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URIC ACID: A BIOMARKER FOR VASO-OCCLUSIVE CRISIS IN SICKLE CELL ANAEMIC CHILDREN?

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ABSTRACT

Background: Sickle cell anaemia (SCA) is a genetic disorder that affects about 2-3% of the Nigerian population with an alarmingly high mortality rate in children. Uric acid, an oxidative stress and inflammation biomarker, has been implicated in complications arising in SCA during crises and steady states.
Aim: This study aimed to investigate and compare uric acid levels, along with other biochemical and haematological parameters, in children with sickle cell anaemia during crisis and steady states.
Methods: One hundred and fifty (150) children aged 2-18 years were recruited from the sickle cell clinic at Specialist Hospital, Sokoto, comprising 50 children in crisis, 50 in a steady state, and 50 apparently healthy controls. Five millimeters of blood samples were collected from the subjects to assess biochemical (uric acid, urea, creatinine), electrolytes and haematological parameters using standard techniques. Uric acid levels were measured using the uricase method, while urea and creatinine were analysed using the diacetyl monoxime and Jaffe's method, respectively. Electrolytes (Na^+, K^+, Cl^- and HCO_3^-) were analysed using an ion-selective electrode machine, and haematological parameters (haematocrit, white blood cell count, platelet count) were measured using a Sysmex haematology analyser.
Results: There was no statistically significant difference in uric acid levels between SCA children during crisis and steady states compared to the control group ($p>0.05$). There were significant differences ($p<0.05$) in urea, creatinine, sodium, and potassium levels, but the values were all within reference ranges. Haematological parameters also showed significant differences, with lower haematocrit and higher white blood cell counts during the crisis state ($p<0.05$).
Conclusion: This study found that uric acid levels do not significantly differ during crisis and steady states in SCA children, hence cannot serve as a biomarker in sickle cell children during vaso-occlusive crisis.
Keywords: Sickle cell anaemia, uric acid, steady and crisis states, kidney function profile, haematological parameters.

INTRODUCTION

Sickle cell anaemia (SCA) is a genetic disorder caused by the substitution of a single nucleotide, GTG for GAG, at the sixth codon of the β-globin gene on chromosome 11 [1]. Sickle cell anaemia (SCA) is one of the most common genetic disorders globally, affecting millions of individuals and leading to significant morbidity and mortality. An estimated 300,000 children are born annually with sickle cell disease (SCD) worldwide, predominantly in sub-Saharan Africa, but also

in regions such as the Middle East, India, and the Mediterranean, as well as among populations in Europe and the Americas due to migration patterns [2, 3]. This global burden is compounded by significant healthcare challenges, including inadequate early detection and limited access to effective treatment, particularly in low-income regions [2]. Nigeria bears the largest burden of SCD globally, with an estimated 150,000 children born annually with the condition, accounting for nearly half of the global cases [3]. Despite considerable advancements in SCD research and treatment globally, Nigeria continues to face high rates of complications and mortality due to a lack of healthcare infrastructure and genetic screening programs [4]. Therefore, addressing SCA in Nigeria not only highlights a critical local health issue but also reflects broader global healthcare disparities in managing genetic diseases. Under low oxygen conditions, HbS polymerizes and causes the red blood cells (RBCs) to assume sickle shapes. This process is integral to the pathophysiology of SCA in that the repeated deformation of RBCs reduces flexibility and mechanical stability [1]. The sickled cells have the potential to obstruct small-sized blood vessels, a process implicated in recurrent vaso-occlusive crises (VOCs) and many chronic complications in SCA patients. VOCs are the most common acute complication of SCA, which occurs when the sickled erythrocytes block the blood vessels, resulting in ischemia of the tissues or organs that the vessels supply [1, 5]. The chronic organ damage over time, resulting from this cycle of haemolysis and vascular occlusion, contributes much to the morbidity and mortality associated with the disease [6]. Pain, a hallmark of SCA, is often episodic and unpredictable, and its intensity usually leads to hospitalizations, particularly during VOCs. The pain in this condition arises from the obstruction of the microcirculation brought about by sickled red blood cells. This factor precipitates into ischemia, necrosis, and ultimately leads to tissue and organ damage [7].

