Original Research Article

Microalbuminuria and its clinical correlates in individuals with Sickle cell trait: A comparative study

ABSTRACT

Background: Sickle Cell Disease (SCD) is a relatively common genetic disorder in Nigeria with attendant kidney disease. There is growing evidence that Sickle cell trait (SCT) may have smothering kidney disease. Microalbuminuria is a sensitive predictor of kidney damage.

Aims: To determine the prevalence of microalbuminuria and its clinical correlates in individuals with SCT.

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: A hospital based cross-sectional study of 200 age and sex matched SCD patients divided equally into 2 groups of sickle cell anemia (SCA) and SCT with 100 controls with HbAA. All participants had blood hematology, chemistry and urine albumin/creatinine ratio (UACR) done.

Results: The SCA group comprised of 86 HbSS and 14 HbSC, SCT group had 96 HbAS and 4 HbAC while the control were all HbAA. The prevalence of microalbuminuria was 61%, 12% and 8% ($p<0.0001$) respectively across the group. Serum alanine aminotransferase and aspartate aminotransferase were the clinical parameters associated with the presence of microalbuminuria but was insignificant on regression analysis.

Conclusion: Microalbuminuria is more prevalent in the SCD and SCT population and thus there may be a need to adopt measures of early detection and institute aggressive lifestyle modification to prevent chronic kidney disease.

Keywords: SCT, SCD, SCA, Microalbuminuria, CKD, Renal disease

1. INTRODUCTION

Sickle Cell Disease (SCD), an autosomal recessive genetic disorder in Africa, most especially in Nigeria. It is also prevalent in the Middle East, Central India, and countries bordering the Mediterranean Sea, especially Italy and Greece.(1)

Sickle cell gene (hemoglobin S or HbS) is caused by a single base pair DNA mutation encoding the β-globin molecule, resulting in substitution of valine for glutamic acid at the sixth position of β-globin chain(2). The inheritance of HbS gene in the homozygous state results in sickle cell anemia (SCA) while inheritance in the heterozygous state results in sickle cell trait (SCT), examples include AS, AD (D trait), AC (C trait) and thalassemia trait. The presence of HBS gene in any form is called the sickle cell disease. The SCT is not considered a disease; however some environmental co-factors can predispose to disease entities.(3)

While sickle cell gene confer some protection against malaria in endemic malaria countries where sickle cell gene is prevalent, it also causes several cardiovascular(4) and renal abnormalities(2). Sickle cell nephropathy describes the structural and functional abnormalities of the kidney in individuals with sickle cell genes.(5)

Renal involvement can occur throughout the life of a patient with SCD. It can manifest as early as in childhood as hyperfiltration, hypertrophy and impaired urinary concentrating ability. The incidence of albuminuria increases with age, occurring more in early to middle adulthood. Renal complications of SCD are documented in many studies and are a leading cause of morbidity and mortality in patients with SCD(5),(6). These overt renal abnormalities have been well documented in individuals with SCA and less seen in SCT.

Microalbuminuria (MA) is a sensitive biomarker used in detecting early kidney disease, it also predicts individuals that may progress to overt proteinuria and chronic kidney disease. Thus, these sensitive biomarkers will help detect sickle cell nephropathy in the early phases and may help monitor the

progression of kidney damage. Quantitative estimation of microalbuminuria (Urine albumin/creatinine ratio UACR) has been shown to be superior to qualitative dip stick methods. There is however paucity of data on UACR in evaluation of microalbuminuria in SCT.

Some clinical and laboratory parameters have also been previously identified as associations of microalbuminuria and overt proteinuria in patients with kidney disease, therefore, if microalbuminuria is present in the various subgroups of SCD, it will be necessary to identify its associative factors and correlates.

The objective of this study therefore is to determine the presence or otherwise of microalbuminuria in the various subgroups of SCD using quantitative method and find the clinical and laboratory correlates associated with microalbuminuria in individuals with SCT.

2. MATERIALS AND METHODS

This cross-sectional study involved a total of 200 participants divided equally into 2 groups of SCA and SCT while 100 participants with hemoglobin AA served as controls. It was conducted between May 2016 to April 2017 simultaneously at2 tertiary health institutions (Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State and Federal Medical Centre, Owo, Ondo State), located in southwest Nigeria. The study participants were consecutively recruited until the required sample size was reached. The participants in the SCA group were recruited as they presented to the hematology outpatient clinics of the two hospitals during the study period. Consecutive recruitment of staff and students of Obafemi Awolowo University Teaching Hospital, Ile-Ife and Federal Medical Centre, Owo were done for the SCT and control groups.

