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RENAL MANIFESTATIONS OF SICKLE CELL DISEASE

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ABSTRACT

Background: Patients with sickle cell disease (SCD) are at increased risk of serious morbidity and mortality. Renal abnormalities in SCD are well known but renal involvement in Syrian patients with SCD has not been studied. **Aim:** We sought to identify the renal manifestations of sickle cell anemia among patients attending Tishreen University Hospital in Lattakia. **Materials and Methods:** This descriptive observational study included 76 patients (42 males, 34 females) diagnosed with sickle cell anemia confirmed by hemoglobin electrophoresis, and followed at Tishreen University Hospital in Lattakia, during the period between 2019 - 2020. The glomerular filtration rate was estimated (eGFR) using the 'modification of diet in renal disease' (MDRD) formula. All patients underwent evaluation by urine examination to detect hematuria, and 24- hour urine collection to measure to quantitate proteinuria. We constructed a multivariate logistic regression model to assess the association between hydroxyurea and proteinuria. **Results:** The renal manifestations of sickle cell anemia were as follows: glomerular hyperfiltration (9.2%), impaired renal function (31.6%), proteinuria (39.5%), and hematuria (19.7%). Patients with impaired renal function had a greater mean age and a higher prevalence of proteinuria compared with patients with normal renal function. A statistically significant inverse linear relationship was found between age and eGFR values ($r = -0.547$, $p < 0.001$). The mean age of patients with proteinuria was greater compared to patients without proteinuria ($P < 0.05$). Use of hydroxyurea is associated with a lower prevalence of proteinuria in patients with sickle cell anemia. The mean eGFR in patients treated with hydroxyurea was significantly greater compared to patients not treated with hydroxyurea ($P < 0.05$). **Conclusion:** Renal abnormalities are present in a significant number of Syrian patients with SCD and proteinuria is the most common abnormality. Hydroxyurea use may prevent development of overt nephropathy or the progression of sickle cell disease nephropathy to end- stage renal disease.

KEYWORDS: Sickle cell disease, Renal manifestation, Hydroxyurea.

INTRODUCTION

Sickle cell hemoglobinopathies are a group of genetic disorders that result from a single base pair DNA mutation in the globin gene, which leads to the formation of an abnormal hemoglobin tetramer, hemoglobin S.[1]

When the S-globin gene is inherited in a homozygous pattern (SS disease), it results in a severe disease, with profound anemia and multiple organ involvement, including cerebrovascular events, acute vaso- occlusive episodes, retinopathy, acute chest syndrome, and renal damage.[2]

The term sickle cell nephropathy encompasses all the structural and functional abnormalities of the kidney seen in sickle cell disease (SCD).[3] It is primarily a consequence of glomerular hypertrophy and resultant focal segmental glomerulosclerosis.[4]

Chronic sickling underlies several mechanisms for end-organ damage including kidney disease. The process of kidney damage is mediated by adherence of the polymerized sickle cell hemoglobin to the erythrocyte membrane. This alters the blood rheology and leads to binding of sickle cell to the endothelium, thereby causing microvascular injury which eventually leads to vaso-occlusion and ischemia ultimately culminating in end-organ damage.[5–7]

In the kidneys this leads to worsening of medullary hypoxia and hypertonicity leading to loss of vasa recta and resulting in a defect in the concentrating capacity with consequent isosthenuria.[8] The medullary hypoxia has been found to lead to edema, focal scarring, and interstitial fibrosis resulting in tubular atrophy.[9] Interstitial fibrosis and scarring would naturally lead to progression of chronic kidney disease (CKD). Renal hemodynamics in SCD reveals increases in renal blood flow leading to hyperfiltration and glomerular hypertrophy. As the disease progresses, impairment of glomerular permselectivity develops with increased ultrafiltration coefficient, worsening glomerular hyperfiltration, and consequent proteinuria.[9,10] Prolonged glomerular hyperfiltration may cause further glomerular injury resulting in focal segmental glomerulosclerosis which is commonly seen in adults with SCD.[11,12] Further progression of the disease leads to ischemia and fibrosis with obliteration of glomeruli which would manifest as progressive renal insufficiency ultimately leading to reduced ultrafiltration capacity, renal plasma flow and resulting in end-stage renal disease.[9,13,14]

MATERIALS AND METHODS

Adult patients with SCD followed up at the hematology and nephrology outpatient clinic, Tishreen University Hospital, Lattakia, were prospectively studied.

