Original Article

Chronic Kidney Disease amongst Sickle Cell Anaemia Patients at the University of Maiduguri Teaching Hospital, Northeastern Nigeria: A Study of Prevalence and Risk Factors

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Abstract. *Background:* Involvement of the kidneys in patients with sickle cell anaemia is a well recognised chronic complication. This study seeks to determine the prevalence of chronic kidney disease in patients with homozygous sickle cell disease (HbSS) and to identify risk factors associated with its development.

Methodology: The subjects consisted of adolescents and adults with HbSS recruited sequentially from the adult haematology outpatient clinic and Daycare ward of the unit. Clinical variables including age at diagnosis of SCA, the frequency of vaso-occlusive crisis and transfusion therapy, as well as laboratory data including haematological profile and renal function tests were obtained. The glomerular filtration rate was estimated (eGFR) using the 'modification of diet in renal disease' (MDRD) formula.

Results: Two hundred and eighty-four HbSS patients were recruited. The prevalence of CKD amongst them was 38.9%. Further stratification of the patients based on eGFR showed that sixty-nine (26.8%) had hyperfiltration; 35 (13.6%) stage 1 CKD; 53 (20.6%) stage 2 CKD; 33 (12.8%) stage 3_a CKD; 28 (10.9%) stage 3_b CKD; 30 (11.7%) stage 4 CKD and 9 (3.5%) had end stage renal disease. There was significant association between eGFR and clinical parameters such as age (r -0.353, p=0.000), SBP (r -0.148, p= 0.021), DBP (r -0.213, p=0.001) and total number of blood received (r -0.276, p=0.000); and laboratory parameters such as PCV (r 0.371, p=0.000); urea (r 0.527, p=000); creatinine (r 0.625, p=0.000) and uric acid (r -0.419, p=0.000).

Conclusions: The present study has revealed a high prevalence of CKD amongst patients with SCA in our region. Clinical and laboratory predictors of CKD using eGFR were identified to include age, SBP, number of units of blood transfusion, PCV, urea, creatinine and uric acid levels.

Keywords: Sickle cell anaemia, Kidney disease, Nigeria.

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Introduction. Homozygous sickle cell disease (HbSS) is an inherited disorder of haemoglobin resulting from single nucleotide change i.e. substitution of thymine for adenine in the sixth codon of the beta globin-chain gene, this causes coding of amino acid valine instead of glutamate in position 6 of the beta-globin chain resulting in formation of an abnormal haemoglobin termed haemoglobin S (HbS).[1] The haemoglobin S derived

from this mutation forms polymers if it undergoes deoxygenation;[2] this polymerisation is the primary though not the exclusive cause of the clinical manifestation of sickle cell anaemia (SCA).[1,2,3] The net effects of polymerized haemoglobin are membrane damage,[4] cell dehydration[5,6] and altered rheology[7] with resulting chronic haemolysis and vaso-occlusion;[8] hence the dominant clinical features of haemolytic anaemia and painful crisis. The clinical manifestation of SCA varies, ranging from mild clinical disease diagnosed incidentally to very severe debilitating disease[1]. Individuals with HbSS disease can be in relatively good health termed 'steady state' or present with acute exacerbation of symptoms termed 'crisis' or can present with chronic complications manifesting in virtually all systems in the body such as the brain, skeletal system and the kidneys.[1,3,9]

Involvement of the kidneys by sickle cell anaemia is termed sickle cell nephropathy and is a well-recognised entity in sickle cell disease.[10-15] The renal manifestations of sickle cell disease include hyposthenuria, haematuria due to papillary necrosis, proteinuria which can vary from microalbuminuria to nephrotic range, focal glomerulosclerosis that can lead to end-stage renal disease and renal medullary carcinoma.[10,13-15] Sickle cell nephropathy (SCN) progresses steadily with different manifestations in various decades of life.[10,11,14,15] This heterogeneity in presentation manifests in the first decade of life as decreased medullary blood flow, nocturia, enuresis, hyposthenuria and glomerular hyperfiltration;[11] these proceed to microscopic haematuria due to renal papillary necrosis and loss of vasa recta in the second decade of life.[11,14] The findings in patients in the third decade may include gross haematuria secondary to renal papillary necrosis, interstitial nephritis, membranoproliferative glomerulonephritis, decreased renal blood flow and glomerular filtration rate. Pyelonephritis, decreased uric acid clearance and hypertension starts from the fourth decade of life[11,14,15] with eventual progression to chronic kidney disease (CKD)/ end-stage renal disease.[14,15]

The index study is a single centre study aimed at finding the prevalence of chronic kidney disease and at identifying its risk factors among adult patients with HbSS. The previous studies[12,13] have revealed the enormous burden of CKD and SCN with varying reports of prevalence of SCN ranging from 5-18% of the total SCA population worldwide.[15,16,17,18] Studies by Arogundade[16] et al. and later by Bolarinwa et al[17] identified the risk factors and clinical course of SCN in South-Western Nigerian. But such study does not exist in our centre which may be different being located in Northeastern Nigeria, a region having one of the worst health care indices in the country[19] and peculiar geographical characteristics which have been shown to affect the morbidity of SCA,[20] which further buttress the justification for this study.

