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Implication of Nephropathy in Sickle Cell Anaemia

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study sought to investigate the effect of sickle cell anemia on kidney using endogenous biomarkers.
Methodology: This study is a case-control study which enrolled 60 sickle cell anemia patients (30 males and 30 females) in a stable state at the Obafemi Awolowo University Teaching Hospital in Ile-Ife, Osun State, Nigeria, as well as 60 healthy controls (30 males and 30 females). Each participant had five millilitres (5 mL) of venous blood taken and dispensed into a lithium heparin sample vial. Renal biomarkers were assessed using established procedures utilizing the blood sample. Urinalysis was also conducted for 41 sickle cell patients and 11 control subjects.
Results: According to the findings of this investigative study, renal indices, except uric acid were lower in sickle cell anemia patients than in control subjects and are related to glomerular hyperfiltration in sickle cell nephropathy. It is noteworthy that the effect of sickle cell anemia on renal parameters was stronger in male patients than in females. Furthermore, the identical plasma creatinine levels could be attributed to the sickle cell participants' similarities in muscle mass. Protein was found in the urine of 21.95% of sickle cell patients.
Conclusion: The results of this study confirmed that kidney abnormality could be implicated in sickle anemia.

Keywords: Nephropathy; sickle cell anemia; steady state; proteinuria.

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1. INTRODUCTION

Sickle cell anemia is a hereditary disorder in which the oxygen-carrying protein "hemoglobin" becomes defective. This defect makes the red blood cells sickle when exposed to a relatively deoxygenated state inside the vasculature [1]. As a result of this single action, sickle cell anemia is portrayed as a life-threatening illness and one of the most common hereditary diseases worldwide [2,3]. Sickle cell disease is more prevalent in Sub-Saharan Africa [1]. This is probably due to the rate of malaria transmission among the people in these areas. It was proposed that hemoglobinopathies, especially the mutated gene that induces sickle cells may protect against malaria's severe life-threatening effects [3-5]. Sickle cell anemia affects multiple organs and has acute and chronic consequences [6]. An example of these multiple-organ systems in the body is the kidney. The kidneys are a pair of bean-shaped organs present in all vertebrates [7]. The kidneys play a unique role in the elimination of wastes (majorly creatinine, uric acid, and urea) and extra fluids (electrolyte/acid-base balances) from the body, and deterioration in its functions is known as nephropathy [3]. Sickle cell nephropathy (SCN) is prevalent in sickle cell disease and is characterized by medullary hypoperfusion, renal vasoconstriction, and kidney and/or cortical hyperperfusion [8]. The hallmark of this disease is the presence of sickled red blood cells in the renal medullary vessels which leads to a disturbance in tubular function, glomerular filtration, blood pressure regulation, and water and electrolyte metabolism [6]. The aftermath result of sickle cell nephropathy may be a progressive end-stage kidney disease with an elevated risk of morbidity and mortality [7,9] if it is not quickly detected and properly managed. Plasma creatinine, urea, and uric acids (to a lesser extent) are part of the commonest and generally recognized parameters often used in the assessment of GFR-kidney functions and as such, their elevated level is an indicator of impaired renal function [10-13]. In this study, we evaluated the impact of sickle cell anemia on the kidney using endogenous markers such as creatinine, uric acid, and urea as well as urine parameters.

2. METHODOLOGY

2.1 Research Design

This study carried out in the Obafemi Awolowo University Teaching Hospital in Osun State, Nigeria, is a cross sectional research on adult SCA patients in the steady state. The study was authorized by the Hospital's Ethical and Scientific Committee. Adult Nigerians of both genders who volunteered and given informed written consent were used as research subjects. Patients who came to the hematology clinic were enrolled in the order in which they arrived. People without sickle cell anemia served as the control group.

The study included 60 SCA patients (30 males and 30 females) and 60 control volunteers (30 males and 30 females). Each participant had five millilitres (5 mL) of venous blood collected and distributed into a lithium heparin sample container for the measurement of liver parameters.

2.2 Inclusion Criteria for Patients

SCA patients 16 years of age and older in steady state (a period of stable clinical condition occurring at least one week before or three weeks after a VOC or three months after a haemolytic crisis requiring a blood transfusion).

2.3 Inclusion Criteria for Control Subjects

Healthy individuals with Hb A from the Ile-Ife community who were 16 years of age and older.

2.4 Exclusion Criteria for Controls

People who are taking any drugs as well as those who smoke or drink too much alcohol (14 units per week for females and 21 units per week for males) were excluded from the study.

