

Microalbuminuria among children and adolescents with sickle cell disease

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Abstract:

BACKGROUND: Sickle cell nephropathy, a heterogeneous group of renal abnormalities resulting from complex interactions of sickle cell disease (SCD)-related factors and non-SCD phenotype characteristics, is associated with an increased risk for morbidity and mortality.

AIMS: The aims of this study were to determine the frequency of microalbuminuria (MA) among pediatric patients with SCD and to determine risk factors for MA among those patients.

SUBJECTS AND METHODS: A case-control study was carried out on 120 patients with SCD, 2–18 years old, registered at Basrah Center for Hereditary Blood Diseases, and 132 age- and sex-matched healthy children were included as a control group. Investigations included complete blood panel, blood urea, serum creatinine (Cr), urinalysis, and urinary albumin-to-Cr ratio (ACR). Logistic regression analysis was used to assess the predictors of MA.

RESULTS: Among SCD patients, 39 (32.5%) had MA compared to 6 (4.5%) in the control group. The mean levels of blood urea, serum Cr, and ACR were significantly higher, and the urine-specific gravity was significantly lower in SCD patients than in the control group ($P < 0.05$). Logistic regression analysis revealed that frequent painful crisis (odds ratio [OR]: 12.146, confidence interval [CI]: 3.439–42.952), high serum ferritin (OR: 8.146, CI: 1.802–36.827), deferoxamine therapy (OR: 23.423, CI: 3.961–60.509), and female sex (OR: 4.590, CI: 1.225–17.202) are independent risk factors for MA ($P < 0.05$).

CONCLUSION: The frequency of MA was high among our pediatric SCD patients. Risk factors for MA include female sex, nutritional factors, painful episodes, and iron overload. This is important for planning for future follow-up and management of this common disease in our locality.

Keywords:

Children, microalbuminuria, predictors, sickle cell disease

Introduction

Sickle cell disease (SCD) is the most common monogenic disorder with remarkable phenotypic diversity.^[1] SCD results from a single point mutation (Glu6Val) that causes polymerization of the mutant hemoglobin (HbS), resulting in sickling of red blood cells (RBCs). Inflammation, hemolysis, microvascular obstruction, and organ damage characterize the clinical course of the disease.^[2]

SCD results from either homozygosity for HbS (HbSS), also known as sickle cell anemia (SCA), or compound heterozygosity with β -thalassemia mutations and other β -globin structural variants such as Hb C.^[3] Although SCD has a high prevalence in Africa, the Middle East, the Mediterranean Basin, and India, SCD now has a worldwide distribution because of population migration, and a substantial number of children are born with the condition in Europe and North and South America.^[4]

SCD is a multisystem disease associated with episodes of acute illness and progressive organ damage. The clinical course is

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characterized by anemia, recurrent episodes of severe pain, and potentially life-threatening complications such as infection, splenic sequestration, acute chest syndrome (ACS), stroke, and chronic organ damage.^[5]

With the improved survival of young children with SCD due to the quality of care provided to these patients, including more timely initial visits, preventive interventions for young children, and the use of hydroxyurea (HU) as a disease-modifying agent,^[6] the disease is now regarded as a chronic condition that requires comprehensive and life-long management. Although vaso-occlusive pain episodes and ACS are the two main causes of morbidity in SCD, other challenges include SCD-related chronic pulmonary disease and end-stage organ damage from sickle cell vasculopathy, especially nephropathy, and cardiovascular complications.^[3]

SCD may lead to alterations in renal hemodynamics, tubular dysfunction, hematuria, and proteinuria related to glomerular injury. Endothelial dysfunction related to chronic hemolysis and the relative renal hypoxia caused by vaso-occlusion by sickled RBCs are probably two key factors for sickle cell nephropathy (SCN) development.^[7] Clinical manifestations start during early childhood with glomerular hyperfiltration, hyposthenuria, and distal renal tubular acidosis initially, followed by subsequent development of albuminuria.^[8]

The appearance of albumin in the urine can be detected in 9.6%–30.7% of children and young adults with SCD (prevalence increasing with age), and it marks the onset of SCN.^[8-10] Microalbuminuria (MA) and proteinuria are noted to be strong predictors of subsequent renal failure.^[7] The use of HU can prevent the onset of albuminuria, especially when initiated earlier in life, and treat patients who have developed albuminuria.^[11,12]

The risk for the development of renal disease is influenced by genetic factors, anemia severity, and disease severity.^[7] However, the risk factors and biomarkers for SCN and the optimum management for pediatric SCD patients with SCN are controversial.^[13] Therefore, this study aimed to estimate the frequency of MA among children and adolescents with SCD and to determine the risk factors associated with MA among these patients.