Patients and Methods. This was a single centre cross-sectional study carried out at University of Maiduguri teaching hospital, Borno state, northeastern Nigeria. The subjects consisted of adolescents and adults with SCA diagnosed using Hb electrophoresis at pH 8.6. Patients were recruited sequentially from the adult haematology outpatient clinic and Daycare ward of the unit from January 2013 to April 2018 (5 years period). Socio-demographic (age, sex), anthropometric (height, weight), systolic and diastolic blood pressure were recorded during a routine physical examination. Clinical variables including age at diagnosis of SCA, the frequency of vaso-occlusive crises, number of hospitalisations per annum and transfusion therapy were collected. Laboratory data including haematological profile, renal function test were also obtained. The glomerular filtration rate was estimated (eGFR) using the 'modification of diet in renal disease' (MDRD) formula [21]. Proteinuria was reported as trace or 1+–4+ from the dipstick. The staging of kidney disease was based on the Kidney Disease Outcome Quality Initiative (K/DOQI)[22] recommended classification system as follows: G_1: GFR >90 ml/min/1.73 m^2; G_2: GFR 60–89 ml/min/1.73 m^2; G_{3a}: GFR 45–59 ml/min/1.73 m^2; G_{3b}: GFR30-44, G_4: GFR 15–29 ml/min/1.73 m^2 , G_5: GFR <15 ml/ min/1.73 m^2 . Albuminuria level A_1: <30mg/g, A_2: 30-300mg/g, A_3: >300mg/g. Patients who have GFR <60ml/min/1.73m^2 and/or albuminuria >30mg/g are considered to have chronic kidney disease. Hyperfiltration is defined as GFR >120ml/min/1.73m^2 and albuminuria <30mg/g in females and >130ml/min/1.73m^2 and albuminuria <30mg/g in males. In the current study, CKD was classified based on EGFR only.

Statistical analysis. Data collected were transferred into Excel (Microsoft, Seattle, WA, USA) and SPSS version 20 (IB Corp. Armonk, NY, USA). Variables were log transformed where appropriate to obtain a normal distribution. The student t-test was used for continuous variables and chi-square for categorical variable for comparisons of means and proportions amongst subgroups. Associations between continuous variables were assessed using Pearson's correlation. For all analysis, a *p*-value of <0.05 was considered significant.

Results.
Clinical and laboratory parameters of study participants. Two hundred and eighty-four patients were recruited during the study period, 27 (9.5%) patients were excluded from the study due to incomplete data. There were a roughly equal number of males 129 (50.2%) and females 128 (49.8%).

Table 1. Description of the study participants.

Variables	Median or Ratio	IQR	Observations (n)
Demography			
Sex(Male/Female)	129/128		286
Age (years)	27	13	86
Age at diagnosis (months)	12	6	283
Clinical events			
VOC/ yr	2	3	241
Hospitalisation/yr	0	1	236
Total Blood transfusion	3	6	251
Anthropometrics			
Weight(kg)	44	14	253
SBP (mmHg)	110	20	265
DBP (mmHg)	70	10	265
Haematological indices			
PCV(%)	17	4	258
WBC (x 10^9/l)	9	7.9	204
Platelets (x 10^9/l)	460	260	109
Biochemical indices			
Urea (mmol/l)	5.4	2.5	259
Creatinine (μmol/l)	106	101	258
Uric acid (μmol/l)	562	373	177
eGFR (MDRD)	120	100	257
albumin (g/dl)	40	5	186
Protein (g/dl)	71	8.5	160

VOC: vaso-occlusive crisis, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PCV: packed cell volume, WBC: white blood cell count.

The clinical and laboratory parameters of the participants are shown in **Table 1.**

Prevalence and various stages of CKD. A total of 257 HbSS patients had glomerular filtration estimates available. The median serum creatinine was 106μmol/l (IQR 101) and eGFR was 120 ml/min/1.73m^2 (IQR 100) (**Table 1**). The results showed that one hundred patients (38.9%) had CKD (GFR<60ml/minute) whereas 157 (61.1%) patients had normal renal parameters. Further stratification of subjects based on eGFR showed that sixty-nine (26.8%) had hyperfiltration and 9 (3.5%) had end-stage renal disease (**Table 2**). The prevalence of CKD was slightly higher amongst the male patients (55%) compared to the female population (45%)

Table 2. Prevalence of the various stages of chronic kidney disease amongst the study participants**.**