Inclusion criteria included

- Age of 18 years or older
- Documented homozygous or heterozygous SCD confirmed by hemoglobin electrophoresis.

Patients with sickle cell trait, diabetes mellitus, pregnant females, patients with acute pain episodes during the two weeks prior to the assessment, suspected urinary tract infection or renal stones, and patients who refused to participate in the study were excluded.

All patients gave informed consent. A total of 76 patients with SCD were studied. All patients had blood extraction for blood urea nitrogen (BUN), serum creatinine, complete blood count (CBC), Na and K determination. The estimated glomerular filtration rate was calculated at admission using the MDRD equation.[15]

eGFR [mL /min/1.73 m2] = 186 x (Serum creatinine - 1.1054) (mg / dL) x (age - 0.203) (years old) x 0.742 (if woman).

In addition, all patients had 24-hour urine collection to quantify proteinuria. 24-hour urine were collected from 8 AM to 8 AM next day according to the standard protocol. Protein concentration was measured with an automatic Mindray BS-380 device via the SYRBIO® Pyrogallol method. At a temperature of 37 degrees Celsius and expressed as grams / 24 hours". Proteinuria was defined as the excretion of more than 0.150 g/24 hours.

Urine samples were collected in the morning (not necessarily the first sample in the morning). Urine samples were tested for the presence of blood, protein, hemoglobin and other abnormalities. Hematuria was defined as the presence of 3 red cells in the field (high magnification).

According to the National Kidney Foundation recommendations,[16] patients were divided into six groups:

- Hyperfiltration (eGFR ≥ 140 mL /min/1.73 m2).
- Normal renal function (eGFR 90-139 mL /min/1.73 m2).
- Mild renal insufficiency (eGFR 60-89 mL /min/1.73 m2).
- Moderate renal insufficiency (eGFR 30-59 mL /min/1.73 m2).
- Severe renal insufficiency (eGFR 15-29 mL /min/1.73 m2).
- Renal failure (eGFR < 15 mL /min/1.73 m2).

Then we conducted a statistical analysis after dividing the patients into two groups:
1- Normal renal function: eGFR ≥ 90 mL/min/1.73 m2
2- Renal impairment: eGFR < 90 mL/min/1.73 m2

Statistical analysis

The analysis was performed using the Statistical Package for Social Sciences (SPSS) (version 20) (IBM Corporation, Armonk, New York, USA) and Excel 2010 program. A predictive value less than 0.05 was considered statistically significant. Continuous data were expressed as minimum, maximum, median and range while categorical data were expressed as percentages. Clinical parameters were compared between groups using the Mann-Whitney U test for non-parametric data. Chi- square (X2)was used as appropriate to assess the relationship between categorical variables. In addition, Spearman's correlation was used to assess the association between variables.

RESULTS

Patients' characteristics

Our study included 76 sickle cell anemia patients, males were 42 patients (55.3%) and females were 34 patients (44.7%).The mean age of patients was 25 ± 12.5 years in a range of 18-61 years. The largest proportion of research patients were in the 20-29 age group. The distribution of additional baseline characteristics is presented in (Table 1).

Table 1: Demographic and clinical characteristics of patients.

Characteristics	Number	Percent
Age (years)		
<20	9	11.8%
20 – 29	36	47.4%
30 – 39	19	25%
40 – 49	5	6.6%
50 – 59	5	6.6%
≥ 60	2	2.6%
Gender		
Male	42	55.3%
Female	34	44.7%
hydroxyurea therapy		
Yes	20	26.3%
No	56	73.7%

Table 2: Hematological and biochemical indices of patients.