Subjects and Methods

This was a case–control study that was carried out on children and adolescents with SCD who attended the Basrah Center of Hereditary Blood Diseases for follow-up, while in steady state, their ages ranged from 2 to 18 years.

Full demographic and clinical data were obtained including age at presentation, age at diagnosis, history of acute painful crisis, ACS, urinary tract infection (UTI), stroke, leg ulcer, acute splenic sequestration crisis, aplastic crisis and avascular bone necrosis, transfusion history, and previous operations.

A history of urinary symptoms such as hematuria, polyuria, increased frequency, nocturia, dysuria, and edema was evaluated. Furthermore, drug history, including iron chelating agents (deferrioxamine and deferasirox) and HU, was assessed.

The above information was obtained by directly interviewing patients and/or parents, in addition to reviewing the patient's records in the Center of Hereditary Blood Diseases.

A thorough physical examination was performed, including blood pressure (BP) and growth measures, and body mass index (BMI) was calculated. According to the BMI percentiles, the patients were divided into underweight (BMI <5th percentile), normal BMI (BMI ≥5th percentile), overweight (BMI between the 85th and 95th percentiles), and obese (BMI ≥95th percentile).^[14]

Patients were assessed while in steady state, defined as no history of acute painful episode requiring hospitalization for the last 4 weeks, no history of blood transfusion in the previous 3 months, no history of intercurrent illness such as infection in the last 4 weeks, and no history of treatment with medications such as antibiotics that may affect the blood counts in the last 3 weeks.^[15]

Regarding painful crisis, the patients were divided into three subgroups: patients with no history of painful crisis, patients with <3 painful crises/year, and those with ≥3 painful crises/year indicating severe SCD.^[16]

Diagnosis of the type of SCD was recorded for all patients depending on baseline hemoglobin electrophoresis and high-performance liquid chromatography results.

Control group

This group included age- and sex-matched apparently healthy children who were randomly selected from three schools in Basrah city. The following data were obtained: age, sex, history of recent fever and symptoms and signs of UTI, past medical history, and hospitalization. Physical examination was carried out for children and adolescents, including BP.

Children excluded from the study were children with a history of hospitalization, a history of febrile illness within the preceding 2 weeks of presentation, fever at presentation, female adolescents with ongoing

menstruation, and children who presented with UTIs.^[17,18]

Other exclusion criteria were hypertension (systolic and diastolic BP >90th percentile for age, height, and sex), nephrotic syndrome, and diabetes mellitus.^[19]

Informed consent was obtained from at least one parent before recruitment in the study for all children and adolescents. The study was approved by the Ethical Committee of Basrah Medical College.

Methods

Venous blood was collected from the patients and controls under standardized conditions.

A portion of each blood sample was added to EDTA tubes and sent for complete blood count (CBC) analysis by a hematology analyzer (Mindray BC-5300, Shenzhen, China). The remainder was transferred to plain tubes for the rest of the biochemical analyses. After sera separation, specimens were either immediately analyzed or stored in freezing conditions until analysis within 2 days. The biochemical tests included blood urea, which was estimated spectrophotometrically using a urease-modified Berthelot reaction kit supplied by BioMérieux SA, France. Serum creatinine (Cr) was estimated spectrophotometrically using an alkaline picrate assay kit from Spectrum, Egypt.

