Renal Tubular Dysfunction in Sickle Cell Disease

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Key Words
Sickle cell disease • Kidney disease • Tubular dysfunction • Renal function tests • Renal tubular acidosis

Abstract
Background/Aims: Kidney abnormalities are one of the main chronic complications of sickle cell disease (SCD). The aim of this study is to investigate the occurrence of renal tubular abnormalities among patients with SCD. Methods: This is a prospective study with 26 SCD adult patients in Brazil. Urinary acidification and concentration tests were performed using calcium chloride (CaCl₂), after a 12h period of water and food deprivation. Fractional excretion of sodium (FE\textsubscript{Na}), transtubular potassium gradient (TTKG) and solute free water reabsorption (Tc\textsubscript{H₂O}) were calculated. The SCD group was compared to a group of 15 healthy volunteers (control group). Results: Patient’s average age and gender were similar to controls. Urinary acidification deficit was found in 10 SCD patients (38.4%), who presented urinary pH >5.3 after CaCl₂ test. Urinary osmolality was significantly lower in SCD patients (355±60 vs. 818±202mOsm/kg, p=0.0001, after 12h period water deprivation). Urinary concentration deficit was found in all SCD patients (100%). FE\textsubscript{Na} was higher among SCD patients (0.75±0.3 vs. 0.55±0.2%, p=0.02). The TTKG was higher in SCD patients (5.5±2.5 vs. 3.0±1.5, p=0.001), and Tc\textsubscript{H₂O} was lower (0.22±0.3 vs. 1.1±0.3L/day, p=0.0001). Conclusions: SCD is associated with important kidney dysfunction. The main abnormalities found were urinary concentrating and incomplete distal acidification defect. There was also an increase in the potassium transport and decrease in water reabsorption, evidencing the occurrence of distal tubular dysfunction.

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Introduction

Sickle cell disease (SCD) is the most frequent hematologic hereditary disorder in the world, and the prevalence of sickle cell trait is around 7% [1, 2]. The disease is characterized by multisystem involvement, with episodes of acute illness and progressive organ damage [2].

Kidney involvement in SCD includes a variety of glomerular and tubular disorders, which are associated with increased mortality [3-5]. The pathophysiology of sickle cell nephropathy includes the polymerization of erythrocytes into renal medulla, a region which predisposes to this phenomenon due to its low local oxygen pressure, low pH, and high osmolality [4, 6]. These alterations lead to renal tubular function abnormalities, including urinary concentrating and acidification defects, and glomerular hyperfiltration due to an increased prostaglandin production, which can in turn lead to glomerulosclerosis [4, 5].

It is estimated that 4-12% of SCD patients will develop life-threatening end-stage renal disease [5], and this picture can be even worse because the life expectancy of these patients are increasing and so are the complications associated with the chronic course of the disease. The exact incidence and clinical course of sickle cell nephropathy is unknown, as well as all the mechanisms involved in its pathogenesis.

The aim of the present study is to investigate glomerular and tubular dysfunction in adult SCD patients through traditional and new renal tubular function tests, highlighting important possible novel aspects on its pathophysiology.

Patients and Methods

Patients' selection

This is a prospective cohort study with 26 consecutive patients with clinical and laboratory diagnosis of SCD (hemoglobin SS) undergoing consultation in a public health service in Brazil from December 2010 to June 2012. The patients were selected in the outpatients' clinics of Hematology Service. Those who agreed to participate in the study and who gave their written informed consent were included, unless they had any exclusion criteria as patients under 18 years or older than 65 years, use of nephrotoxic drugs, hypertension (systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90mmHg), diabetes mellitus, urinary tract infections, systemic lupus erythematosus, collagen vascular disorder and other conditions which could affect kidney function. The 26 patients were compared with 15 healthy volunteers (randomly selected among blood donors). None of the controls had sickle cell trait.

Ethics

The protocol of this study was revised and approved by the Ethical Committee of the Walter Cantidio University Hospital, Federal University of Ceará, Fortaleza, Brazil. Patients were included in the study after signing the informed consent form.

SCD Diagnosis

All patients had a definitive diagnosis of SCD with hemoglobin electrophoresis. All of them were homozygous and presented hemoglobin S (HbSS).

Protocol of treatment

All patients were treated with folic acid 5mg/day and 12 with hydroxyurea 1g/day (since 1 to 2 years).

Group Definition

A comparison between the studied parameters was done between the study group and controls.