Indices	Median	Range
WBC (109/L)	10.8	7.3 – 13.5
Hgb (g/dl)	7.5	6.7 – 8.9
Plt (109/L)	193	15 – 970
Serum Cr (mg/dl)	0.6	0.4 – 9.3
Urea (mg/dl)	16.8	8 – 228
eGFR (ml/m/1.73m2)	129.1	50.8 – 240
NA (mEq/L)	135	125 – 141
K (mEq/L)	4.4	3.2 – 5.2
24h urine volume (ml)	3577	1400 – 9000
24h urine protein (g/day)	0.15	0.04 – 13.4

The median and range of hematological and biochemical indices of patients is presented in (Table 2).

Table 3: Shows the distribution of kidney function according to eGFR.

Table 3: The distribution of kidney function according to eGFR.

eGFR (ml/m/1.73m2)	Number	Percent
≥ 140 (Hyperfiltration)	7	9.2%
139 – 90 (Normal renal function)	45	59.2%
89 – 60 (Mild renal insufficiency)	11	14.5%
59 – 30 (Moderate renal insufficiency)	6	7.9%
29 – 15 (Severe renal insufficiency)	4	5.3%
<15 (Renal failure)	3	3.9%

Median protein excretion in 24-hours for the patient cohort was abnormal (0.15 g/day, range 0.04-13.4). Proteinuria was found in 30 patients (39.5%). Majority of the patients with protein in the urine had mild proteinuria while five patients (6.6%) had nephrotic range proteinuria (> 3 g/day). Hematuria was found in 15 patients (19.7%). Table 4 shows the renal manifestations of sickle cell anemia in study population.

Table 4: Renal manifestations of sickle cell anemia in study population.

Renal manifestations	Number	Percent
Proteinuria	30	39.5%
Hematuria	15	19.7%
Hyperfiltration (eGFR ≥ 140 mL/min/1.73 m2)	7	9.2%
Renal impairment (eGFR < 90 mL/min/1.73 m2)	24	31.6%

Patients' characteristics according to kidney function

Table 5 shows comparison of the demographic, clinical, hematological and biochemical characteristics between patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m2) and patients with renal impairment (eGFR < 90 mL/min/1.73 m2)

Table 5: Comparison of the demographic, clinical, hematological and biochemical characteristics between patients with normal renal function and patients with renal impairment.

Characteristics	eGFR		Test	P-value
	< 90	**≥ 90**		
Gender				
Male	13 (54.2%)	29 (55.8%)	0.017**	0.89
Female	11 (45.8%)	23 (44.2%)		
Age	29.7 ± 10.7	23.3 ± 13	2.116*	0.0376
Age groups				

< 20	2 (22.2%)	7 (77.8%)	0.414**	0.519
20 – 29	9 (25%)	27 (75%)	0.457**	0.499
30 – 39	5 (26.3%)	14 (73.7%)	0.325**	0.568
40 – 49	2 (40%)	3 (60%)	0.176**	0.674
50 – 59	4 (80%)	1 (20%)	5.8**	0.015
≥ 60	2 (100%)	0 (0%)	4.45**	0.034
Proteinuria				
Yes	14 (58.3%)	16 (30.7%)	5.222**	0.022
No	10 (41.7%)	36 (69.3%)		
Hematuria				
Yes	6 (25%)	9 (17.3%)	0.613**	0.433
No	18 (75%)	43 (82.7%)		
Biochemical indices				
WBC (109/L)	10.7 ± 3.8	11 ± 3.07	0.366*	0.714
Hgb (g/dl)	7.80 ± 2.1	7.3 ± 2.2	0.934*	0.353
Plt (109/L)	195 ± 90	210 ± 112	0.575*	0.566
Serum Cr (mg/dl)	1.9 ± 0.8	0.6 ± 0.1	11.61*	<0.0001
Urea (mg/dl)	24 ± 5.4	13.6 ± 4.1	9.27*	<0.0001
eGFR (ml/m/1.73m2)	54 ± 8	135 ± 3	64.2*	<0.0001
NA (mEq/L)	133±2.4	135.7 ± 10	1.3*	0.197
K (mEq/L)	4.7 ± 1	4.2 ± 1.2	1.77*	0.08
Blood pressure				
SBP	125 ± 13	124 ± 10	0.367*	0.714
DBP	67 ± 4	64 ± 10	1.414*	0.161

* Mann-Whitney U test
**Chi-square (X2) test

We studied the linear correlation between age and eGFR values (figure1), There is a significant inverse correlation between age and eGFR values, eGFR values decrease with aging (r= -0.547, P<0.001).