A total of 100 individuals with sickle cell anemia, 100 with sickle cell trait and 100 apparently normal HbAA diagnosed using hemoglobin electrophoresis matched for age and gender were eventually recruited for the study.

An interviewer administered structured proforma was used to document the demographic data and obtain relevant clinical information. All enrolled subjects and controls were given a well-labeled universal urine bottle for collection of 10mls of early morning urine for the determination of urine albumin/ creatinine ratio (UACR), urine osmolality and specific gravity. Venous blood samples were collected from all participants into EDTA and lithium heparin bottles after thorough cleaning of the venipuncture site with a swab soaked with 70% alcohol. The following parameters were determined

from the EDTA blood samples; hemoglobin genotype, stable hemoglobin levels, white blood cell count, platelet counts, reticulocytes index and the mean corpuscular volume.

Serum creatinine, urea, liver enzymes and albumin were also determined from the lithium heparin blood samples. Renal function was determined using the Chronic Kidney Disease- Epidemiology survey (CKD-EPI)equation.(7)

Hematological parameters were analyzed using SYSMEX XS 2IN Auto- hematology Analyzer; SYSMEX DIAGNOSTIC U.S.A. Serum creatinine evaluation was done using the colorimetric Jaffe's method.

Urine Albumin was determined based on a quantitative sandwich enzyme immunoassay technique, using Assay Max Human Albumin Elisa kit while Urine Creatinine was assayed using commercially manufactured kit by Agappe diagnostics Switzerland. The random urine albumin and urine creatinine was converted to the albumin/creatinine ratio using this calculation.

ACR (mg/g) = urine albumin (mg/dl) / urine creatinine (g/dl). Normal ACR ratio was taken as<30 mg/g.

2.1. Statistical Analysis

Data was analyzed on a personal computer using Statistical Package for Social Sciences (SPSS) software version 20.0. Normally distributed numeric variables were summarized using their mean and standard deviation (Mean±SD) while for nonparametric data, median and interquartile range was used. Categorical variables are summarized and presented using frequency tables with proportions and charts as appropriate. The chi-square test was used for comparison of categorical variables while independent student t- test was used to compare means. Binary logistic regression model was also used to determine further associations between the continuous variables. In instances where mean values of parameters were compared by variables with three or more categories, the one-way analysis of variance (ANOVA) was performed. A P-value of 0.05 was taken to be statistically significant.

3. RESULT

Table 1 showed the distribution of the various hemoglobin genotypes across the studied population. Table 2 and 3 showed the clinical characteristics of the study subjects. The groups were age and sex matched. The mean body mass index (BMI) for the SCD subjects was significantly lower (*P<0.001*).

{19.1(3.2) kg/m2} compared to the SCT subjects and controls {24.1(3.4) kg/m2 and 26.0(5.1) kg/m2 respectively}. Also, the difference in the mean values of the body weight, body surface area (BSA), systolic, diastolic and mean arterial blood pressures across the studied groups were statistically significant (*P=0.05*).

Table 4 shows the various laboratory characteristics across the various genotype groups. Figure 1 shows the comparison of the presence of MA across the various hemoglobin genotype groups. The percentage of individuals with MA was significantly higher in the SCD subjects compared to the SCT and control groups (61% vs 12% vs 8%, *P<0.001*).

Table 5 shows the various clinical, hematological and biochemical characteristics of SCT subjects with or without MA. No difference was observed in the clinical and hematological characteristics of SCT subjects with or without MA. However, the mean ALT {14.0(18.8) IU/L vs 9.4(3.4) IU/L, *P=0.046*} and AST {16.8(7.8) IU/L vs 12.9(6.2) IU/L, *P=0.048*} reached significant difference. Table 6 shows the further statistical analysis using binary logistic regression analysis of the independent determinants of MA in the SCT subjects. No significant difference was observed in ALT and ALT values in SCT subjects with or without MA.