Uric acid, considered a product of purine metabolism, has emerged in recent years as a biomarker of oxidative stress and inflammation, both being significant contributors to SCA pathophysiology [8]. Besides haemoglobin abnormalities, the participation of oxidative stress and inflammation in the pathophysiology of SCA is a focus of current research on SCA [9]. Whereas one-third is excreted through the skin, nails, hair, saliva, and GIT, two-thirds of uric acid is excreted through the kidneys [10]. Elevated uric acid levels are commonly observed in conditions associated with increased cellular turnover, haemolysis, and tissue damage, as seen in SCA [9]. During VOCs, oxidative stress and inflammation are increased, which may further elevate the level of serum uric acid. This relationship between uric acid and VOCs may have greater relevance in SCA, where a higher breakdown of RBCs and ischaemic injury of tissues might give an additional contribution to the rise in uric acid levels [11]. Some studies have examined serum uric acid levels in individuals with SCA, particularly comparing levels during VOCs and steady states. Some of such studies suggested that uric acid levels might be higher during crisis periods, and may be associated with increased haemolysis and oxidative stress. Uche et al. [12] and Abiola & Atinuke [8] found higher levels of serum uric acid in Nigerian children with SCA during crisis states than in steady states. Similar observations have been reported by al-Naama et al. [13] among Iraqi children and Khalid et al. [14] in Western Sudan, which linked the increase in uric acid during crises to heightened purine catabolism. This also points to uric acid as a possible biomarker for disease severity and inflammatory activity in patients with SCA. However, studies such as those by Pandey et al. [15] among the Indian population and Nduka et al. [16] among the Saudi population have yielded conflicting results, with no significant differences in mean uric acid levels observed between crisis and steady states in certain populations. This disparity outlines the need for further research that is context-specific to decipher these findings. In addition to uric acid, haematological parameters such as haematocrit, platelet count, and total and differential white blood cell (WBC) counts, are critical in assessing the disease's severity and the body's response to inflammation [17]. In SCA patients, the haematocrit is usually low due to chronic haemolysis, while the WBC count is high, being a marker of systemic inflammatory response [18]. Platelet counts may fluctuate with thrombocytosis often during steady states and thrombocytopenia during crises, due

to increased consumption of the platelets in response to vascular injury [18]. Monitoring these parameters alongside uric acid could provide a more comprehensive picture of disease progression and management. This, therefore, calls for a study that assesses and compares uric acid and key haematological parameters of normal children with those of children with SCA during VOCs and steady states. By exploring these differences, this study seeks to provide valuable insights into the potential role of uric acid as a biomarker of disease severity and contribute to more effective disease monitoring and management strategies in this population.

MATERIALS AND METHODS

Study Design

This was a case-control study designed to determine the uric acid levels of 150 children aged 2 to 18 years attending the Specialist Hospital Sokoto. The participants were recruited from the Sickle Cell Clinic and classified into three groups: (1) Group A consisted of 50 children with sickle cell anaemia (SCA) in crisis state, (2) Group B comprised 50 children with SCA in steady state, and (3) Group C included 50 apparently healthy children with haemoglobin type AA or AS, who served as the control group. Hyperhaemolysis patients were excluded from the study.

Ethical approval

Ethical approval was obtained from the Health Research Ethics Committee of Specialist Hospital, Sokoto. The ethical approval number is SHS/SUB/133/VOL.1

Sample Collection

Five millimetres of venous blood sample was collected using a needle and syringe. About 2.5mL was dispensed into plain tubes for the estimation of uric acid, electrolytes, urea, and creatinine, and the remaining 2.5mL was dispensed into ethylene diamine tetraacetic acid (EDTA) container for full blood count (FBC) determination. The blood samples collected in the plain tubes were allowed to clot at room temperature and then centrifuged at 4000 rpm for 5 minutes to obtain a clear serum sample. The separated serum was transferred into a labelled sterile cryovial and then stored at -20^{o}C until the biochemical parameters were analysed. The EDTA sample was processed on the day of sample collection and used to analyse the haematological parameters.

Analytical Procedures

Serum uric acid was estimated using the Praetorius Method [21], urea by Wybenga Method [22], creatinine using Jaffe's Method [23], and electrolytes (sodium, potassium chloride, and bicarbonate) were estimated using the Genrui Electrolyte analyzer (GE200 Model) Ion Selective Electrode method [27]. Full Blood Count was carried out using the Sysmex analyzer (XS 1000i model) method by Coulter [25].

Data analysis

Data were analysed using the statistical software GraphPad Prism Version 7.0 (GraphPad Software Inc., San Diego, CA, USA) and expressed as mean ± standard deviation. A one-way analysis of variance (ANOVA) was used to determine the differences between the groups, followed by a Bonferroni *post hoc test*

RESULT

Demographic Data

Figure 1 shows the sex distribution of the study subjects. A total of 81 which represents 54% of the subjects were females, while 69 representing 46% of the subjects were males.