Stage	No (%)
G_1	104 (40.5)
G_2	53 (20.6)
G_{3a}	33 (12.8)
G_{3b}	28 (10.9)
G_4	30 (11.7)
G_5	9 (3.5)

Association of clinical and laboratory parameters amongst patients with and without CKD. Patients with CKD were found to be older than patients with normal kidney function (p=0.000). There was no gender

Table 3: Comparison between patients with CKD and those with normal kidney function

Parameter	Normal kidney function (n=157)	CKD (n=100)	P
Age(years)	22.45±5.46	26.52±6.98	0.000*
Sex			
Male	74(47.1%)	55(55%)	χ^2 =0.219**
Female	83(52.9%)	45(45%)	
Age at diagnosis (mon)	28.23±3.44	31.37±98.62	0.847
Frequency of crises (no/yr)	2.82±3.44	2.53±2.99	0.536
Admissions/year	0.90±1.47	0.75±1.01	0.425
Total blood transfused	2.61±5.47	7.91±8.68	0.000*
Weight (Kg)	45.32±10.85	45.76±9.46	0.742
SBP (mmHg)	111.51±13.15	113.95±14.74	0.179
DBP (mmHg)	64.43±10.89	67.19±12.59	0.071
WBC (x 10^9/L)	10.65±3.67	10.40±3.85	0.650
Platelets (x 10^9/L)	399.84±144.42	341.91±164.57	0.056
Urea (mmol/L)	5.79±4.33	13.45±6.35	0.000*
Creatinine (μmol/L)	85.13±26.63	273.73±184.71	0.000*
Haemturia	39%	46%	1.09***
Uric acid (mmol/L)	459.42±196.32	637.16±242.63	0.000*

*significant student t-test **chi-square *** Odds ratio. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PCV: packed cell volume, WBC: white blood cell count.

variation between patients with CKD compared with those with normal kidney function (p=0.219). Also, there was no significant difference between the age of diagnosis of SCA (p=0.847), a number of vaso-occlusive crises (p= 0.536) and the total number of admissions per annum (p=0.425) amongst patients with and without CKD. Similarly, the weight (p=0.742), SBP (p=0.179) and DBP (p=0.071) showed no comparable difference. In contrast to these clinical parameters, there was a significant difference in the median PCV (p=0.000), urea (p=0.000), creatinine (p=0.000) and uric acid (p=0.000) of patients with CKD compared to those without (**Table 3**).

Clinical and laboratory factors affecting eGFR. The eGFR was significantly and negatively associated with the median values for age (r -0.353, p=0.000), SBP (r -0.148, p= 0.021), DBP (r -0.213, p=0.001) and total number of blood units received (r -0.276, p=0.000). The median PCV (r 0.371, p=0.000), urea (r 0.527, p=000), creatinine (r 0.625, p=0.000) were all positive predictors of eGFR. There was a negative correlation between eGFR and uric acid level (r -0.419, p=0.000). There was no significant association between the eGFR and clinical parameters such as patient sex, number of vaso-occlusive crises per annum and age at diagnosis of SCA; or laboratory indices such as WBC and platelets count (**Table 4**).

Out of 257 patients studied, 85 (33.1%) had haematuria whereas 172 (66.9%) had no haematuria. Haematuria was noted in 36 (35.0%) of the patients with GFR < 60ml/min/1.73m^2 and 49 (32.0%) of those with GFR > 60ml/min/1.73m^2 (**Table 5**).

Table 4. Clinical and laboratory factors affecting eGFR

Variables	Correlation coefficient (r)	P value
Clinical parameters		
Age (years)	-0.353	0.000*
Sex	-0.109	0.081
Age at diagnosis of SCA (mon)	-0.085	0.436
Weight (kg)	-0.146	0.027*
SBP (mmHg)	-0.148	0.021*
DBP (mmHg)	-0.213	0.001*
VOC/yr	0.012	0.862
Total blood transfusion	-0.276	0.000*
Haematological parameters		
PCV (%)	0.371	0.000*
WBC (x 10^9/L)	0.006	0.931
Platelets (x 10^9/L)	0.146	0.131
Biochemical indices		
Urea (mmol/l)	0.527	0.000*
Creatinine (µmol/l)	0.625	0.000*
Uric acid (mmol/l)	-0.419	0.000*

* Significant result. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PCV: packed cell volume, WBC: white blood cell count.

Table 5. Prevalence of haematuria across the various stages of CKD.