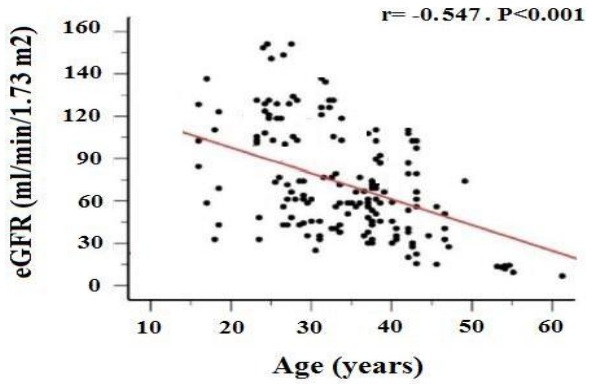

Figure 1: Correlation between eGFR and age in our study.

Patients' characteristics according to proteinuria

Table 6 Shows comparison between patients with and without proteinuria.

Table 6: Comparison between patients with and without proteinuria

Characteristics	Proteinuria		Test	P-value
	Yes	No		
Age (years)	28.4 ± 11	23.5 ± 10	2.007	0.048
eGFR (ml/m/1.73m2)	98 ± 20	133.5 ± 15	8.82	<0.0001

Patients' characteristics according to hydroxyurea therapy

The number of patients treated with hydroxyurea in the study was 20 patients (26.3%). Proteinuria was found in 25% of them, and in 44.6% of those not treated with hydroxyurea. Table 7 illustrates the relationship between proteinuria and eGFR and hydroxyurea therapy and in patients with sickle cell anemia in the study.

Table 7: The Relationship between proteinuria and Egfr and hydroxyurea therapy.

Characteristics	hydroxyurea therapy		Test	P-value
	Yes	No		
Proteinuria				
Yes	5 (25%)	25 (44.6%)	4.308**	0.037
No	15 (75%)	30 (55.4%)		
eGFR (ml/m/1.73m2)	136 ± 27	122 ± 23	2.23*	0.0287

* Mann-Whitney U test **Chi-square (X2) test

DISCUSSION

Sickle cell disease is one of the most common severe single-gene genetic disorder in the world. Despite simple molecular causation, sickle cell disease is a multi-organ disease with episodes of acute disease and progressive organic injury. Renal impairment in the settings of sickle cell disease includes many glomerular and tubular disorders and is associated with increased mortality if left untreated. Kidney disease begins in childhood and progresses with age. Our study was aimed to determine the renal manifestations of sickle cell anemia in patients attending Tishreen University Hospital in Lattakia. The study included 76 patients (42 males, 34 females) diagnosed with sickle cell anemia confirmed by hemoglobin electrophoresis. Patients ages ranged between 18-61 years with a mean age of 25 years. 54 patients (71%) had fewer than 3 episodes of sickle cell crises per year, 15 patients (19.5%) had 3-5 episodes per year, and 7 patients (9.2%) had more than 5 episodes per year was.

Advances in the medical care of patients with Sickle cell anemia 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.[17] Therefore, it is not surprising that the mean age of patients in our study was 25 years. Aleem et al,[18] reported a mean age of 23 years, Arogundade et al,[19] reported a mean age of 23 years, Bukar et al,[20] reported a mean age of 27 years, Drawz et al,[21] reported a mean age of 36.6 years.