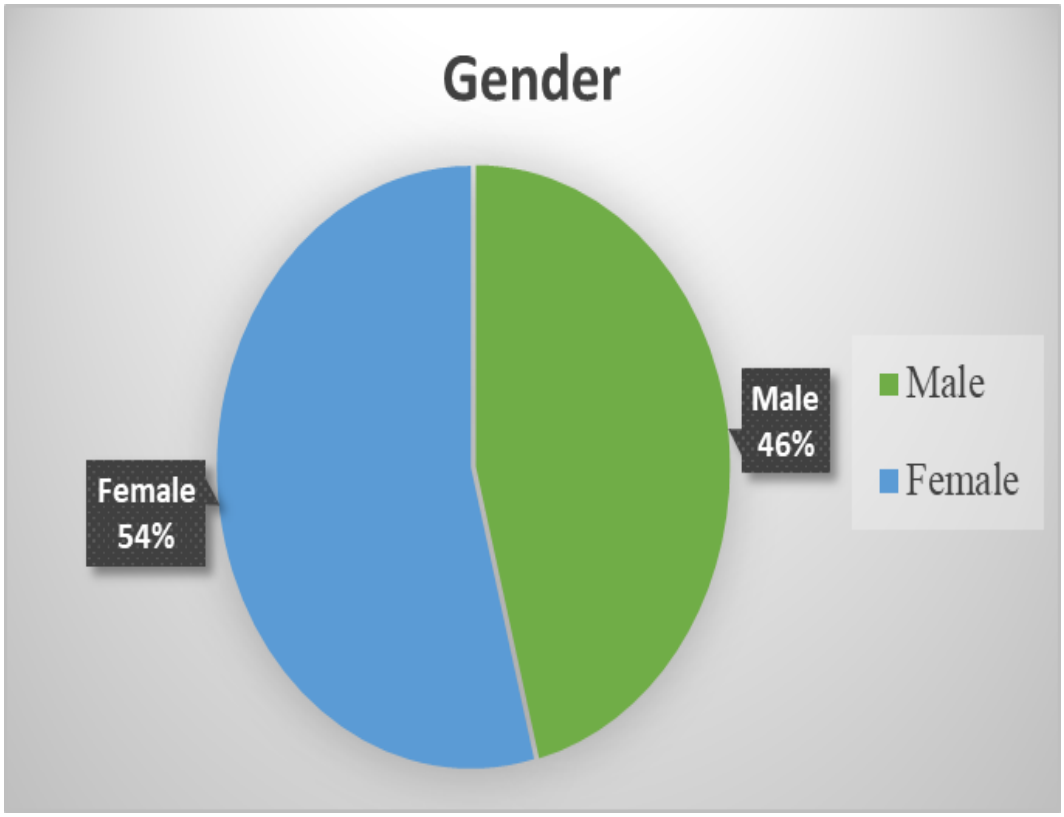

Figure 1: Sex distribution of the study subjects

Serum Concentration of Urea and Uric Acid in Sickle Cell Anaemic Children in Crisis and Steady States

Table 1 shows urea and uric acid serum concentrations in sickle cell anaemia children in crisis state, steady state, and controls.

The mean plasma urea concentration was significantly higher in the steady-state group (4.69±0.29 mMol/L) and the crisis group (4.04±0.15 mMol/L) compared to the control group (3.78 ±0.14 mMol/L), with p-values of 0.004 and 0.006, respectively. However, there was no significant difference in the plasma uric acid levels between the control (3.51 ± 0.20 mg/dL) and steady-state group (3.49 ± 0.36 mg/dL), though the crisis group had a slightly lower uric acid concentration (2.96±0.22 mg/dL) than controls (p=0.065). Creatinine levels were significantly reduced in both the steady-state group (0.74±0.05 mg/dL) and crisis group (0.52±0.04 mg/dL) compared to controls (1.02±0.06 mg/dL), p=0.001. All values showed significantly increased differences between the steady-state and crisis groups.