Clinical and laboratory parameters

At the time of medical consult all symptoms and signs were evaluated and the following data were recorded: race, age, gender, previous chronic diseases (heart failure, arterial hypertension and diabetes...
mellitus), use of drugs, blood pressure and weight. The following laboratory parameters were evaluated: total blood count, plasma urea (P_{Ur}), creatinine (P_{Cr}), sodium (P_{Na^+}), potassium (P_{K^+}), fasting glucose, osmolality (P_{osm}), arterial pH and bicarbonate (HCO_{3^-}) A 24-hour urinary volume (UV) sample was collected for creatinine (U_{Cr}), urea (U_{Ur}), sodium (U_{Na^+}), potassium (U_{K^+}) and albuminuria measurements. Urine samples were collected for osmolality (U_{osm}) and pH (U_{pH}) determination, as described below.

**Kidney function evaluation**

Glomerular filtration rate (GFR) was calculated by 24-hour urine collection for creatinine measurement. Severe kidney function loss was considered when GFR was <60mL/min/1.73m^2. Glomerular hyperfiltration was considered as GFR>120mL/min/1.73m^2. Albuminuria was determined by 24-hour urine collection and abnormal values were considered when >30mg/day. To assess tubular function, fractional excretion of sodium (FE_{Na}) was calculated through standard formula. Solute free water reabsorption (T_cH_{2O}) was calculated by the formula: T_cH_{2O} = Cosm – V (where Cosm = U_{osm} / P_{osm}; V = urinary flow), and the transtubular potassium gradient (TTKG) by the formula: TTKG = (P_{osm} x U_{K^+})/(P_{K^+} x U_{osm}).

All patients underwent food and water deprivation for 12 hours. Urinary concentration ability was evaluated through the ratio between urinary and serum osmolality (U_{osm}/P_{osm}) after 12 hours water deprivation. Urinary acidification was evaluated through the measure of urinary pH before and after administration of oral CaCl_{2} 2mEq/kg (T_0 and T_4), as it is more tolerable than ammonium chloride [7]. Acidification defect was determined by the inability in decreasing U_{pH} for less than 5.3 after the administration of the acid load, as described before [8].

**Analytical methods**

Urea was determined by colorimetric uricase method (Labtest®). The results were expressed in mg/dL. Serum and urinary creatinine were determined by colorimetric method, picric acid, Taussky and Bonsness (Labtest®). The results were expressed in mg/dL. Serum and urinary sodium and potassium (P_{Na^+} and P_{K^+}) were determined by photometry technique with spectrophotometry, model B462 MICRONAL (Instrumentation Laboratory, Inc. USA). The results were expressed in mEq/L. Glucose was determined by colorimetric glucose oxidase method (Labtest®). The results were expressed in mg/dL. Arterial pH and bicarbonate (HCO_{3^-}) were determined through “Blood gas analyzer” machine (chiron diagnostic 238 - Bayer®). The results were expressed in mEq/L for bicarbonate. Urinary pH (U_{pH}) was measured by pHmetro Digital pG1000, model GEHAKALT. Urinary osmolality was determined by the technique pressure steam in osmometer model 5100C (Wescor Inc., USA). The results were expressed in mOsm/Kg.H_{2}O. Albuminuria was measured through immunoturbidimetry methods, using Tina-quant® kit (Roche) and the results were expressed in mg/day.

**Statistical analysis**

The SCD group was analyzed as a general group and was compared with the control group. A comparison between SCD patients according to the use of hydroxyurea and age was also done. Fisher’s exact test and X^2 test were used to analyze allele frequencies in the patients’ group. Differences between two independent variables were evaluated using Student’s t test or Mann-Whitney test as appropriate. Data were expressed as means ± SD, and p<0.05 was considered statistically significant. The SPSS software for Windows, release 10.0 (SPSS Inc., Chicago, Ill., USA) was used in all analyses.