The mean estimated GFR calculated according to the MDRD equation was: 129.1 ± 36 mL/min/1.73 m2. Glomerular hyperfiltration (defined as eGFR ≥ 140 mL/min/1.73 m2) was found in 7 patients (9.2%), and renal impairment (defined as eGFR < 90 mL/min/1.73 m2) in 24 patients (31.6%). Proteinuria was found in 39.5% of patients, and hematuria in 19.7%.

Bhaskar et al,[22] found a hyperfiltration rate of 9.9%. Bukar et al,[20] found a hyperfiltration rate of 26.8%. In the study by Ephraim et al,[23] hyperfiltration rate was 68.4% in children and 31.2% in adults.

Glomerular changes in SCD occur early in the first decade of life even though SCD patients remain asymptomatic. These are characterized by high renal blood flow, hyperfiltration and hypertrophy. Current data suggest that infants with SCD develop a hyperfiltration phase, which plateaus during early childhood. As early as the first year, renal enlargement is observed in correlation to hyperfiltration. Hyperfiltration is a well-known phenomenon in SCD even though the pathogenesis and pathophysiology is less well understood. As a result of hyperperfusion, increased amount of fluids is presented to the proximal tubule triggering more tubular reabsorption of sodium and water in order to restore glomerulotubular balance. Increased proximal tubular sodium reabsorption is associated with high metabolism and adaptive cellular response leading to overall renal enlargement. This complex phenomenon might be relevant to the glomerular hypertrophy that occurs in SCD.[24]

Our study demonstrated that 24 patients (31.6%) had renal impairment (defined as eGFR < 90 mL/min/1.73 m2). Renal impairment rates in previous studies was 38.9% (Bukar et al),[20] 20.6% (Bhaskar et al),[22] 55.2% (Guasch et al),[25] 31.6% in children and 68.4% in adults (Ephraim et al).[23]

When the factors associated with impaired renal function were studied, no significant difference was found according to gender (P=0.89). Patients with renal impairment were older compared to patients with normal renal function (P= 0.0376). When studying the correlation between age and eGFR values, a statistically significant inverse correlation was found (r= -0.547, p <0.001). Patients with renal impairment had more proteinuria (58.3%) compared to patients with normal renal function (30.7%) (P=0.022). Hematuria was present in 25% of patients with renal impairment and in 17.3% of patients with normal renal function, the difference was not statistically significant (P> 0.05). Patients with renal impairment had a significantly higher concentrations of serum creatinine and urea and a significantly lower rate of glomerular filtration. No significant differences in the mean systolic or diastolic pressure was found between the two groups.

Our results are consistent with the study of Arogundade et al.[19] which showed that eGFR decreases with age, with a linear correlation (r = -0.245, P <0.001) (Figure 2).

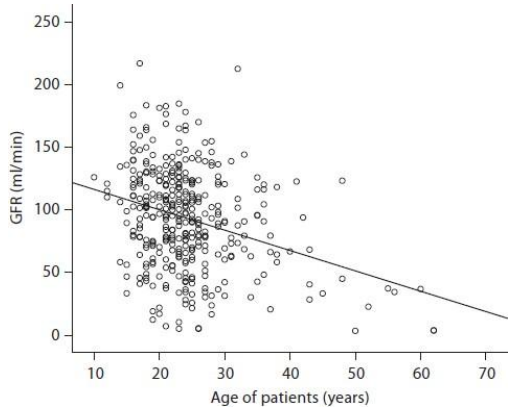

Figure 2: Correlation between eGFR and age (Arogundade et al).[19]

Geard et al,[26] also showed that eGFR decreases with age with a linear correlation (r = -0.55, P <0.001) Figure (3).

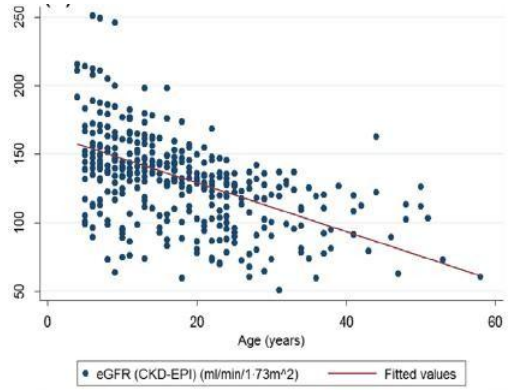

Figure 3: Correlation between eGFR and age (Geard et al).[26]

Proteinuria was found in 39.5% of the patients in our study. The mean age of patients with proteinuria was greater than patients without proteinuria (P =0.048). Patients with proteinuria had a significantly lower eGFR compared to patients without proteinuria (P <0.0001).