KDIGO	Haematuria		Total
	Negative n(%)	Positive n(%)	
G$_1$	80 (76.9)	24 (23.1)	104
G$_2$	28 (52.8)	25 (47.2)	53
G$_{3a}$	23 (69.7)	10 (30.3)	33
G$_{3b}$	18 (64.3)	10 (35.7)	28
G$_4$	21(70.0)	9 (30.0)	30
G$_5$	2 (22.2)	7 (77.8)	9

Discussion. Advances in the medical care of patients with SCA has made it possible for this individual to live longer and as such, they are confronted with long-term complications of the condition such as chronic kidney disease. This study is the first in Northeastern Nigeria to determine the prevalence of CKD amongst patients with SCA and risk factors contributing to its development. The median age of the patients in this study was similar to that found in several similar studies by Arogundade et al.[16] and Bolarinwa et al.[17] in South-West Nigeria as well as Powars et al.[18] The results indicate a high prevalence of CKD (38.9%) amongst the sickle cell population. This finding is similar to that obtained in the study by Arogundade et al;[16] however, this is higher than the prevalence of CKD in the non-sickle cell population in Nigeria,[23,24] indicating an additional impact of HbSS on the prevalence of kidney disease.

The prevalence of glomerular hyperfiltration of 26.8% was comparable to the previous study by Bolarinwa from South Western Nigeria; but differ with previous occurrence rates in reports from other parts of the world.[25,26,27] Hyperfiltration is an early marker of renal dysfunction, with an increased risk of progression into CKD and ESRD.[11,28] Vazquez et al[26] have found increased levels of nephrin in the urine of HbSS patients with persistent hyperfiltration suggests that glomerular damage is caused by hyperfiltration. Future research on this group of patients could lead to the discovery of useful interventions that can prevent the progression into sickle cell nephropathy. About one-third of our patient's population belonged to the category of early stage renal disease (34% combined rates for stages 1 and 2 CKD), in contrast to 66.7%,[17] 88.8%[28] and 53%[30] rates previously observed. The British guideline on the classification of CKD recognises this group to be associated with the tendency for worsening kidney function and cardiovascular complications.[31] The K/DOQI also recognises individuals in this category of renal disease to be at risk of progressive disease.[22] The prevalence rates for stage 3 renal disease was 23.7%, in contrast, Bolarinwa et al. and Yusuf et al. reported lower rates of 2.7% and 9.5% respectively, and Aneke et al.[30] reported a higher rate of 42% from their study. Stage 3 renal disease marks a critical point in the spectrum of CKD because it represents the beginning of established

kidney disease.[22] Identifying patients in this category is important in ensuring measures can be taken to slow the progression to more advanced stages.

Furthermore, our result showed a combined prevalence rate of 15.2% for stage 4 CKD and ESRD, in contrast to previously reported rates of 1.4% and 5% from earlier studies.[29,30] However, these other studies investigated a a small number of subjects compared to our large cohort. Overall, our result shows that more than two third of our patients present with advanced stage CKD (stage 3 and above). It is possible that other yet to be identified factors may be explaining these differences, such as environmental and social factors.

The current study identified some important risk factors associated with the development of renal dysfunction. Our results replicate the previously reported positive association of eGFR with clinical parameters including age,[23,24,25] DBP[25] and total blood transfusion received;[30] and with laboratory parameters, such as haematocrit, serum levels of urea, creatinine and uric acid.[25] Recent studies by Drawz et al.[26] has shown that age is inversely related to GFR among HbSS patients. Both age and DBP have been associated as risk factors for the development of microalbuminuria, a marker of early renal impairment.[11,17] Several earlier studies have shown that anaemia correlated with GFR.[16,17,18] An elaborate study by Saraf et al[33] showed that haemoglobinuria was associated with progression of CKD in SCA. However, the index study did not assess for haemoglobinuria, but the prevalence of haematuria was assessed and noted to be more in patients with CKD. Chronic kidney disease patients have reduced response

to erythropoietin. Thus their anaemia tends to worsen with the progression of the disease process. In this study, there was a slight male preponderance among patients who developed kidney disease which is consistent with male sex being a risk factor for kidney disease and its progression.[25] However, markers of severity of sickle cell disease, such as the frequency of painful crisis and age at diagnosis of SCA were not associated with the development of renal dysfunction in contrast with previous reports.[16,17,18] It is possible that a large proportion of patients who were diagnosed early in this study may have received care that reduced their risk of developing kidney disease.

Conclusions. The present study has revealed a high prevalence of CKD amongst patients with SCA in this region (38.9%; N=257). About a quarter of these patients had hyperfiltration, while more than two-third had advanced stage CKD (stage 3 and above). Age, SBP and DBP, total blood transfusion were important clinical predictors of eGFR; while haematocrit, urea, creatinine and uric acid levels significantly predicted eGFR.

Future direction and way forward. Monitoring and detection of early stages will allow for interventions which may delay progression into advanced stages and ESRD. Further studies to correlate such parameters as following up those with hyperfiltration and also studies to elucidate yet to be identified environmental, genetic or epigenetic risk factors for CKD in SCA in our region will be pursued.

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