Table 1: Distribution of hemoglobin genotype across the studied population

	SCD group N=100 N (%)		SCT group N=100 N (%)		Control group N=100 N (%)
Genotype	SS	SC	AS	AC	AA
	86(86.0%)	14(14.0%)	96(96.0%)	4(4.0%)	100(100.0%)

SCD – Sickle cell disease, SCT – Sickle cell trait

Table 2: Socio-demographic characteristics of the study subjects

	SCD N=100 N (%)	SCT N=100 N (%)	CONTROL N=100 N (%)	*P value*
Age				
≤20	18(38.0)	10(10.0)	12(12.0)	**.082**
21-29	44(24.0)	58(58.0)	52(52.0)	
30-39	26(26.0)	14(14.0)	20(20.0)	
40-49	6(6.0)	14(14.0)	14(14.0)	
50-59	4(4.0)	4(4.0)	2(2.0)	
≥60	2(2.0)	0(0.0)	0(0.0)	
Gender				
Male	48(48.0)	48(48.0)	42(42.0)	**.617**
Female	52(52.0)	52(52.0)	58(58.0)	
Ethnicity				
Yoruba	98(98.0)	86(86.0)	88(88.0)	**.006**
Hausa	0(0.0)	4(4.0)	0(0.0)	
Igbo	2(2.0)	6(6.0)	10(10.0)	
Others	0(0.0)	4(4.0)	2(2.0)	
Marital status				
Single	78(78.0)	68(68.0)	66(66.0)	**.177**
Married	22(22.0)	32(32.0)	32(32.0)	
Occupation				
Civil Servant	12(12.0)	30(30.0)	44(44.0)	**<.001**
Trading	18(18.0)	0(0.0)	0(0.0)	
Schooling	50(50.0)	68(68.0)	56(56.0)	
Farming	0(0.0)	2(2.0)	0(0.0)	
Artisan	10(10.0)	0(0.0)	0(0.0)	
Retiree	2(2.0)	0(0.0)	0(0.0)	
Others	8(8.0)	0(0.0)	0(0.0)	
Educational Qualification				
Primary	4(1.3)	0(0.0)	0(0.0)	**<.001**
Secondary	30(10.0)	2(0.7)	0(0.0)	
Tertiary	66(22.0)	98(32.7)	100(33.3)	
BMI				
Underweight	50(50.0)	2(2.0)	0(0.0)	**<.001**
Normal	46(46.0)	66(66.0)	54(54.0)	
Overweight	3(3.0)	28(28.0)	20(20.0)	
Obese	1(1.0)	4(4.0)	26(26.0)	

SCD – Sickle cell disease, SCT – Sickle cell trait, BMI – Body mass index, P=.05

**: Fishers' exact test applied*

Table 3: Clinical characteristics of the study subjects

	HB Genotype			
	SCD	SCT	CONTROL	P value
	$\bar{X}$ ±SD	$\bar{X}$ ±SD	$\bar{X}$ ±SD	
Age (years)	28.8±9.9	29.0±8.6	28.7±8.7	.969
[1]Weight(kg)	54.1±10.8	66.1±10.2	70.9±13.5	<.001
[2]BMI(kg/m^2)	19.1±3.2	24.1±3.4	26.0±5.1	<.001
[3]BSA(m^2)	1.6±0.2	1.7±0.1	1.8±0.2	<.001
[4]DBP(mmHg)	69.9±9.1	72.9±8.4	69.5±9.1	.015
[5]SBP(mmHg)	111.8±14.5	114.3±10.8	109.7±11.9	<.001
[6]MABP(mmHg)	84.0±9.3	86.4±7.9	82.9±8.7	.014
T (^{0}C)	36.5±0.5	36.6±0.4	36.6±0.5	.554
Pulse rate(b/m)	80.7±10.6	76.8±10.8	77.5±10.8	.081