Proteinuria is more sensitive than elevated serum creatinine as a marker for detecting glomerular injury, and it has been reported as an early manifestation of sickle-cell nephropathy. In our study, proteinuria was found in 30.7% of patients with normal renal function, and in 58.3% of patients with renal impairment. Aleem et al.[18] reported that proteinuria was found in 41% of patients with sickle cell anemia. Guasch et al.[25] found that proteinuria was present in 37.1% of patients. It is known that proteinuria in sickle cell anemia is age dependent. The prevalence of proteinuria in the first three decades of life is up to 27% increasing to 68% in older SCD patients.[27]

Hematuria was found in 19.7% of the patients in our study. Some studies reported higher prevalence rates, Bukar et al[20] reported the prevalence of hematuria in 33.1%. Aleem et al.[18] found that hematuria was present in 8.5% of patients. Haematuria is among the most common renal manifestations of SCD, and can present as microscopic or macroscopic haematuria; the latter can be lifethreatening.[28] Haematuria reflects capillary congestion, especially in the medullary vessels, with extravasation of RBCs into the tubular lumen. Congestion and rupture of the submucosal capillaries in the renal pelvis can also be responsible for haematuria, these vessels branch from the efferent arterioles of the juxtamedullary nephrons, from which the vasa recta also arise. Blockage of the vasa recta can divert blood flow to capillaries that supply the mucosa of the renal pelvis and to the peritubular capillaries of the juxtamedullary nephrons. Haematuria emanates more frequently from the left kidney than the right because of the socalled nutcracker phenomenon imposed upon the left renal vein as it passes between the aorta and the superior mesenteric artery, this phenomenon leads to compression of the vein.

In our study, treatment with hydroxyurea was associated with a lower prevalence of proteinuria. The mean eGFR in patients treated with hydroxyurea was significantly greater compared to patients not treated (P = 0.0287). Laurin et al.[29] showed that the use of hydroxyurea was associated with a lower prevalence of albuminuria (34.7% vs 55.4%). The use of hydroxyurea was also associated with a higher eGFR (151 versus 128 ml/min/1.73 m2). In another study Geraldo B. Silva Junior et al.[30] showed that the use of hydroxyurea was associated with a lower prevalence of proteinuria, but no significant difference was found in eGFR between hydroxyurea treated and untreated patients (112 versus 105 ml/min/1.73 m2) (p = 0.504).

CONCLUSIONS

1. The most common renal manifestations of sickle cell anemia are: Glomerular hyperfiltration (9.2%), impaired renal function (31.6%), proteinuria (39.5%), and hematuria (19.7%)
2. Patients with renal impairment are older than patients with normal renal function. There is a significant inverse correlation between age and eGFR (r = -0.547, p <0.001).
3. The prevalence of proteinuria among patients with impaired renal function (58.3%) is significantly higher compared to patients with normal renal function (30.7%) (P = 0.022).
4. The mean age of patients with proteinuria was greater than patients without proteinuria (P =0.048). Patients with proteinuria had a significantly lower eGFR compared to patients without proteinuria.
5. Treatment with hydroxyurea was associated with a lower prevalence of proteinuria. The mean eGFR in patients treated with hydroxyurea was significantly greater compared to patients not treated.

Recommendations

1. Renal complications associated with sickle cell anemia are common and progressive. Therefore, we emphasize the recommendations regarding periodic follow-up for patients.
2. Conducting more studies on the factors predicting the

development of these complications by following-up the patients for long periods of time.
3. Conducting more studies on the effect of drug interactions on the progression of sickle cell nephropathy.
4. Hydroxyurea is recommended to relieve kidney disease.

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