Urine samples were collected in the morning from all subjects enrolled in the study. Urinalysis was performed within an hour of collection using a 10-parameter urinalysis test strip (dipstick from Cybow, Germany) to detect urinary RBCs, white blood cells, and protein and to measure urine pH and specific gravity. Patients were considered to have proteinuria based on dipstick urinalysis when the protein concentration was ≥ 30 mg/dl ($\geq +1$). On the other hand, samples that were negative or trace for proteinuria (albuminuria) were subsequently tested for MA. Urine samples were deeply frozen and analyzed thereafter for estimation of urinary albumin and Cr. Urine albumin was measured in spot urine samples by immunoturbidimetry using a kit from Human Diagnostica (Germany), and urine Cr was measured as that for serum (after dilution). The MA test is also known as the albumin-to-Cr ratio (ACR) test, and the urine albumin test is expressed as the urinary ACR (mg/g). The ACR was estimated on two occasions for patients and once for the control group. Urine albumin excretion, expressed as mg albumin/g Cr, was defined as normoalbuminuria (<30 mg/g Cr), MA (30–299 mg/g Cr) or macroalbuminuria (≥ 300 mg/g Cr).^[20]

Statistical analysis

Statistical analysis was performed using SPSS V17 (IBM,

Chicago, IL, USA, SPSS Inc.). Data were presented as the mean \pm standard deviation or number and percentage (*n* and %) as appropriate. Comparisons of the proportions were performed with crosstabs using the Chi-square test and Fisher's exact test. The statistical comparison between means was measured by paired *t*-tests and one-way analysis of variance (ANOVA). For all tests, $P < 0.05$ was considered statistically significant. Significant factors ($P < 0.05$) in the bivariate analysis were entered in the binary logistic regression analysis (OR and 95% CI) to determine variables that predict MA.

Results

A total of 120 children and adolescents with SCD (57 with SCA, 57 with sickle/ β -thalassemia and 6 with hemoglobin S/D disease) were included in the study, and their mean age was 8.87 ± 3.85 years. No statistically significant difference among patients and the control group regarding age, sex or BP (systolic and diastolic) was reported [$P > 0.05$, Table 1].

Although the blood urea and serum Cr were within normal values in both patients and the control group, the mean level of blood urea was significantly higher, while serum Cr was significantly lower in SCD patients than in the control group ($P < 0.05$). Furthermore, urine-specific gravity was significantly lower and the ACR was significantly higher in patients than in the control group ($P < 0.001$ and $P < 0.05$, respectively).

Table 1: Selected demographic, hematological and renal variables among patients and the control group

Variables	Patients (n=120)	Control group (n=132)	P
Age (years), n (%)			
≤ 5	15 (12.5)	25 (18.9)	>0.05*
6-9	56 (46.7)	59 (44.7)	
≥ 10	49 (40.8)	48 (36.4)	
Age (mean \pm SD)	8.87 \pm 3.85	8.43 \pm 3.91	>0.05 [†]
Sex, n (%)			
Male	70 (58.3)	70 (53)	>0.05*
Female	50 (41.7)	62 (47)	
BP (mean \pm SD)			
Systolic BP (mmHg)	96.33 \pm 5.93	97.72 \pm 6.51	>0.05 [†]
Diastolic BP (mmHg)	63.29 \pm 7.46	64.31 \pm 7.83	>0.05 [†]
Hb g/dl	7.58 \pm 1.07	11.11 \pm 1.33	<0.001 [†]
WBC ($\times 10^9$)	5.99 \pm 1.01	6.35 \pm 1.10	>0.05 [†]
Platelet count ($\times 10^9$)	223.45 \pm 64.41	260.22 \pm 40.12	>0.05 [†]
Blood urea (mmol/l)	4.63 \pm 1.08	3.64 \pm 0.49	<0.001 [†]
Serum creatinine (mmol/l)	54.22 \pm 10.54	60.60 \pm 8.02	<0.05 [†]
Urine-specific gravity	1.014 \pm 0.006	1.025 \pm 0.005	<0.001 [†]
ACR (mg/g)	37.60 \pm 23.03	18.0 \pm 0.56	<0.05 [†]
MA, n (%)	39 (32.50)	6 (4.50)	<0.001*

*Chi-square test was used, [†]t-test was used. Hb=Hemoglobin, WBC=White blood cell, ACR=Albumin/creatinine ratio, SD=Standard deviation, BP=Blood pressure, MA=Microalbuminuria

Among SCD patients, 39 (32.5%) had MA in comparison to 6 (4.5%) in the control group [$P < 0.001$, Table 1].

