Prevalence and Risk Factors for Microalbuminuria in Children with Sickle Cell Disease in the King Abdulaziz University Hospital: A Retrospective Cross-sectional Study

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Research note

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Abstract

Objectives Studies have not addressed microalbuminuria in the sickle cell disease (SCD) pediatric population in Jeddah, Saudi Arabia. This study aimed to determine the prevalence of microalbuminuria and to identify associated risk factors in children with SCD in the King Abdulaziz University Hospital.

Results Overall, 42.5% of the patients enrolled were Saudi Arabian and 51% were boys. Patients' mean age was 12.4 years, and the highest percentage (40%) was in the age group of 15–18 years. The prevalence of microalbuminuria was 9.6%, and hematuria was present in 8% of cases. The percentage of patients with hematuria in the microalbuminuria group (22.6%) was significantly higher than that in the non-microalbuminuria group (6.5%) (P=.007). The percentage of patients with acute chest syndrome was higher in the microalbuminuria group (26%) than in the non-microalbuminuria group (8%) (P=0.005). The percentage of patients with gallbladder stones was higher in the microalbuminuria group (13%) than in the non-microalbuminuria group (2.4%) (P=.014). The mean number of blood transfusions was higher in the non-microalbuminuria group than in the microalbuminuria group (P=.002). Sickle cell nephropathy manifests as microalbuminuria, begins in the early ages of life, occurs in all types of SCD, and is associated with disease severity.

Introduction

Sickle cell disease (SCD) is one of the most important autosomal recessive diseases. The prevalence in the Kingdom of Saudi Arabia (KSA) for the sickle-cell trait ranges from 2 to 27%, and up to 2.6% of individuals develop SCD in KSA.[1] SCD is characterized by vaso-occlusive events, hemolytic crises, and organ damage.[2]

A chronic complication of SCD is renal impairment, which is a major factor in mortality.[3,4] This association with mortality is stronger than that observed with an episode of acute stroke, a febrile episode with positive blood culture, acute chest syndrome, and severe acute anemia.[5] Chronic renal complications occur in 5–18% of SCD cases, and >9% of deaths in young adults are due to renal involvement.[4–6]

In SCD, microalbuminuria is one of the most common clinical manifestations of sickle cell nephropathy (SCN),[7,8] which appears to be associated with a more rapid deterioration in renal function.[9] Microalbuminuria screening in patients with SCD is a predictor of end-organ disease including renal damage.[10,11]

Children with SCD experience hyperfiltration and hyperperfusion, which are associated with renal damage.[12,13] Early detection of microalbuminuria may represent an important early sign of renal disease.[14] A prolonged period of microalbuminuria precedes persistent proteinuria, which is followed by renal failure in SCD patients.[15] Varied incidence of microalbuminuria in children with SCD ranges from 18.4% to 46%.[16–18]

The identification of risk factors for microalbuminuria may allow earlier intervention to prevent renal complications.[16] Considering the high burden of SCD in the KSA with a prevalence rate of 2.6% in newborns[1] in a population of >24 million, children with SCD are prone to developing microalbuminuria and chronic renal failure with advancing age.

Research in Saudi Arabia has not addressed this problem. Thus, this study aimed to determine the prevalence of microalbuminuria in children with SCD and to identify risk factors associated with microalbuminuria in children with SCD in the King Abdulaziz University Hospital (KAUH).

Main Text

Patients and Methods

The study was approved by the Institutional Review Board of the KAUH. This cross-sectional prevalence study retrospectively reviewed all medical records of children aged 2–18 years diagnosed with SCD in the KAUH Pediatric Sickle Cell Clinic between June 2010 and April 2019. We excluded all patients without urine analysis testing.

Data obtained from the recent outpatient follow-up visit included: sex, age, nationality, weight, height, ABO blood group system, sickle cell genotype, the number of hospitalizations, blood transfusion (BT) status, and the number of transfusions (NOH). The frequency of the vaso-occlusive events and SCD complications were collected.

Hydroxyurea (HU) therapy and its associations with the number of BTs and NOH were studied. In urine analysis, microalbuminuria was defined as >1+ protein, and red blood cells (RBCs) were counted and defined as hematuria if >5.

