



Prevalence and Determinants of Microalbuminuria in Sickle Cell Disease Patients

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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

Introduction: Sickle cell disease (SCD) is a common cause of Chronic kidney disease (CKD) and microalbuminuria is a predictor of CKD.

Aims: To determine the prevalence of microalbuminuria (MA) in SCD patients as well as the clinical correlates of MA in these individuals.

Study Design: A hospital-based cross-sectional study.

Place and Duration of Study: Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State and Federal Medical Centre, Owo, Ondo State, between May 2016 to April 2017

Methodology: This cross-sectional study involved a total of 100 individuals with SCD. Blood and urine samples were obtained for haematology, chemistry and urine albumin/ creatinine ratio (UACR).

Results: All the 100 studied subjects completed the study. The SCD group comprises both HbSS (86%) and HbSC (14%) subjects. The percentage of individuals with MA in the SCD subjects was 61%. The mean age of individuals with MA was 30.5(11.3) years compared to mean age of 25.3(6.8) years in those without MA ($p=0.012$). In SCD subjects with microalbuminuria, eGFR was found to be significantly lower ($p=0.044$). The reticulocyte index, serum aspartate aminotransferase and serum albumin are the clinical correlates associated with MA in individuals with SCD.

Conclusions: MA is prevalent among subjects with SCD and should be a routine method of detecting early onset of sickle cell nephropathy.

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1. INTRODUCTION

Sickle Cell Disease (SCD) is a major genetic disease noted to be prevalent in most countries in Sub-Saharan Africa, and Nigeria has the highest number of sickle cell genes per country in the world with a prevalence rate of 20-25 [1].

Patients with SCD may develop a glomerulopathy with proteinuria and progressive renal insufficiency, which invariably leads to ESRD with the consequent need for renal replacement therapy. Glomerular disease is common in sickle cell disease and mechanisms of damage are glomerular hyperfiltration and hypertrophy occurring within the first 5 years of life [2]. Approximately 15 – 30% of patients develop proteinuria in the first three decades and about 5% progress to ESRD. The occurrence of kidney damage in SCD as typified by increasing proteinuria is seen with increasing age, frequent hemolysis, worsening bone crisis, worsening anemia and poor bone marrow response with reduced reticulocytosis. Other factors associated with kidney damage are cholelithiasis, acute chest syndrome, and stroke [3].

Microalbuminuria is an early predictor of nephropathy in SCD; it is also an early sign of progressive cardiovascular and renal disease in individuals with diabetes [4]. Kidney Disease Outcome Quality Initiative (KDOQI) guidelines recommend screening for albuminuria in patients with risk factors for chronic kidney disease, including diabetes, hypertension, systemic illnesses, age greater than 60 years, family history of chronic kidney disease (CKD), recurrent urinary tract infections, urinary obstruction, or a systemic illness that affects the kidneys [5]. Microalbuminuria as a surrogate marker of kidney damage is a useful tool in SCD and its detection and quantification assist in the early detection of nephropathy providing the platform for the institution of interventional measures, this helps in retarding the progression of renal disease. The primary aim of this study is to determine the prevalence and determinants of microalbuminuria in patients with sickle cell disease.

2. MATERIALS AND METHODS

This cross-sectional study was completed between May 2016 to April 2017 in 2 tertiary health institutions located in the South-Western

region of Nigeria. The study population included 100 individuals with SCD diagnosed by haemoglobin electrophoresis aged 18 years and above.

An interviewer-administered structured pro forma was used to document the demographic data and obtain relevant clinical information including medication use, steady-state haemoglobin levels, resting-state blood pressures (BP), frequency of vaso-occlusive pain crises (VOC), frequency of hospitalizations, and records of prior blood transfusions.

All subjects are subjected to full clinical examination using standard protocols. Brachial blood pressure measurements were taken by the auscultatory method using a standard mercury sphygmomanometer (Accoson®), London with a 16x30cm cuff size after each participant had rested for at least 5 minutes and recorded in millimeter of mercury (mmHg).