Table 1: Plasma uric acid concentration and creatinine in sickle cell anaemia children in crisis (C) and steady state (B) and Controls (A)

Parameter	Control (A)	Steady (B)	Crisis (C)	A vs B	A vs C	B vs C
Urea (2.5-6.5mMol/L)	3.78 ±0.14	4.69±0.29	4.04±0.15	0.004	0.006*	0.001*
Uric acid (3.0-7.0 mg/dL)	3.51 ± 0.20	3.49 ± 0.36	2.96±0.22	0.944	0.065	0.001*
Creatinine (0.7-1.40 mg/dL)	1.02 ± 0.06	0.74±0.05	0.52±0.04	0.001	0.001*	0.001*

N= 50, *, statistically significant at p<0.05, X, mean; SD, standard deviation.

Serum Electrolyte Levels in Sickle Cell Children in Crisis and Steady States

Table 2 shows the serum concentration of electrolytes (Na^+, K^+, Cl^- and HCO_3^-) in SCA children in crisis, steady-state and control. In terms of kidney function, the sodium levels were significantly lower in both the steady-state (140.20 ± 0.78 mMol/L) and crisis group (140.68±0.57 mMol/L) compared to the control group (142.84 ± 0.41 mMol/L), with p-values of 0.001 and 0.003, respectively (Table 2). Potassium levels were significantly elevated in both the steady-state (4.80 ± 0.21 mMol/L) and crisis (4.39±0.19 mMol/L) groups compared to controls (3.86 ± 0.04 mMol/L), with p=0.001 for both. Chloride levels were also significantly lower in the steady-state group (108.76 ± 0.85 mMol/L) compared to controls (113.08 ± 0.77 mMol/L), p=0.001, but no significant difference was found between controls and the crisis group (p=0.215). Bicarbonate levels showed no significant difference across the groups.

Table 2: Kidney function profile (electrolytes) in sickle cell anaemic children in crisis (C) and steady state (B) and control group (A)

Parameter	**Control (A)**	**Steady (B)**	**Crisis (C)**	**p-value**		
				A vs B	**A vs C**	**B vs C**
Sodium (135-149 mMol/L)	142.84 ± 0.41	140.20 ± 0.78	140.68±0.57	0.001*	0.003*	0.006*
Potassium (3.5-5.2 mMol/L)	3.86 ± 0.04	4.80 ± 0.21	4.39±0.19	0.001*	0.001*	0.001*
Chloride (96-106 mMol/L)	113.08 ± 0.77	108.76 ± 0.85	111.16±1.55	0.001*	0.215	0.001*
Bicarbonate (21-31 mMol/L)	19.14 ± 0.36	18.04 ± 0.78	18.40±0.65	0.142	0.278	0.013*

*, statistically significant at p<0.05, X, mean; SD, standard deviation.

Some Haematological Parameters in Sickle Cell Children in Crisis and Steady States

Table 3 shows some haematological parameters of SCA children in crisis and steady-state and control. The haematocrit was significantly lower in both the steady-state (21.37 ± 0.79%) and crisis (19.99±0.26%) groups compared to controls (31.51 ± 1.13%), p=0.001 for both. The white blood cell (WBC) count was

significantly elevated in both steady-state (16.00±1.09 x10⁹/L) and crisis groups (17.51±1.59 x10⁹/L) compared to controls (6.94±0.22 x10⁹/L), p=0.001 for both, indicating increased inflammation or infection in sickle cell patients. Granulocyte levels were also significantly higher in the steady-state group (56.93±2.13%) compared to controls (43.09 ± 1.31%), p=0.001, but not significantly different between controls and the crisis group (p=0.086). Lymphocyte levels were significantly elevated in the steady-state group (46.06 ± 1.31%) compared to controls (33.48 ± 1.98%), p=0.001. At the same time, platelet count was significantly higher in both the steady-state (421.36±40.13 x10⁹/L) and crisis (421.36±40.13 x10⁹/L) groups compared to controls (335.86±12.31 x10⁹/L), with p-values of 0.001 and 0.012, respectively.

Table 3: Some haematological parameters in sickle cell anaemic children in crisis (C) and steady state (B) and control group (A)

Parameter	Control (A) X±SD	Steady (B) X±SD	Crisis (C) X±SD	p-value		
				A vs B	A vs C	B vs C
Haematocrit (36.0-56.0 %)	31.51 ± 1.13	21.37 ± 0.79	19.99±0.26	0.001*	0.001*	0.013*
WBC (x10^9/L) (4.0-11.0)	6.94± 0.22	16.00±1.09	17.51±1.59	0.001*	0.001*	0.192
Granulocytes (40.0-75.0 %)	43.09 ± 1.31	56.93± 2.13	49.21±4.16	0.001*	0.086	0.012*
Lymphocytes (21.0-40.0 %)	33.48 ± 1.98	46.06 ± 1.31	39.94±4.44	0.001*	0.099	0.033*
Platelets (93-450 x10^9/L)	335.86±12.31	421.36±40.13	421.36±40.13	0.001*	0.012*	1.00

*, statistically significant at p X, mean; SD, standard deviation.