2.5 Exclusion Criteria for Patients

- ✓ Any additional medical conditions, such as hypertension or diabetes mellitus.
- ✓ Patients with sickle cell anemia who smoke or drink excessively (14 units per week for females and 21 units per week for males). 12 pint of beer (approx. 300 mL) equals 1 unit of alcohol (8-l0 g): 25 mL distilled spirit 1 glass sherry, 1 glass wine Patients in crisis or those who have had a blood transfusion within the last three months.

2.6 Determination of Renal Indices

Creatinine concentration was determined using Jaffe reaction described by Toora and Rejagopal [14]. Urea and uric acid concentrations were

determined using a Randox Commercial Kit based on the methods of Fesus et al. [15].

2.7 Urinalysis

Urinalysis was conducted for 41 sickle cell patients and 11 Control subjects using dipsticks (Combi 9)

2.8 Statistical Analysis

The mean and standard deviation are used to express the results. One-way Analysis of Variance (ANOVA) and Tukey's test were used to determine the degree of homogeneity among the groups. P values less than 0.05 were considered statistically significant in all analyses performed with Graph Pad Prism Software Version 8.00.

3. RESULTS AND DISCUSSION

The effect of sickle cell disease on the concentrations of creatinine, uric acid and urea in both male and female patients are presented in Figs. 1- 3 respectively.

3.1 Discussion

There is a range of abnormalities that could arise in the kidney of a sickle cell patient. These abnormalities vary from hematuria, proteinuria, hypertrophy, hypertension, decreased renal blood flow, acidification defect (acidosis), and urinary concentration defect (UCD) [8,16]. Biochemical indices (such as creatinine, uric acid, and urea) are of great importance in the assessment of kidney functions and abnormalities, particularly the estimated glomerular filtration rate and tubular renal function.

Creatinine is a non-toxic metabolic waste product of creatine and creatine phosphate that is produced during muscular activity (muscle wear and tear) and excreted mainly by the kidney in healthy individuals [17]. Unlike urea which is being reabsorbed, creatinine undergoes filtration and secretion. Hence, it is a better indicator of

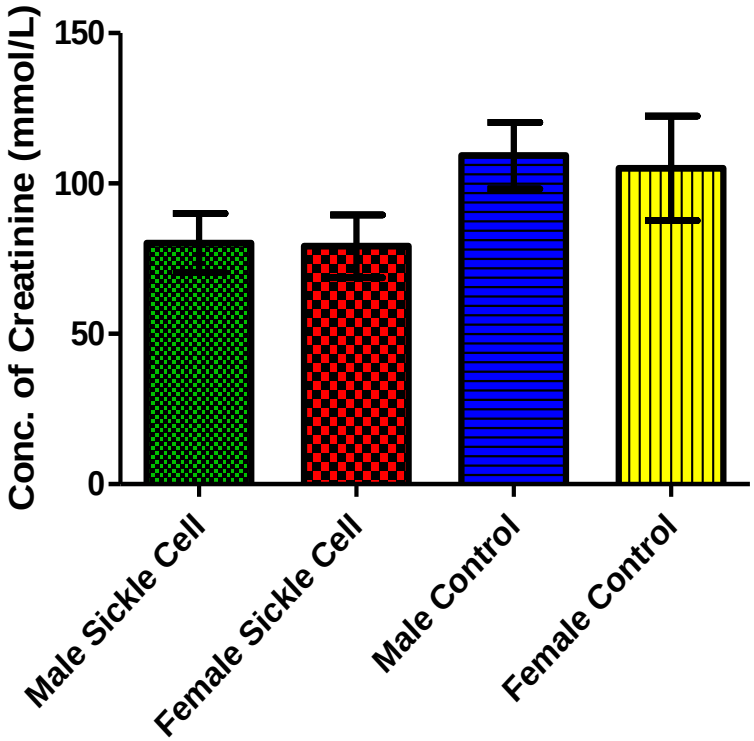

Fig. 1. Effect of sickle cell disease on the concentration of creatinine in male and female patients