All enrolled subjects and controls were given a well-labelled universal urine bottle for collection of 10mls of early morning urine for the determination of urine albumin/ creatinine ratio (UACR).

Venous blood samples (5 milliliters) were collected in EDTA bottles after thorough cleaning of the venepuncture site with a swab soaked with 70% alcohol, from all participants and the following parameters were determined; hemoglobin genotype, stable hemoglobin levels, white blood cell count, platelet counts, reticulocytes index and the mean corpuscular volume.

Blood samples (5 milliliters) for creatinine, urea, liver enzymes, and albumin were also collected in a lithium heparin bottle. Renal function was determined using the Chronic Kidney Disease-Epidemiology survey (CKD-EPI) equation. Haematological parameters like white blood count, platelet count, hemoglobin concentration and mean corpuscular volume were analyzed using SYSMEX XS 2IN Auto-hematology Analyzer, SYSMEX DIAGNOSTIC U.S.A while serum creatinine (SCr) evaluation was done using colorimetric Jaffe's method.

Urine Albumin was determined based on a quantitative sandwich enzyme immunoassay technique, using the Assay Max Human Albumin

Elisa kit while Urine Creatinine was assayed using a commercially manufactured kit by Agappe diagnostics Switzerland. The random urine albumin and urine creatinine was converted to the albumin/creatinine ratio using this calculation;

$$\text{ACR (mg/g)} = \text{urine albumin (mg/dl)} / \text{urine creatinine (g/dl)}. \text{ Normal ACR ratio is } <30 \text{ mg/g.}$$

2.1 Statistical Analysis

Statistical Package for Social Sciences (SPSS) software, version 20.0, was used to analyze the data on a personal computer. Normally distributed numeric variables were summarized using their mean and standard deviation (Mean±SD) while for nonparametric data, the median and interquartile range was used. Frequency tables, along with the relevant proportions and charts, are used to summarize and present categorical variables.

When comparing categorical variables, the chi-square test was employed, and when comparing means, the independent student t-test. A binary logistic regression model was also used to determine further associations between continuous variables. A P-value of 0.05 was taken to be statistically significant.

3. RESULTS

A total of 100 subjects were studied. Table 1 shows the distribution of hemoglobin genotypes in the SCD group. The SCD group comprises both HbSS (86%) and HbSC (14%) subjects Fig. 1 shows the prevalence of MA among SCD subjects. The percentage of individuals with MA in the SCD subjects was 61%.

Table 2 and 3 show the comparison of different clinical parameters between the SCD groups with and without MA. When the clinical parameters were analyzed with MA status, SCD subjects with MA were significantly older than those without MA. The mean age of individuals with MA was 30.5(11.3) years compared to the mean age

of 25.3(6.8) years in those without MA (p= 0.012). There was no significant difference between the mean body mass index (BMI), body surface area (BSA), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MABP) in those with and without MA. There was no significant difference between gender, family history of hypertension, diabetes and CKD in those with or without MA in SCD subjects. The clinical history of prior hospitalizations, blood transfusions, episodes of painful crisis and hydroxyurea use was not associated with the presence of MA.

Table 4 show the comparison of laboratory parameters among SCD patients with or without MA. There was a significant difference in the mean reticulocyte index between SCD subjects with or without MA while the other hematological parameters were not. The mean reticulocyte index was significantly lower in the MA group, p - value of 0.036.

All the SCD subjects had normal sCr {61.6(27.9) µmol/l} and urea {2.8(1.3) mmol/l} values. The eGFR was also found to be supra-normal in SCD subjects, however significantly higher levels are found in SCD patients without MA, p value=0.044. Other biochemical parameters found to be significantly different in both groups were serum albumin and AST while ALT, ALP, urine osmolality and urine specific gravity did not reach statistical difference. In the subset of SCD subjects with MA, serum albumin was reduced in contrast to SCD without MA {32.8(4.8)g/l vs 35.3(5.4)g/l, p value=0.020} and AST was significantly higher in SCD with MA compared with SCD without MA{22.5(8.6)IU/L vs 17.8(7.4)IU/L, p value=0.005}.