Among SCD pediatric patients, the frequency of MA was found to be significantly higher among individuals with increasing age ($P < 0.001$), longer disease duration, and female sex ($P < 0.05$). Furthermore, the frequency of MA was significantly higher in patients with frequent acute painful episodes, ACS, on iron chelators, and with a history of UTI [$P < 0.05$, Table 2].

The study also found that SCD patients with MA had lower Hb levels and higher mean serum ferritin, blood urea and Cr, urinary ACR, and pH [$P < 0.05$, Table 3].

Logistic regression analysis revealed that frequent painful crisis, high serum ferritin level, deferoxamine therapy, and female sex were independent risk factors and predictors for MA [$P < 0.05$, Table 4].

Discussion

SCN is a well-defined group of renal abnormalities resulting from a cascade of events occurring in the kidneys and is associated with an increased risk for morbidity and mortality in patients with SCD.^[21,22] Albuminuria represents an early stage of chronic kidney disease, starts in childhood, and may predict early mortality in SCD.^[23]

Therefore, the identification of risk factors for MA is important to plan for the prevention of SCN.

The overall prevalence of MA in children with SCD in this study was 32.5%, and the prevalence significantly increased with increasing age, with all patients with MA being above 5 years of age.

The frequency of MA reported in this study is higher than that reported among children with SCD in the KSA

Table 2: Frequency of microalbuminuria among patients with sickle cell disease in relation to selected demographic and clinical variables

Variables	MA (n=39), n (%)	NA (n=81), n (%)	Total (n=120), n (%)	P
Age (years)				
<5	-	15 (18.5)	15 (12.5)	<0.001*
5-9	13 (33.3)	43 (53.1)	56 (46.7)	
≥ 10	26 (66.7)	23 (28.4)	49 (40.8)	
Sex				
Male	17 (43.6)	53 (65.3)	70 (58.3)	<0.05**
Female	22 (56.4)	28 (34.7)	50 (41.7)	
Genotype				
SCA	15 (38.5)	42 (51.9)	57 (47.5)	>0.05**
S/β thalassemia	22 (56.4)	35 (43.2)	57 (47.5)	
Others	2 (5.1)	4 (4.9)	6 (5)	
Duration of disease (mean±SD)	8.09±3.61	4.39±3.55	5.84±3.99	<0.05†
Painful episodes/year				
No episode	-	5 (6.2)	5 (4.2)	<0.001*
<3	4 (10.3)	45 (55.5)	49 (40.9)	
≥3	35 (89.7)	31 (38.3)	66 (54.9)	
ACS	11 (28.2)	6 (7.4)	17 (14.2)	<0.05**
ASSC	1 (2.6)	2 (2.5)	3 (2.5)	>0.05*
UTI	18 (46.2)	9 (11.1)	27 (22.5)	<0.05**
Blood transfusions/year				
None	15 (38.5)	8 (9.9)	23 (19.2)	<0.05**
≤ 12	8 (20.5)	56 (69.1)	64 (53.3)	
>12	16 (41)	17 (21)	33 (27.5)	
Iron chelation				
DFO	28 (71.8)	9 (11.1)	37 (30.8)	<0.05**
DFX	8 (20.1)	5 (6.2)	13 (10.8)	<0.001*
Total	36 (92.3)	14 (17.3)	50 (41.6)	<0.05**
Hydroxyurea	3 (6.4)	5 (6.8)	8 (6.7)	>0.05*
BMI (kg/m ²) <5 th percentile	13 (33.3)	20 (24.7)	33 (27.5)	>0.05**
Blood pressure (mean±SD)				
Systolic	97.08±7.21	94.75±4.43	96.33±5.93	>0.05†
Diastolic	66.66±10.94	61.50±5.87	63.29±7.46	>0.05†

*Fisher's exact test, **Chi-square test, †Independent t-test were used to assess the P value. SCA=Sickle cell anemia, ACS=Acute chest syndrome, ASSC=Acute splenic sequestration crises, UTI=Urinary tract infection, DFO=Deferoxamine, DFX=Deferasirox, BMI=Body mass index, MA=Microalbuminuria, NA=Normoalbuminuria, SD=Standard deviation