Statistical analysis

Descriptive statistics are used to describe study participants' demographic characteristics. Mean±standard deviations and median values are used to describe continuous variables. Frequencies with proportions are used to report categorical variables. A comparison of numerical variables between the groups was performed using the independent *t*-test, whereas a comparison of categorical variables was performed using the chi-square and Fisher's exact tests. Statistical significance was set at $P<.05$. All statistical analyses were performed using IBM SPSS statistics, version 23 (IBM, Armonk, NY, USA).

Results

In total, 322 pediatric patients with SCD were studied for the prevalence of microalbuminuria and its associated factors. Patient characteristics are presented in Table 1. The NOH and BT were not statistically significantly different between patients who did and did not receive HU (Table 2).

Characteristics of the non-microalbuminuria group (291 patients) and microalbuminuria group (31 patients) and a comparison of different variables between non-microalbuminuria and microalbuminuria patients are shown in Table 3. Only hematuria was statistically significantly different; it was higher in the microalbuminuria group than in the non-microalbuminuria group (P = 0.007). There was some difference in the distribution of blood groups (P =.022). The percentage of acute chest syndrome was significantly higher in the microalbuminuria group than in the non-microalbuminuria group (P =.005). The percentage of gallbladder stones was significantly higher in the microalbuminuria group than in the non-microalbuminuria group (P =.014). The mean number of BTs was higher in the non-microalbuminuria group than in the microalbuminuria group (P = 0.002). The remaining variables showed no significant differences between the groups.

Discussion

Renal failure secondary to SCD can affect 5-–20% of the adult population. The progressive process starts from childhood and eventually leads to renal failure.[19] Microalbuminuria is one of the earliest manifestations of SCN. Hence, many studies have been concerned with determining the prevalence of microalbuminuriaamong SCD patients to assess the severity of the condition.[20,21] We determined the prevalence of microalbuminuria to be 9.6% among pediatric patients with a mean age of 12.4 years, starting from a very young age (2 years) and continuously progressing to its highest percentage in the young adult group (15–18 years), reaching a prevalence of 51.6% in this group. Patients' mean age and the average percentage of microalbuminuria among older patients were consistent with a prevalence of 46% reported by Dharnidharka et al[20] and a prevalence of 39–43% in adults with SCD reported by McBurney et al.[16] However, the overall prevalence of microalbuminuriaamong all patients (9.6%) was lower than the average prevalence reported by those previous studies. Additionally, Alkhunaizi et al[22] determined that the prevalence of microalbuminuria among adult Saudi Arabian patients (>18 years) was 25%, which was very similar to our findings with respect to the same age group.

Dharnidharka et al[20] and McBurney et al[16] reported that no microalbuminuria was detected in children <7 years old. Conversely, we found that 9.7% of microalbuminuria patients were aged 2–5 years. These findings were supported by Aloni et al[23] who confirmed the presence of microalbuminuria among their patients aged <7 years. This early deterioration of glomerular function could be explained by the presence of certain factors including a genetic predisposition, the level of fetal hemoglobin (HbF), environmental factors, efficacy of medical care, and lifestyle in the developing countries.[24] Another reasonable explanation for these contradictory results is our study's small sample size. However, 104 and 151 patients were enrolled in the studies by Dharnidharka et al[20] and by McBurney et al,[16] respectively.

Interestingly, when compared the microalbuminuria and non- microalbuminuria groups, there was no statistical difference in terms of age (P =.432), which indicated that age was not a defining variable for both groups. However, age was a defining variable in the progression of microalbuminuria in the affected group.

A female predominance of microalbuminuria has been reported in the literature. Jones et al reported a prevalence of 9.7% of microalbuminuria among female patients and 6.1% among male patients.[8] Further, Okpere ET al[25] reported consistent results of female predominance (45.3%) compared to male predominance (20.4%). However, no significant difference in sex was detected between the microalbuminuria and non-microalbuminuria groups in our study or the studies of McBurney et al[16] and Dharnidharka et al.[20] Consequently, additional study is necessary to provide further evidence regarding these contrary results.