**Results**

**Subject characteristics**

A total of 26 SCD patients were studied, with a mean age of 32.1±9.9 years (range 20-53 years), and 16 (61%) were females. There was no significant difference regarding age, gender, mean arterial blood pressure and body weight between the SCD and control group (Table 1). All patients had sickle cell anemia (HbSS) and a mean fetal hemoglobin of 10.9±6.9% at the time of the last medical visit. Patients with SCD had lower levels of hemoglobin (9.1±1.4 vs. 13±1.3g/dl, p=0.0001) and hematocrit (26±4.2 vs. 41±4.2%, p=0.0001) than controls, as well as higher leukocytes count (9725±3065 vs. 6350±409/mm^3, p=0.0001). Platelets count had
Kidney function evaluation

Glomerular filtration rate and proteinuria. GFR was similar in both groups (114±53 vs. 102±17ml/min/1.73m², p=0.40). Glomerular hyperfiltration was found in 9 SCD patients (34.6%). GFR<60ml/min/1.73m² was observed in 3 cases (11.5%). The distribution of patients according to GFR and the classification of chronic kidney disease is illustrated in Figure 1. Albuminuria was higher among SCD patients than in controls (66±121 vs. 6.5±6mg/day, p=0.0001), as shown in Table 2. Microalbuminuria was found in 7 cases (27%). Diuresis was higher in SCD patients than in controls (1819±704 vs. 1028±273, p=0.0002). The distribution of patients according to the occurrence of proteinuria is shown in Figure 2.

Sodium, potassium and water tubular transport. In basal conditions, SCD group had a significantly higher FENa (0.75±0.3 vs. 0.55±0.2, p=0.02), TTKG (5.5±2.5 vs. 3.0±1.5, p=0.001) and TcH₂O (0.22±0.3 vs. 1.1±0.3L/day, p=0.0001), when compared to the control group (Table 2).

Urinary concentration ability. When the maximum urinary concentration ability was assessed, patients in the SCD group had lower Uosm (355±60 vs. 818±202mOsm/Kg, p=0.0001) after a 12h period of water deprivation when compared to controls, as well as lower Uosm/Posm (1.1±0.2 vs. 2.8±0.7,
p=0.0001), as can be seen in Table 3. All SCD patients had the relation $U_{\text{osm}}/P_{\text{osm}}$ lower than 2.8, evidencing urinary concentration inability.

**Urinary acidification ability.** The $U_{\text{pH}}$ before CaCl$_2$ load was higher in the SCD group when compared to controls (5.9±0.3 vs. 5.6±0.5, p=0.02). The inability to decrease urinary pH to less than 5.3 after use of CaCl$_2$ was observed in 10 patients (38.4%) as shown in Table 3. Patients’ response to CaCl$_2$ load, according to urinary pH values, is illustrated in Figure 3. There were 3 patients with after load pH<5.0. Serum bicarbonate ($HCO_3^-$) was lower in SCD patients before (24±1.7 vs. 26±2.3mEq/l, p=0.01) and after CaCl$_2$ test (22±1.8 vs. 24±2.3mEq/l, p=0.01). Arterial pH was similar in both groups before and after the CaCl$_2$ load, while urine pH was higher among SCD patients, as a possible consequence of urinary acidification inability (Table 3). There was only one patient with metabolic acidosis, which was associated with renal failure (GRF=62ml/min). Urinary pH for this patient was 6.1 before CaCl$_2$ load and 6.0 after CaCl$_2$ load. The distribution of patients according to the occurrence of urinary concentration and acidification deficits and proteinuria is shown in Figure 4.

**Discussion**

The results of the present study clarify important aspects of glomerular and tubular dysfunction in SCD patients. They were all asymptomatic, which calls our attention to the

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**Table 3.** Comparison of concentration and acidification test results between patients with SCD and controls

| Parameters                        | SCD (N=21) | Control (N=15) | P     |
|-----------------------------------|------------|----------------|-------|
| $U_{\text{osm}}, mOsm/kg$         | 355±60     | 818±202        | 0.0001|
| $U_{\text{osm}}/P_{\text{osm}}$   | 1.19±0.21  | 2.8±0.7        | 0.0001|
| Arterial pH$_{70}$                | 7.35±0.03  | 7.37±0.04      | 0.31  |
| Arterial pH$_{14}$                | 7.34±0.03  | 7.35±0.03      | 0.31  |
| $HCO_3^-, mEq/L$                  | 24±1.7     | 26±3.3         | 0.01  |
| $HCO_3^-, mEq/L$                  | 22±1.8     | 24±3.4         | 0.01  |
| $U_{\text{pH}}_{70}$              | 5.9±0.3    | 5.6±0.5        | 0.02  |
| $U_{\text{pH}}_{14}$              | 5.3±0.3    | 5.1±0.3        | 0.04  |

$U_{\text{osm}}$ - urinary osmolality, $U_{\text{pH}}/P_{\text{osm}}$ - ratio urinary and plasmatic osmolality, $U_{\text{pH}}_{70}$ - urinary pH in $T_0$, $U_{\text{pH}}_{14}$ - urinary pH in $T_4$. Data are shown as means±SD. Significant P < 0.005
importance of performing regular kidney function assessment in all SCD patients, including more specific tests, such as the urinary concentration and acidification tests.