Results are presented as mean ± standard deviation with n = 30

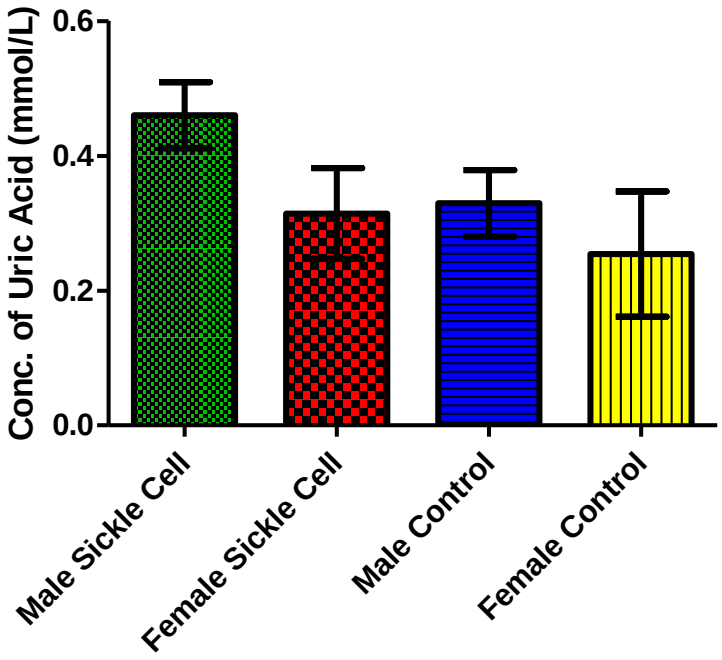

Fig. 2. Effect of sickle cell disease on the concentration of uric acid in male and female patients

Results are presented as mean ± standard deviation with n = 30

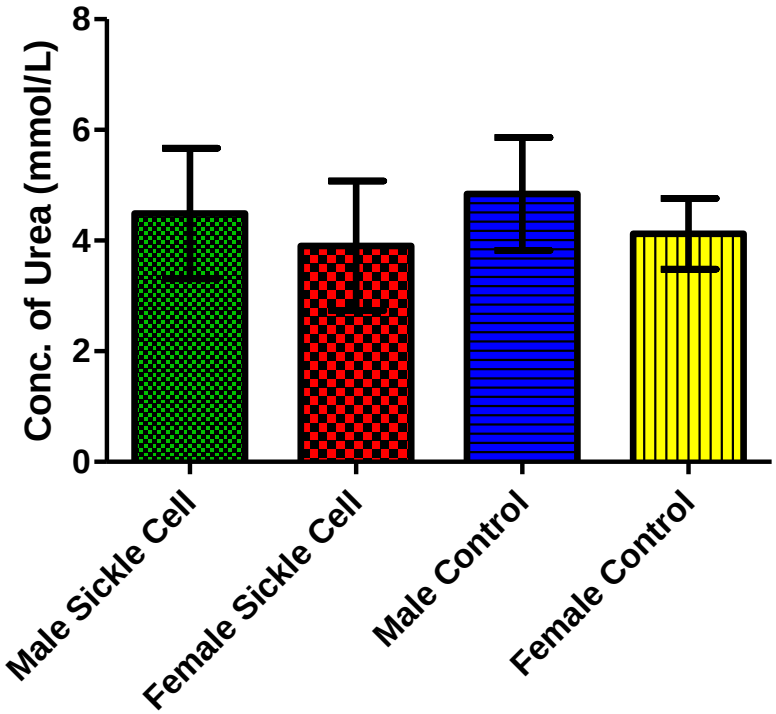

Fig. 3. Effect of sickle cell disease on the concentration of urea in male and female patients

Results are presented as mean ± standard deviation with n = 30

Table 1. Urinalysis of sickle cell patients and control subjects

Parameter	Sickle Cell Patients (n = 41)		Control Subjects (n = 11)	
	Positive	Negative	Positive	Negative
Protein	9	32	3	8
Nitrite	3	38	0	11
Blood	5	36	0	11
Bilirubin	4	37	0	11
Urobilinogen	12	29	1	10
Leukocytes	26	15	2	9

renal function and estimator of glomerular function. Urea on the other hand is a toxic end product of protein metabolism. It is partially reabsorbed by the renal tubules and could be influenced by protein diets [7,9]. Urea and uric acid undergo filtration, secretion, and reabsorption, therefore, these biomarkers are often used together with other parameters (like creatinine and inulin) to assess renal function. Uric acid is a toxic metabolic waste product of purines. Diets high in purines can influence the level of uric acid in the body [18], thus leading to hyperuricemia. Hyperuricemia can settle as crystals (urate) in the joints and then develop into painful gout. When these crystals also settle in the kidneys, they form kidney stones that lead to kidney diseases. For sickle cell individuals, hyperuricemia is linked with an increase in erythrocyte turnover [18]. Creatinine, urea, and uric acid are all nitrogenous products of protein metabolism, and their elevated levels in the body are called Azotemia [7,19].