DISCUSSION

The results from this study provide important information on uric acid and haematological parameters in sickle cell children under steady and crisis states, drawing a comparison with a healthy control group. High mean plasma urea concentrations were observed both in the steady state and the crisis group, as compared to the control group, but within the reference range, hence our finding may not suggest an impaired renal function in these patients but may be due to other factors such as increased protein catabolism, dehydration etc. This elevation in urea contrasts with the findings of Abiola and Atinuke (8). However, it mirrors the findings of Uche et al (12) in Enugu state, Nigeria, and Airhomwanbor (2018) in Edo state, Nigeria, that highlight the propensity for renal impairment in sickle cell patients due to recurrent ischemic damage to renal tissues and glomeruli, resulting from the sickling of the erythrocyte. Urea, being a by-product of protein metabolism, reflects reduced renal clearance and its elevation supports the view that sickle cell patients experience subclinical kidney dysfunction, even in the absence of overt nephropathy (8). In contrast, plasma uric acid concentrations did not significantly differ between the steady-state group and the control group, suggesting that steady-state sickle cell patients maintain adequate uric acid excretion. While in the crisis group, the mean uric acid was lower; this difference was not significant. This finding is inconsistent with that of Nduka et al. (16), which found uric acid in a higher concentration in sickle cell patients when in crisis. This may be explained by the difference in the selection of patients and exclusion of hyperhaemolysis in this current study since it is known that hyperhaemolysis increases uric acid due to an increased cell turnover. These comparable uric acid levels, therefore, suggest that vaso-occlusive crises may not be an important determinant of uric acid production in these patients with preserved renal urate clearance. Additional evidence that support our explanation that our patients may not have

impaired renal function is seen in the levels of creatinine that are significantly reduced in both the steady state and crisis groups when compared to controls in this study. While creatinine typically serves as a glomerular filtration rate (GFR) marker, its reduction in sickle cell patients may reflect low muscle mass, poor nutrition, or increased tubular secretion, as highlighted by Gupta et al. (28). This present study's finding of reduced creatinine was in contrast to reports of elevated creatinine levels in sickle cell patients during VOCs by Uche et al (12), and Abiola & Atinuke (8). Our findings in this study did not indicate kidney functions impairment, elevated urea and creatinine levels are biomarker of kidney dysfunction, which was not the case in this study. The increase or decrease in electrolyte values observed among the children in this study may not indicate electrolytes disturbance because they were all within the reference range. The sodium, chloride and bicarbonate levels were higher while potassium values were higher in the control than in the patients' group, but all within normal range, hence these findings may not be renal related.

Haematologically, the significantly lower haematocrit levels in the steady-state and crisis groups compared to controls align with the chronic anaemia characteristic of sickle cell disease. This results from the shortened life span of the erythrocytes that become sickled, exacerbated during vaso-occlusive crises by increased haemolysis. These findings are consistent with that of Nduka et al., (16) that demonstrated the link between haemolysis and anaemia severity in sickle cell disease. Additionally, the elevated white blood cell (WBC) count in both patient groups points to the chronic inflammatory state that is a hallmark of sickle cell disease. The crisis group's WBC count was slightly higher than that of the steady-state group , suggesting an acute inflammatory response during vaso-occlusion, which is in line with the study by Maitra et al., (32), indicating that WBC count is a predictor of crisis severity and frequency.

Granulocyte and lymphocyte counts were much higher in the steady-state group, perhaps reflecting a chronic inflammatory or immune response constituent in this patient population. Interestingly, platelet counts were significantly higher in both steady-state and crisis groups compared with controls. This can be a compensatory thrombocytosis in response to ongoing haemolysis and may play a role in the prothrombotic state of sickle cell patients, thus predisposing them to vaso-occlusive crises (15).

CONCLUSION

The findings of this study indicate no significant changes in uric acid level in sickle cell anaemic children in steady or in crisis states. This study demonstrates significant haematological changes both in steady state and during vaso-occlusion in children with sickle cell disease. From our findings, it can be concluded that uric acid level cannot serve as a biomarker during vaso-occlusive crisis in sickle cell children.

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Conflict of interest

The authors declare no conflict of interest.

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