Table 3: Selected hematological and biochemical variables among patients with sickle cell disease in relation to microalbuminuria

Variables	Patients with SCD (120), mean±SD		P
	MA (n=39)	NA (n=81)	
Complete blood picture			
Hb (g/dl)	7.04±0.90	7.91±1.03	<0.001
WBC (×10 ⁹)	6.02±1.13	6.43±1.20	>0.05
Platelets (×10 ⁹)	240.42±68.30	217.12±56.48	>0.05
Serum ferritin (ng/ml)			
Mean	3836±2681.17	1829±1210.60	<0.001
<1000*	1 (2.6)	51 (63)	<0.001†
1000-3000*	11 (28.2)	17 (21)	
>3000*	27 (69.2)	13 (16)	
HbF (%)	16.04±10.91	18.60±11.97	>0.05
Blood urea (mmol/L)	5.37±0.76	3.95±0.93	<0.001
Serum creatinine (mmol/L)	47.17±8.28	60.60±8.02	<0.05
ACR (mg/g)	52.85±17.83	15.28±3.53	<0.001
Urinary pH	6.73±0.58	6.05±0.54	<0.001
Urinary-specific gravity	1.015±0.008	1.013±0.004	>0.05

*Values are expressed as n (%), †Chi-squared test was used. A t-test was used to assess the P value between the mean values. Hb=Hemoglobin, HbF=Fetal hemoglobin, ACR=Albumin/creatinine ratio, MA=Microalbuminuria, NA=Normoalbuminuria, WBC=White blood cells, SD=Standard deviation, SCD=Sickle cell disease

Table 4: Logistic regression analysis of factors associated with microalbuminuria

Risk factors for MA	OR	CI 95%		P
		Lower value	Upper value	
Deferoxamine	23.423	3.961	60.509	<0.001
Frequent painful crisis	12.146	3.439	42.952	<0.05
Iron overload	8.146	1.802	36.827	<0.05
Female sex	4.590	1.225	17.202	<0.05
Duration of disease	2.673	0.791	9.028	>0.05
ACS	1.493	0.257	8.060	>0.05
Deferasirox	1.256	0.382	4.133	>0.05
Platelet count	1.289	0.373	4.931	>0.05
White blood cells	0.936	0.253	3.315	>0.05
Infrequent transfusion	0.871	0.229	3.467	>0.05
Low Hb (%)	0.692	0.194	2.465	>0.05
Age	0.633	0.182	2.204	>0.05

ACS=Acute chest syndrome, Hb=Hemoglobin, CI=Confidence interval, OR=Odds ratio, MA=Microalbuminuria

by Alzahrani *et al.* (9.6%)^[9] and in Nigeria by Ocheke *et al.* (26%).^[24]

SCN is a heterogeneous condition that results from complex interactions between SCD-related risk factors and non-SCD phenotype characteristics. Among the risk factors are genetic predisposition (albuminuria is more likely to occur in patients who express specific single-nucleotide polymorphisms in the MYH9 and APOL1 genes), coinheritance of α -thalassemia, and environmental factors. Patients with SCD may develop proteinuria from other causes, such as hepatitis C virus or human immunodeficiency virus-associated

nephropathy.^[22,25] Many studies in different countries also reported an increased frequency of MA with age.^[20,23,26] The high prevalence of MA among our patients can be explained, in part, by the fact that a high proportion of patients (40.8%) were more than 10 years old.

The current study did not report any significant difference in the frequency of MA in relation to the type of SCD. This finding was similar to that reported by Alzahrani *et al.* in the KSA^[9] and McPherson Yee *et al.* in Georgia, USA.^[27] SCA and Hb S/ β^0 are clinically identical conditions that are associated with severe anemia and disease complications including abnormalities of renal function.^[27]

In this study, there was a significant correlation between MA and female sex. This finding was similar to that reported by Niss *et al.* in a multicenter study in USA and Jamaica^[23] and by Imuetinyan *et al.* in Nigeria.^[17] However, the association of MA with sex was not found in other studies.^[26,28] The exact causes are not clear; one possible explanation is the higher rate of UTIs among females.