Table 5 shows the binary logistic regression analysis of the independent determinants of MA among SCD subjects. Reticulocyte index, serum aspartate aminotransferase and serum albumin remained statistically significant. Therefore, the main determinants of MA among SCD subjects were hemolysis, hypoalbuminemia and reduced reticulocyte index.

Table 1. Distribution of hemoglobin genotype across the studied population

Genotype	SCD group N=100 N (%)	
	SS	SC
	86(86.0%)	14(14.0%)

SCD – Sickle cell disease

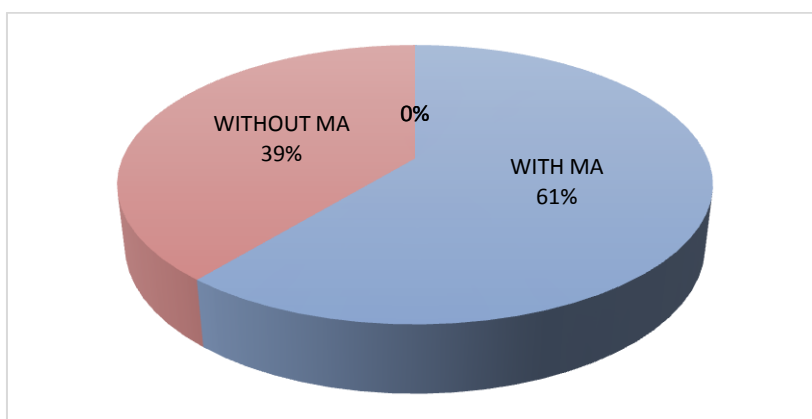


Fig. 1. Pie chart showing the prevalence of Microalbuminuria in the studied subjects

Table 2. Comparison of clinical characteristics of SCD subjects with or without MA

Clinical Characteristics	Microalbuminuria		t-test	P value
	Present $\bar{X} \pm SD$	Absent $\bar{X} \pm SD$		
Age(years)	30.5±11.3	25.3±6.8	-2.562	.012
Weight(kg)	52.8±9.9	56.0±11.9	1.375	.174
BMI (kg/m ²)	19.0±3.2	19.4±3.2	0.656	.514
BSA (m ²)	1.6±0.2	1.6±0.2	1.809	.074
SBP (mmHg)	112.1±11.9	111.4±18.6	-0.185	.854
DBP (mmHg)	71.2±9.2	68.1±8.6	-1.726	.088
MABP (mmHg)	85.0±8.3	82.5±10.7	-1.294	.199

BMI – Body mass index, BSA – Body surface area, SBP – Systolic blood pressure, MAP – Mean arterial blood pressure *t-test applied

Table 3. Comparison of other clinical characteristics in SCD subjects with or without MA

	Microalbuminuria		X ²	P-value
	Present N (%)	Absent N (%)		
Gender				
Male	26(42.6)	22(56.4)	1.812	.178
Female	35(57.4)	17(43.6)		
Family Hx of HTN				
Yes	10(16.4)	8(20.5)	0.274	.601
No	51(83.6)	31(79.5)		
Family Hx of DM				
Yes	8(13.1)	8(20.5)	0.969	.325
No	51(86.9)	31(79.5)		
Family Hx of CKD				
Yes	5(8.2)	1(2.6)	1.338	.247
No	56(91.8)	38(97.4)		
Previous Hospitalizations/year				
None	18(29.5)	12(30.8)	0.185	.980
Once	29(47.5)	17(43.6)		
Twice	8(13.1)	6(15.4)		
≥Twice	6(9.8)	4(10.3)		
Previous Painful episodes/year				
None	4(6.6)	2(5.1)	5.449	.142
Once	20(32.8)	8(20.5)		

Microalbuminuria				
	Present N (%)	Absent N (%)	X²	P-value
Twice	11(18.0)	15(38.5)		
≥Twice	26(42.6)	14(35.9)		
Previous Blood Transfusions/year				
None	24(39.3)	20(51.3)	6.750	.080
Once	23(37.7)	17(43.6)		
Twice	6(9.8)	2(5.1)		
≥Twice	8(13.2)	0(0.0)		
Hydroxyurea use in the last 1 year				
Yes	10(16.4)	6(15.4)	0.018	.893
No	51(83.6)	33(84.6)		