Our findings demonstrated that microalbuminuria occurs in most of the hemoglobin genotypes, with the highest percentage in the Hb-ss genotype (74.2%) in the microalbuminuriagroup, which is similar to that reported in previous studies conducted by Wigfall et al.[26] However, no microalbuminuriawas detected in the HB-Sβ0 (Beta-Zero) thalassemia sub-group. In most previous studies, patients with Sβ-thalassemia were few in number, and there have been limited studies with mixed results about this patient group. Becton et al[21] reported that only one patient with Sβ-thalassemia had microalbuminuria.

We further examined the percentage of several clinical complications that may be associated with microalbuminuria (Table 3). Next, we compared the microalbuminuriaand non-microalbuminuria groups to identify definitive variables that significantly varied between the groups. Interestingly, we found that most patients in the microalbuminuriagroup experienced acute chest syndromes, gallbladder stones, osteomyelitis, pneumonia, and spleen sequestration, but none reported priapism, avascular necrosis, aplasia, stroke, acute coronary syndrome (ACS), or dactylitis. These findings were consistent with those reported by Dharnidharka et al[20] and McBurney et al,[16] who found no significant correlation between microalbuminuriaand stroke. McBurney et al[16] and Kalpathi et al[21] reported no significant correlation between microalbuminuriaand ACS. We found a significant association between acute chest syndrome and the microalbuminuria group (P =.005), which was consistent with other findings reported by Alvarez et al.[27]

In contrast Bodas et al[28] reported that the glomerular filtration rate was not correlated to episodes of stroke or acute chest syndrome, which suggests that the etiologies of these complications may differ from the etiologies of the development of SCN. However, only 48 patients were enrolled in their study and the small sample size, compared to our sample, may have likely influenced the significant correlation between the two conditions.

Furthermore, we found a significant correlation between the microalbuminuriagroup and development of gallbladder stones (P =.014%). Our findings were consistent with those of Alexander-Reindorf et al[29] and Bond et al,[30] who reported a significantly higher morbidity and more hospital admissions for SCD patients with gallbladder stones. Additionally, the mean age of the microalbuminuriagroup was 13.74 years, which was consistent with Martins et al's[31] 11- and 29-year-old study cohort with a higher prevalence of cholelithiasis and gallbladder stones.

HU is an effective drug associated with an increasing hemoglobin concentration, MCV, and HbF level in adults and children. High levels of HbF reduces sickling of RBCs and glomerular damage of the kidney.[32]

We attempted to identify a correlation between the administration of HU and the NOH or BTs in SCD patients. However, we found no significant effect of administrating the drug and NOH or BT in both groups (*P* =.7). This finding could suggest that the effect of HU as a renoprotective agent is effective when treatment starts during infancy.[27]

We found that the number of BTs was significantly associated with a decreased level of microalbuminuria. This finding suggests that BTs are a renoprotective process in the management of SCD. Alvarez et al.[27] reported similar results when they indicated that starting transfusion at an early age could help the kidney and hinders the deterioration of SCN. However, the side effects of transfusion, iron overload, must be considered before starting the process. Aloni et al[23] reported that BT is not a significant factor when comparing bothgroups.

Kalpathi et al[21] stated that 36% of SCD patients presented with hematuria. However, they reported no significant difference in the level of hematuria between the microalbuminuriaand non- microalbuminuria groups. We determined the percentage of hematuria among SCD patients and found a statistically significant difference in the percentage of hematuria between the two groups (*P* =.007). These results were consistent with the findings of Sesso et al,[34] who reported a higher level of hematuria among Hb-ss and Hb-as groups. They stated that hematuria is caused by increased sickling of RBCs in the renal medulla, resulting in extravasation and ischemia.

We also determined that most SCD patients have O RhD+ blood, which was significantly different between the two groups (P =.022). This result is consistent with that of Alagwu et al,[35] who reported a percentage of 63% for blood group O among Hb-ss patients. This finding could be explained by the fact that blood group O Rh+ is the most prevalent group among all humans.

