serum iron (µg/dL), mean ± SD | 109.0 ± 39.2 | 113.4 ± 47.4 | 0.53[b] |
| TIBC (µg/dL), mean ± SD | 341.6 ± 68.0 | 339 ± 54.6 | 0.80[b] |
| TSAT (%), mean ± SD | 31.8 ± 10.7 | 33.5 ± 14.0 | 0.36[b] |
| <20 | 21 (18%) | 10 (12%) | |
| 20–50 | 95 (80%) | 66 (82%) | 0.29[c] |
| >50 | 3 (2.5%) | 5 (6%) | |
| **Red cell indices** | | | |
| Hb (g/dL), mean ± SD | 8.3 ± 2.9 | 8.7 ± 1.6 | 0.28[b] |
| MCV (fL), mean ± SD | 91.7 ± 10.1 | 91.1 ± 10.9 | 0.72[b] |
| MCH (pg), mean ± SD | 30.6 ± 4.3 | 30.3 ± 4.2 | 0.99[b] |
| MCHC (pg), mean ± SD | 32.9 ± 3.1 | 33.4 ± 1.4 | 0.18[b] |
| **Renal function** | | | |
| UACR (mg/g), median (IQR) | 97.5 (53.5 –157.5) | 13.9 (7.7–21.1) | <0.001[a] |
| Serum Cr (µmol/L), median (IQR) | 55.8 (44.5–70.4) | 53.2 (45.4–63.9) | 0.28[a] |
| eGFR (mL/min/1.73 $m^2$), median (IQR) | 128.0 (101.0–143.0) | 129.0 (113.0–146.0) | 0.32[a] |
| Serum albumin (g/L), mean ± SD | 42.6 ± 4.5 | 42.9 ± 3.4 | 0.59[b] |
| Other laboratory findings | | | |
| CRP (mg/L), median (IQR) | 3.9 (1.8–7.5) | 3.6 (2.2–7.8) | 0.81[a] |

Abbreviations: IQR, interquartile range; SD, standard deviation; TIBC, total iron-binding capacity; TSAT, percentage transferrin saturation; Hb, haemoglobin concentration; MCV, mean cell volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; CRP, C-reactive protein; UACR, urine albumin-to-creatinine ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; [a]Mann–Whitney U test; [b]Student's t-test; [c]chi-squared test.

**Table 3.** Comparison of iron and red cells indices by gender.

| Variable | Patients with SCN | | P value | Patients without SCN | | P value |
|---|---|---|---|---|---|---|
| | Male | Female | | Male | Female | |
| Ferritin (ng/mL), median (IQR) | 253.9 (66.5–452.8) | 299.7 (133.6–536.1) | 0.21 | 189.4 (78.6–397.5) | 286.8 (174.8-573.0) | 0.11[a] |
| Serum iron (µg/dL), mean ± SD | 103.6 ± 40.9 | 113.0 ± 37.8 | 0.19 | 100.6 ± 43.5 | 121.1 ± 48.4 | 0.06[b] |
| TIBC (µg/dL), mean ± SD | 349 ± 67.3 | 336.0 ± 68.7 | 0.33 | 339.8 ± 53.2 | 338.9 ± 55.9 | 0.94[b] |
| TSAT (%), mean ± SD | 29.7 ± 10.6 | 33.3 ± 10.6 | 0.07 | 28.8 ± 11.5 | 36.2 ± 15.0 | 0.03[b] |
| Hb (g/dL), mean ± SD | 8.8 ± 4.2 | 7.9 ± 1.4 | 0.10 | 9.0 ± 2.0 | 8.5 ± 1.2 | 0.25[b] |
| MCV (fL), mean ± SD | 91 ± 10.1 | 92.0 ± 10.2 | 0.58 | 87.3 ± 11 | 93.4 ± 10.1 | 0.02[b] |
| MCH (pg), mean ± SD | 30 ± 4.7 | 31.0 ± 4.1 | 0.70 | 29.0 ± 4.1 | 31.0 ± 4.1 | 0.04[b] |
| MCHC (pg), mean ± SD | 32 ± 4.5 | 33.0 ±1.5 | 0.13 | 33.3 ± 1.8 | 33.5 ± 1.1 | 0.06[b] |
| Serum albumin (g/L), mean ± SD | 41.6 ± 5.6 | 43.2 ±3.5 | 0.08 | 42 ± 3.0 | 43.0 ± 3.6 | 0.10[b] |
| eGFR (mL/min/1.73 $m^2$), median (IQR) | 131.0 (109.0–159.0) | 123.0 (75.0–141.0) | 0.049 | 134 (115.0–165.0) | 126.0 (107.0–143.0) | 0.01[a] |
| CRP (mg/L), median (IQR) | 5.2 (2.3–9.7) | 3.3 (1.7–6.1) | 0.03 | 4.5 (2.0–7.8) | 3.5 (2.4–7.1) | 0.93[a] |

Abbreviations: IQR, interquartile range; SD, standard deviation; TIBC, total iron-binding capacity; TSAT, percentage transferrin saturation; Hb, haemoglobin concentration; MCV, mean cell volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; CRP, C-reactive protein; [a]Mann–Whitney U test; [b]Student's t-test.

this population is probably a reflection of the care provided as well as the exclusion of patients that required blood transfusions in the three months prior to data collection. Akinyanju et al. have previously shown that improved holistic care is associated with better health status, including a reduction in transfusion frequency among SCA patients [7]. This reduced need for transfusion is further reflected in the self-reporting of hydroxyurea use in only four of 200 patients with SCA recruited for this study, as this may be a pointer to disease severity. This low transfusion rate could be potentially responsible for the low prevalence of iron overload recorded for participants in this study. Previous studies have reported that cumulative red cell transfusions of <20 units over a patient's lifetime is infrequently associated with iron overload [29]. This may imply that some patients with SCN require iron supplementation according to the KDIGO guidelines. This was corroborated by other studies that suggested that anaemia treatment should individualized, depending on the underlying CKD aetiology [30,31].

As more patients with SCA develop CKD, more attention will need to be paid to managing their anaemia. Though the current study revealed that only a small proportion of patients with SCA had elevated iron indices (contrary to the common assumption), care must still be taken to guide iron therapy and avoid iron overload. This is even more important in low- and middle-income countries such as Nigeria, where there is a propensity to generalise care due to resource constraints with diagnostic evaluations and treatment options. It is hoped that this study's findings can prompt subsequent in-depth studies into optimal management of anaemia in patients with SCN, to ensure improved outcomes.

The study has some limitations. The presence of nephropathy was assessed on single testing. Since we excluded patients with intercurrent illness or sickling crisis in the four weeks before data collection as well as anyone requiring blood transfusions within the three months of data collection, patients with more severe disease may have been excluded. The study participants therefore represent a cohort of more-stable patients who had near-normal kidney function, limiting the generalisability of our findings. Finally, the study population's transfusion history was based solely on patient recall; for this reason, responses could have been influenced by recall bias.

## CONCLUSIONS

This study showed no statistically significant differences in iron status in participants with or without SCN. Additionally, iron indices were normal in two-thirds of adults with SCN. For such reasons, there is a need for individualised evaluation of iron indices in patients with SCA, especially when they have SCN, to determine the need for iron supplementation, with or without transfusion, to ensure optimal care and consequent reduction in morbidity and mortality in this population.


### Acknowledgment

None


### Conflicts of Interests

None

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