The concentrations of plasma creatinine and uric acid were statistically significant ($p<0.05$) in patients with sickle cell disease when compared to control subjects, as shown in Figs. 1 and 2 respectively. It was speculated that a decline in glomerular filtration rate is associated with a rise in plasma urea, creatinine, and uric acid concentrations [20]. However, in this current study, we experienced an increase in the concentration of uric acids only.

There was a significant decrease in plasma creatinine concentration in both male and female sickle cell patients compared to healthy individuals with HbA. The decrease in the concentration of plasma creatinine and urea is similar to the previous reports from studies conducted in pediatrics and may be attributed to glomerular hyperfiltration [11,21]. In these studies [11,21], glomerular hyperfiltration is common and has been reported as an early manifestation (one of the pathogenic mechanisms) of renal dysfunction among sickle cell children. Another study by Scheinman [13] explained the changing profile of kidney dysfunction in sickle cell disease with respect to age and showed a higher frequency of hyperfiltration in pediatrics. However, other studies [22-24] have shown the possibility of glomerular hyperfiltration in young adult sickle cell patients. Aygun et al. [25] also claimed that the incidence of hyperfiltration increases with age and tends to decrease in the second decade of life with the progression of sickle cell nephropathy and the development of chronic kidney disease. Glomerular hyperfiltration, which is also known as glomerular hypertrophy is defined as an elevated filtration fraction above the mean GFR of healthy individuals (18.7±3.2%) and is suggested to be triggered by the secretion of both prostaglandins and nitric oxide, following an ischemia damage [26,27].

Furthermore, sickle cell patients are fond of having smaller stature compared to their healthy hemoglobin (HbA) counterparts [11,21] and the rate of creatinine production in the body daily is relatively constant and related to the body composition (muscle mass, age, and gender) [28]. This may also explain the reasons for the lower concentrations of plasma creatinine in sickle cell subjects despite being adults. Also, creatinine elimination is constant and is usually higher in males compared to females partly due to the difference in body mass [29], and the higher frequency of hyperfiltration in males [30]. However, for our study in sickle cell patients, we observed similar levels of plasma creatinine.

In this investigative study, there were no significant changes in the urea concentrations of sickle cell patients when compared to the healthy individuals with Hb A in the normal control. This is consistent with the reports of Al-Naama et al. [31]. Urea is produced by the urea cycle enzymes present in the liver [32]. A slight decrease in urea levels was observed in this study and may be correlated to liver dysfunction, hyperfiltration, and other influencing factors such

as diets and hormones. Indeed, Uche et al. [33] recently reported that sickle cell anemia contributes to liver abnormality.

The result of this present study shows a significant increase in the concentration of plasma uric acid in both male and female sickle cell patients compared to the subjects with healthy Hb A. This result is also in agreement with reports from previous studies conducted in both children and adults with SCD [21,34].

Several studies have reported and suggested SCN among pediatrics (7 months-15 years) and the need for early discovery and intervention. Only a few have reported SCN in young adults. This investigative study was conducted on teenagers and adolescents (16 years and above) to show the impact of sickle cell anemia on the kidney, hence the need for periodic renal assessments and comprehensive care.

The results of the urinalysis of this study are presented in table 1. Protein was only found in the urine of 21.95% of the sickle cell patients. Proteinuria is usually an early manifestation of sickle cell nephropathy [35]. In disease state involving the proximal tubule, there is reduced reabsorption of low molecular weight proteins, and consequently increased spillage of these proteins into the urine [36]. This increase of the urinary concentration of low molecular weight proteins is a sensitive marker of tubular dysfunction, and therefore, tubulointerstitial damage [35]. This result is similar to the findings of Nsiah et al. [37] who reported the diagnostic implications of urinalysis of subjects from a Ghanaian sickle cell clinic. It is interesting to know that patients with proteinuria also had elevated creatinine and urea levels in their blood which is an indication of nephropathy.

4. CONCLUSION

Sickle cell nephropathy (SCN) is prevalent in sickle cell anemia and it is associated with severe clinical complications. Sickle cell nephropathy, if not detected early and managed well, can progress to chronic kidney disease and perhaps increase the risk factors for morbidity and mortality. Biochemical markers such as creatinine, urea, and uric acid are of great clinical significance in the early discovery and monitoring of kidney functions and dysfunction in SCD. Further investigations are needed to ascertain the reason for the difference in urea and uric acid levels in male and female sickle cell patients.

CONSENT AND ETHICAL APPROVAL

Before being enrolled in the study, all individuals gave their informed consent. Before beginning the study, the Ethical and Research Committee of OAUTHC, Ile-Ife, was consulted and ethical approval was granted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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