In conclusion, our findings highlight the importance of early investigations, e.g., urine analysis for assessment of microalbuminuria and hematuria, and determination of the degree SCN. The fact that average mean BT was significantly higher in the non-microalbuminuria group than in the microalbuminuria group could suggest a protective role of transfusion in the development of microalbuminuria. However, further investigations need to be conducted to confirm our results. Besides, we reported significantly higher rates of acute chest syndrome and gallbladder stones in microalbuminuria patients, which must be considered, and special care needs to be provided to them. We recommend routine screening of microalbuminuria and hematuria for SCD patients.

Limitations

Patients visiting the pediatric hematology clinic with a diagnosis of SCD do not routinely undergo urine analysis tests, and data were collected solely from registration records.

List Of Abbreviations

SCD, sickle cell disease; KSA, Kingdom of Saudi Arabia; KAUH, King Abdulaziz University Hospital; ACS, acute coronary syndrome; HU, hydroxyurea; RBC, red blood cell; MCV, mean corpuscular volume; HbF, fetal hemoglobin; BT, blood transfusion; SCN, sickle cell nephropathy; NOH, number of transfusions

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the King Abdul-Aziz University Hospitalreference number: 186–19).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Yahya AA, the first author, contributed to the conception and design of the study, analysis and interpretation of data, and final approval of the version of the manuscript to be published.

Yara AA made substantial contribution to the acquisition of data and drafting of the article.

OYS contributed to the conception and design of the study, and critical revision of the article for important intellectual content.

MAA made substantial contribution to the acquisition of data and drafting of the article.

MMA made substantial contribution to the conception and design of the study, and drafting of the article.

HMA made substantial contribution to the acquisition of data and drafting of the article.

JEA made substantial contribution to the acquisition of data and critical revision of the article for important intellectual content.

KMA made substantial contribution to the conception and design of the study, and drafting of the article.

FSA contributed to the conception and design of the study, critical revision of the article for important intellectual content, and final approval of the version of the manuscript to be published.

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Tables

Table 1: Descriptive statistics of all patients enrolled in the study (N=322)

Variable	N	Percentage
Nationality		
Non-Saudi Arabian	185	57.5
Saudi Arabian	137	42.5
Sex		
Female	157	48.8
Male	165	51.2
Age group		
2 to 5 years	30	9.3
6 to 10 years	87	27.0
11 to 14 years	77	23.9
15 to 18 years	128	39.8
Sickle cell genotype		
Hemoglobin SB 0 (Beta-zero) thalassemia	4	1.2
Hemoglobin SB+ (beta) thalassemia	41	12.7
Hemoglobin SS disease (sickle cell disease)	233	72.4
Sickle cell trait (hemoglobin S disease)	44	13.7
Microalbuminuria		
No	291	90.4
Yes	31	9.6
Hematuria		
No	296	91.9
Yes	26	8.1
Blood type		
A RhD negative (A-)	3	0.9
A RhD positive (A+)	84	26.1
AB RhD positive (AB+)	15	4.7
B RhD negative (B-)	3	0.9
B RhD positive (B+)	32	9.9
O RhD negative (O-)	9	2.8
O RhD positive (O+)	176	54.7
Blood transfusions		
No	143	44.4
Yes	179	55.6
Frequency of:		
Pneumonia	30	9.3
Priapism	3	0.9
Avascular necrosis	3	0.9
Acute chest syndrome	31	9.6
Aplasia	2	0.6
Stroke	14	4.3
Acute coronary syndrome	10	3.1
Dactylitis	3	0.9
Spleen sequestration	24	7.5
Gallbladder stones	11	3.4
Osteomyelitis	23	7.1
Hydroxyurea therapy		
No	208	64.6
Yes	114	35.4
Reasons for prescribing hydroxyurea		

Pain		107	33.2
Acute chest syndrome		9	2.8
Transient ischemic attack		0	0.0
Numerical variable			
	Mean	**SD**	**Median**
Age (years)	12.43	4.64	13.00
Number of hospitalizations	16.14	35.56	5.00
Number of blood transfusions	8.67	26.71	1.00

SD, standard deviation

Table 2: Associations of hydroxyurea treatment with the number of hospitalizations and number of transfusions