A similar finding was reported by other researchers.^[20,24] However, King *et al.* reported a significant association between BMI and MA.^[29] In general, children with SCD are often more wasted (due to an imbalance between nutritional intake and metabolic demand and hypermetabolism) than children with a normal hemoglobin genotype.^[29]

Frequent attacks of painful episodes requiring hospitalization (≥ 3 /year), an indicator of disease severity, were found to be significantly associated with MA. Alzahrani *et al.* in the KSA reported that disease severity is associated with MA.^[9] Al-Musawa and Al-Saqladi^[10] in Yemen did not find an association between indicators of disease severity (painful episodes, hospitalization, and blood transfusion) and MA. Baddam *et al.* reported acute kidney injury in 17% of pediatric patients with vaso-occlusive episodes. In addition, acute kidney injury may be explained by the use of non-steroidal anti-inflammatory drugs to control pain.^[30] King *et al.* in Jamaica showed that there was a trend for dactylitis and glomerular hyperfiltration associated with MA. This supports the hypothesis that increased urinary albumin excretion is mediated not only by glomerular hyperfiltration but also by ischemia and infarction in the renal microcirculation.^[29]

Iron overload among patients who had received frequent blood transfusion and those on deferoxamine therapy were both associated with an increasing frequency of MA. An increased MRI iron signal has been identified in the kidney, the signal was highest in

non-transfused patients and it lacked correlation with liver iron content.^[31] Other researchers have reported that intravascular hemolysis, rather than secondary iron loading, is the major contributor to renal iron.^[32,33]

Vichinsky *et al.* reported that both deferasirox and deferoxamine were safe in SCD patients followed for 24 months without evidence of progressive renal dysfunction.^[34]

The frequency of blood transfusion was not associated with MA in our patients. This finding is similar to that reported in other studies.^[20,24]

However, Mawanda *et al.* in Uganda reported that a higher number of blood transfusions in children with SCA was associated with a risk of MA.^[35] In contrast to the role of blood transfusions in preventing MA which is controversial, both ACE inhibitors and HU were reported to prevent and treat MA.^[7,11]

BP (both systolic and diastolic BP) was normal in all subjects included in the study (patients and control group) and between patients with and without MA. Imuetinyan *et al.*^[17] and Ocheke *et al.*^[24] reported a similar finding.

The hemoglobin level was not associated with MA among our patients. Different researchers from different countries have reported conflicting results. Aloni *et al.* in Congo reported a similar result.^[20] Asnani *et al.* in the USA reported that lower hemoglobin levels are predictors for renal disease.^[36] In SCD, chronic RBC hemolysis results in severe anemia, which in turn causes secondary increase in cardiac output, a decrease in peripheral (renal) vascular resistance, and finally an increase in GFR and hyperfiltration.^[37]

The lack of an association between albuminuria and BP or hemoglobin levels in our patients may indicate that sickle cell glomerulopathy does not solely relate to hemodynamic adaptations associated with chronic anemia.^[38]

This study also reported that white blood cell and platelet counts were normal and not associated with MA. Although King *et al.* suggested that increasing evidence for inflammation and podocyte dysfunction may play a role in the pathogenesis of SCD and proteinuric renal diseases,^[29] our findings are similar to that reported by Aloni *et al.*^[20]

Serum Cr was significantly lower in patients with MA than in patients with NA. This study also reported that the levels of serum Cr were lower in patients than in the control group. These findings are similar to that reported

by Ocheke *et al.* in Nigeria which can be attributed to the increased GFR in these patients.^[24]

Defective urine concentration or hyposthenuria is the earliest and most common tubular abnormality in SCD. This condition can appear very early in homozygous individuals.^[39] In this study, the results of urinalysis showed that urine-specific gravity was significantly lower in patients with SCD than in the control group and that urinary PH was significantly higher in patients with MA than in NA patients.

This study has many limitations. First, it was a cross-sectional study, which makes it difficult to differentiate transient from persistent MA. Second, the number of patients on HU was too small to evaluate the role of this drug as renoprotective.

Conclusion

From this study, it can be concluded that the frequency of MA was high among our pediatric SCD patients and that many indicators of disease severity correlate with MA development. This is important for planning for future follow-up and management of this common disease in our locality.

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Conflicts of interest

There are no conflicts of interest.

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