HTN – Hypertension, DM – Diabetes Mellitus, CKD – Chronic kidney disease-value < .05

Table 4. Comparison of hematological and biochemical parameters in the SCD subjects with or without MA

Microalbuminuria				
Hematological Characteristics	Present X̄ ±SD	Absent X̄ ±SD	t-test	P-value
Hb level(g/dl)	8.6±1.7	8.1±1.7	-1.468	.146
WBC (mm ³)	8398.4±3743.2	9633.3±4716.7	1.381	.172
Platelet (mm ³)	236278.7±138860.6	258333.3±132382.5	0.797	.428
RI (%)	2.4±1.3	2.9±1.2	2.132	.036
MCV (fl)	83.7±8.4	83.5±5.3	-0.117	.907
Creatinine(μmol/l)	64.3±32.6	57.4±18.0	-1.346	.181
Urea(mmol/l)	2.9±1.3	2.7±1.3	-0.634	.528
eGFR(ml/min)	137.6±39.7	152.3±31.9	2.040	.044
AST(IU/L)	22.5±8.6	17.8±7.4	-2.877	.005
ALT(IU/L)	19.1±7.8	18.4±9.9	-0.363	.718
ALP(IU/L)	204.9±100.0	178.8±106.2	-1.227	.224
Albumin(g/l)	32.8±4.8	35.3±5.4	2.369	.020
UO (mosm/kg)	392.9±158.2	381.2±128.1	-0.406	.686
Urine SG	1.010±.01	1.010±.01	0.081	.936

eGFR – estimated glomerular filtration rate, AST – Aspartate aminotransferase, ALT – Alanine aminotransferase, ALP – Alkaline Phosphatase, UO – Urine osmolality
Hb – hemoglobin, WBC – White blood cell, RI – Reticulocyte index, MCV – Mean corpuscular volume

Table 5. Binary logistic regression of the independent determinants of MA among SCD subjects

Variable	B	P value
Age(years)	0.063	.079
RI (%)	-0.494	.045
eGFR(ml/min)	-0.028	.173
AST(IU/L)	0.065	.043
Serum Albumin(g/l)	-0.109	.034

B – Regression coefficient, RI – Reticulocyte index, eGFR – estimated glomerular filtration rate, AST – aspartate aminotransferase, P value <.05

4. DISCUSSION

In this study, the prevalence of HbSS and HbSC were 86% and 14% respectively, this was different from that reported by Aoki et al. [6] in the Brazilian black population, the prevalence of

the various sickle cell genotypes HbSS, HbSC and HbSβ-thal found was 40%, 9%, 25% respectively. This prevalence differs significantly from this study because of the methodology, the work by Aoki et al. [6] used a much more sensitive high-performance liquid

chromatography (HPLC), which can identify various hemoglobin genotypes unlike cellulose acetate electrophoresis used in this study. Also, the study by Aoki et al. [6] was community-based while this study was hospital-based. The prevalence of HbSS and HbSC in this study however agrees with the findings of Aderibigbe et al. [7].

Microalbuminuria is a sensitive biomarker to detect early kidney injury, occurring much earlier and more sensitive than creatinine-based eGFR. There are qualitative and quantitative methods of detecting MA and/or proteinuria, the quantitative method is the best of the two in clinical research and determining the burden of disease [5]. It is for this reason that this study applied the quantitative method by way of UACR. The prevalence of MA was 61% in contrast to the studies by Arogundade et al. [8] and Aneke et al. [9] of 16.8% and 20% respectively, both studies however employed the use of semi-quantitative Combi-9 dipsticks in detecting proteinuria while this study applied quantitative UACR. It is thus an underestimation of the burden of sickle cell nephropathy if our data is based on these studies. The prevalence in this study is similar to that of Bolarinwa et al. [10] (44.4%) and Guasch et al. [2] (68%); both studies applied quantitative assessment of MA using UACR.