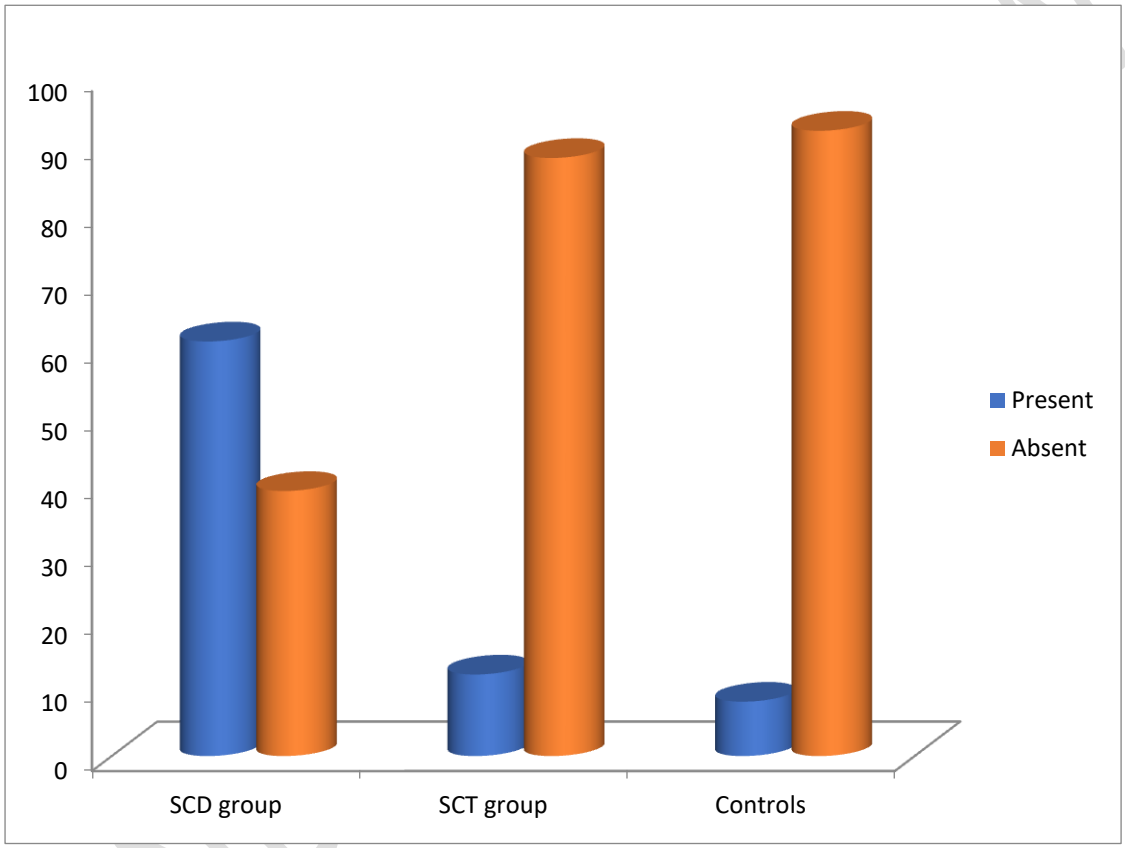
BMI – Body mass index, BSA – Body surface area, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, MABP – Mean arterial blood pressure, T – Temperature
[1-4]post-hoc bonferroni: significance across the 3 HB genotype groups.
[5-6]post-hoc bonferroni: significance between the controls and the SCT group

Table 4: A comparison of laboratory parameters in studied subjects

	HB Genotype			
	SCD	SCT	CONTROL	P value
	$\bar{X}$±SD	$\bar{X}$±SD	$\bar{X}$±SD	
[1]Hb level(g/dl)	8.4±1.7	12.6±1.4	12.5±1.5	<.001
[2]WBC(mm^3)	8880.0±4171.0	6610.0±2607.0	6380.0±1995.5	<.001
Platelet(mm^3)+	173000(149000-317000)	239000(187000-268000)	217000(189000-268000)	.317
[3]RI (%)	2.6±1.3	1.5±0.5	1.4±0.3	<.001
[4]MCV(fl)	83.6±7.4	90.1±6.7	89.9±8.4	<.001
[5]Cr(µmol/l)	61.6±27.9	83.6±13.9	85.5±11.0	<.001
Urea(mmol/l)	2.8±1.3	3.1±0.8	2.8±0.7	.049
[6]eGFR(ml/min)	143.4±37.4	110.3±21.1	106.1±20.6	<.001
[7]AST(IU/L)+	19.4(13.0-28.9)	11.6(9.0-17.1)	10.6(7.1-17.4)	<.001
[8]ALT(IU/L)+	16.3(13.6-25.4)	9.6(7.2-13.3)	9.5(7.4-13.1)	<.001
[9]ALP(IU/L)+	172.5(128.0-240.0)	81.0(64.0-107.0)	85.2(62.5-107.0)	<.001
[10]Albumin(g/l)	34.4±5.3	37.3±5.3	37.5±5.9	<.001
[11]UO(mosm/Kg)	388.4±146.6	514.7±159.6	556.2±169.1	<.001
Urine SG+	1.010(1.005-1.015)	1.015(1.010-1.020)	1.015(1.010-1.020)	.135
[12]UACR(mg/g)+	40.0(20.0-100.0)	17.6(10.0-26.3)	16.7(10.0-24.0)	<.001

Hb – haemoglobin, WBC – white blood cell, RI – reticulocyte index, AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, UACR – urine albumin creatinine ratio, UO – Urine osmolality
+; median (interquartile range)
[1-2]post-hoc bonferroni: significance across the 3 genotype groups.
[3-12]post-hoc bonferroni: significance between SCD group and the other 2 group

Fig 1: Barchart showing the comparison of Microalbuminuria in the studied subjects



SCD – Sickle cell disease, SCT – Sickle cell trait
X axis – frequency
X^2=85.636, P=.05