Total sample (N=322)					
		N	Mean	SD	*P*-value
Number of hospitalizations	Undergoing hydroxyurea therapy	114	18.57	27.09	0.3653
	Not undergoing hydroxyurea therapy	208	14.81	39.43	
Number of transfusions	Undergoing hydroxyurea therapy	114	11.55	20.72	0.1520
	Not undergoing hydroxyurea therapy	208	7.09	29.40	
Non-microalbuminuria patients (N=291)					
		N	Mean	SD	*P*-value
Number of hospitalizations	Undergoing hydroxyurea therapy	104	19.52	28.17	0.3436
	Not undergoing hydroxyurea therapy	187	15.22	41.16	
Number of transfusions	Undergoing hydroxyurea therapy	104	12.38	21.49	0.1558
	Not undergoing hydroxyurea therapy	187	7.52	30.92	
Microalbuminuria patients (N=31)					
		N	Mean	SD	*P*-value
Number of hospitalizations	Undergoing hydroxyurea therapy	10	8.700	4.0014	0.2870
	Not undergoing hydroxyurea therapy	21	11.190	18.0073	
Number of transfusions	Undergoing hydroxyurea therapy	10	2.900	3.2472	0.7590
	Not undergoing hydroxyurea therapy	21	3.238	6.5031	

SD, standard deviation

Table 3: Comparison of different variables between non-microalbuminuria and microalbuminuria patients

	Without microalbuminuria (N=291)		With microalbuminuria (N=31)		*P*-value
	N	%	N	%	
Nationality					
Non-Saudi Arabian	167	57.4	18	58.1	0.942
Saudi Arabian	124	42.6	13	41.9	
Sex					
Female	144	49.5	13	41.9	0.424
Male	147	50.5	18	58.1	
Age group					
2 to 5 years	27	9.3	3	9.7	0.432
6 to 10 years	82	28.2	5	16.1	
11 to 14 years	70	24.1	7	22.6	
15 to 18 years	112	38.5	16	51.6	
Sickle cell genotype					
Hemoglobin SB 0 (Beta-zero) thalassemia	4	1.4	0	0.0	0.928
Hemoglobin SB+ (beta) thalassemia	37	12.7	4	12.9	
Hemoglobin SS disease (sickle cell disease)	210	72.2	23	74.2	
Sickle cell trait (Hemoglobin S disease)	40	13.7	4	12.9	
Hematuria					
No	272	93.5	24	77.4	0.007*
Yes	19	6.5	7	22.6	
Blood type					
A RhD negative (A-)	2	0.7	1	3.2	0.022*
A RhD positive (A+)	75	25.8	9	29.0	
AB RhD positive (AB+)	10	3.4	5	16.1	
B RhD negative (B-)	3	1.0	0	0.0	
B RhD positive (B+)	31	10.7	1	3.2	
O RhD negative (O-)	9	3.1	0	0.0	
O RhD positive (O+)	161	55.3	15	48.4	
Blood transfusions					
No	131	45.0	12	38.7	0.502
Yes	160	55.0	19	61.3	
Frequency of:					
Pneumonia	28	9.6	2	6.5	0.752
Priapism	3	1.0	0	0.0	1
Avascular necrosis	3	1.0	0	0.0	1
Acute chest syndrome	23	7.9	8	25.8	0.005*
Aplasia	2	0.7	0	0.0	1
Stroke	14	4.8	0	0.0	0.377
Acute coronary syndrome	10	3.4	0	0.0	0.607
Dactylitis	3	1.0	0	0.0	1
Spleen sequestration	22	7.6	2	6.5	1
Gallbladder stones	7	2.4	4	12.9	0.014*
Osteomyelitis	20	6.9	3	9.7	0.474
Hydroxyurea therapy					

No	187	64.3	21	67.7	0.7
Yes	104	35.7	10	32.3	
Reasons of Hydroxyurea therapy					
Pain	98	33.7	9	29.0	0.602
Acute chest syndrome	8	2.7	1	3.2	0.603

Numerical variable							
	Without microalbuminuria			**With microalbuminuria**			***P*-value**
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	
Age	12.29	4.62	12.00	13.74	4.68	15.00	0.098
Number of hospitalizations	16.76	37.05	4.00	10.39	14.91	8.00	0.068
Number of transfusions	9.26	27.97	1.00	3.13	5.60	1.00	0.002*

SD, standard deviation; *, Significant *P*-value