In this study, the prevalence of MA was found to be higher compared to other previous works that applied quantitative methods [6,11,12] It is not very clear why the differences existed in the prevalence rates of MA between the studies, however, this may be related to the difference in the haplotypes of the subjects in these differing populations, the haplotype commonly found in this environment is the Benin haplotype of intermediate disease severity in contrast to the Asian haplotype found predominantly in the Middle East [13]. The recruitment of both children and adults in previous works may also be responsible for the observed differences.

SCD subjects with MA were significantly older (30.5 ± 11.3 vs 25.3 ± 6.8 years, p value=0.012). This finding is similar to reports by Abdu et al. [14] who reported that increasing age has a positive impact on SCD transiting to nephropathy. This finding had also been previously reported by other studies [11,15]. Even though more female SCD patients had MA, the difference was not significant. Possible reasons may be due to a higher frequency of UTIs in females which may not be clinically

picked by the urine dipsticks employed in this study.

In this study, it was found that the number of the previous hospitalization(s), blood transfusion(s), and painful episode(s) were not associated with MA to any significant degree. This was unexpected since it was thought that these clinical events are markers of disease severity in SCD subjects. They may not however contribute to the occurrence and progression of renal diseases in them. Interventions offered during these episodes may have contributed to this finding. Various studies, have also not been able to establish a relationship between these clinical events and sickle cell nephropathy [10,16,15]. Anemia was observed in SCD patients with or without MA but there was no difference between mean Hb levels in each group (\pm MA), this was similar to that reported by Bolarinwa et al. [10] and Aoki et al. [6]. Anaemia was observed not to be a predictive factor for sickle cell nephropathy in SCD subjects, this finding refuted earlier reports that lower hemoglobin levels should increase the likelihood of having sickle cell nephropathy. This was attributed to the hypoxic environment in the medulla that is worsened by anaemia [17,18,19].

These conflicting findings can be possibly explained based on differences in patients' characteristics and behaviour of sickle cell gene haplotypes in different parts of the world.

Reticulocyte index was found to be a significant negative predictor of MA in those with SCD, this finding suggests low bone marrow activity. The reticulocyte index is an indicator of bone marrow response, this study observed that the lower the reticulocyte index the greater the risk of developing sickle cell nephropathy suggesting a more disease severity and severe anemia possibly mediated by decreasing erythropoietin levels. Asnani et al. [20] also observed similar findings among Jamaican subjects. No significant relationship was found between other hematological parameters analyzed and MA in this study.

The mean eGFR and serum albumin were significantly lower in SCD patients with MA, while the mean serum AST was higher in those with MA. Given the high rate of chronic hemolysis seen in patients with SCD, there is an expected degree of elevation of liver enzymes. Studies have demonstrated that hemolysis is a marker of increasing severity and mortality in SCD [18].

Maier-Redelsperger et al observed that hemolysis is a strong predictor of kidney disease in SCD patients [21]. On the other hand, Asnani et al. [20] suggested that hemolysis was not associated with MA in Jamaicans with SCD.

Sickle cell nephropathy is associated with glomerular hyperfiltration and hyper-perfusion. Estimated GFR is an important tool for staging and monitoring CKD progression, it is also an independent risk factor for cardiovascular diseases. It starts to decline in the second decade in individuals with sickle cell nephropathy.

In this study, there was no significant difference in the mean serum creatinine level between SCD patients with or without MA. This is due to hyperfiltration, lower muscle mass, and increased tubular secretion of creatinine in such individuals. Therefore, MA is a more reliable marker of early glomerular injury and progression to ESRD, this has been previously reported by other studies [22,23].

5. CONCLUSIONS

MA is very common in subjects with sickle cell disease in contrast to the other genotype groups and should be a routine method of detecting the early onset of sickle cell nephropathy among SCD subjects.

CONSENT AND ETHICAL APPROVAL

Approval of the Ethics and Research Committee of both institutions (Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State and Federal Medical Centre, Owo, Ondo State) was obtained before the commencement of the study. Written informed consent was also obtained from the subjects after a detailed explanation of the study procedure.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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