Table 5: Clinical and laboratory characteristics of SCT subjects with or without MA

	Microalbuminuria		
Clinical Characteristics	Present $\bar{X}$**±SD**	Absent $\bar{X}$**±SD**	P value
Age(years)	31.3±6.5	28.5±8.9	**.295**
Weight(kg)	62.8±9.5	66.5±10.3	**.229**
BMI (kg/m^2)	23.8±2.4	24.1±3.5	**.713**
BSA(m^2)	1.7±0.1	1.7±0.1	**.157**
SBP (mmHg)	115.0±13.1	114.1±10.5	**.835**
DBP (mmHg)	71.8±8.5	73.0±8.4	**.620**
MABP (mmHg)	85.9±7.8	86.5±8.0	**.626**
Hb (g/dl)	12.9±1.9	12.6±1.3	**.669**
WBC (mm^3)	5566.7±1722.2	6752.3±2681.1	**.052**
Platelet (mm^3)	221833.3±77837.6	230102.4±68937.6	**.203**
RI (%)	1.4±0.4	1.5±0.5	**.462**
MCV (fl)	89.6±6.0	90.1±6.9	**.768**
Creatinine(µmol/l)	86.3±10.4	83.2±14.4	**.371**
Urea(mmol/l)	2.9±0.6	3.1±0.9	**.231**
eGFR(ml/min)	105.0±19.9	111.0±21.2	**.353**
AST(IU/L)	16.8±7.8	12.9±6.2	**.048**
ALT(IU/L)	14.0±18.8	9.4±3.4	**.046**
ALP(IU/L)	75.1±37.2	85.8±30.3	**.358**
Albumin(g/l)	37.2±6.5	37.4±5.2	**.921**
UO (mosm/kg)	539.0±220.0	511.4±151.0	**.681**
Urine SG	1.0±0.0	1.6±3.6	**.159**

BMI – Body mass index, BSA – Body surface area, SBP – Systolic blood pressure, DBP – Diastolic blood pressure, MABP – Mean arterial blood pressure,

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

TABLE 6: Binary logistic regression of the independent determinants of MA among SCT subjects

VARIABLE	B	P value
AST(IU/L)	.082	.106
ALT(IU/L)	.130	.179

B – Regression coefficient, AST – Aspartate aminotransferase, ALT – Alanine aminotransferase, P=.05

4. DISCUSSION

Microalbuminuria is a sensitive biomarker to detect early kidney injury, occurs 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(8). It is for this reason that this study applied quantitative method by way of UACR. The prevalence of MA was 61% in contrast to the studies by Arogundade et al(6) 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 with that of Bolarinwa et al(10)(44.4%) and Guasch et al(11)(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(12),(13),(14). 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(15). The recruitment of both children and adults in previous works may also be responsible for the observed differences.

In the SCT group, the prevalence of MA was 12% and this is close to 8% by Sesso et al(13). The clinical implication of this is smothering kidney damage in the SCT cohort. It is therefore apt to continuously screen SCT with the use of quantitative UACR to detect evidence of kidney damage and institute strategies of retarding the progression to ESRD. An increasing prevalence of ESRD had been reported in a cohort of SCT subjects although the relationship of SCT to long-term functional impairment of the kidney has not been firmly established by various studies(16),(17),(18).

In this study, no difference was observed in the clinical and laboratory variables between SCT subjects with and without MA, except serum alanine aminotransferase and aspartate aminotransferase and these became insignificant on regression analysis. There was no possible explanation for these findings, although SCT has been largely considered a benign condition, however renal manifestations like impaired urinary concentration, hematuria, and papillary necrosis has been reported(19). Naik et al(16) observed a greater prevalence of SCT among ESRD African Americans on dialysis, suggesting that SCT to be an independent risk factor for CKD. This observation was also corroborated by Ajayi et al(20), who found that black Africans have a greater prevalence of MA in type 2 diabetes patients with SCT in comparison with controls. It was speculated that the increased prevalence of SCT could be due to accelerated progression of renal disease, either as a direct consequence of SCT or by the enhancement of the deleterious effects of other co-morbid conditions by SCT.(21)

5. CONCLUSION

There is a greater need to adopt measures to stem down the occurrence of sickle cell nephropathy by early detection with the use of microalbuminuria as a biomarker and providing effective treatments to all putative measures.

The SCT subjects have higher prevalence of MA compared to controls, suggesting the need for routine screening for nephropathy especially in the presence of other risk factors.

ETHICAL APPROVAL AND CONSENT

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 detailed explanation of the study procedure.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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