Kidney involvement in SCD has been observed since the first official case of the disease reported in literature, which described the presence of increased diuresis and urine of low specific gravity [9].

Functional and anatomical renal lesions have been described as a consequence of red blood cell sickling in the vasa recta of the renal medulla [10]. It has been recently demonstrated that renal function loss in SCD is associated with hemolysis. Glomerular filtration rate presented a significant correlation with reticulocyte count and bilirubin [11].

In the present study, there was no difference in the mean glomerular filtration rate (GFR) between patients and controls, however there was a significant number of SCD patients with decreased GFR (<60mL/min/1.73m²), which was found in 11.5% of cases, which is higher than the previous found in another study in our region, which found a prevalence of GFR<60mL/min/1.73m² in 5.1% of SCD patients [12]. We have identified 3 patients with renal failure, probably corresponding to chronic kidney disease, and all these 3 patients had concentration and acidification deficit. When excluding these patients still 30% have incomplete tubular acidosis. There were also a significant number of patients with glomerular hyperfiltration (34.6%). An increase in renal blood flow and glomerular filtration is frequently observed in SCD, becoming apparent around 1 year after birth and tending to decrease with aging [13, 14]. In a cohort of 85 children with SCD, 76% had glomerular hyperfiltration [15]. In a recent study performed in our region, hyperfiltration was found in 53% of SCD patients [12], which was higher than the found in the present study.

In a study investigating renal acidification ability in SCD patients, increased GFR was found as a rule in HbSS patients, mainly in the younger age groups [10]. The incidence of glomerular hyperfiltration in SCD varies from 76% in children to 14% in adults [15, 16]. The main long-term effect of glomerular hyperfiltration is GFR decrease due to glomerulosclerosis. The most common glomerulopathy observed in SCD patients is focal and segmental glomerulosclerosis, which can be a result of glomerular hyperfiltration [5, 17].

In the present study significant microalbuminuria, which is an early predictor of glomerular lesion, was observed in 27% of cases, which is lower than the described in previous studies [18-24]. This difference could be attributable to differences in genetics, including different haplotypes. The levels of albuminuria were higher among the younger patients in our cohort, evidencing that this is one of the first manifestations of sickle cell nephropathy. Alvarez et al. [21] have found similar results but showed a significant association between
proteinuria and serum cystatin C. Cystatin C also has an inverse correlation with GFR in SCD [15]. Novel biomarkers are under investigation for use in SCD. Urinary kidney injury molecule-1 (KIM-1) and N-acetyl-b-D-glucosaminidase (NAG) presented a strong correlation with albuminuria in a recent cohort of 116 patients with SCD [25]. Urine endothelin-1 was also found to be associated with microalbuminuria in SCD patients, as well as with urinary concentration defect [26]. Albuminuria has been described in 16 to 60% of adults with SDC [5, 18, 20-22, 27], and has significant correlation with age [11, 19, 24]. No patient in our cohort developed nephrotic range proteinuria, which is really rare in SCD [5]. Proteinuria is an early manifestation of sickle cell glomerulopathy and should be investigated in all patients with SCD [13, 22].

Renal sodium handling was evaluated by FE\textsubscript{Na} measurements and it was found to be significantly higher among SCD group. TTKG was also higher in SCD group and TcH\textsubscript{2}O was lower, suggesting an increased transtubular potassium transport and a higher salt and water lost, pointing to a renal salting wasting syndrome in SCD. A renal salt-losing state has been suggested to explain the low incidence of hypertension in patients with SCD [17]. In fact the levels of blood pressure were similar between SCD patients and controls in our study. It is described that the increase in sodium and water loss from the collecting duct leads to a reactive increase in sodium and water reabsorption by the proximal tubule [5], but even with this possible increase in sodium reabsorption the FE\textsubscript{Na} was higher in SCD patients than in controls, which suggests a possible proximal tubular defect. The loss of other substances, such as glucose, amino acids, phosphate and bicarbonate should also be performed in SCD, configuring Fanconi Syndrome, which has been described in SCD patients, but it was attributable to deferoxamine use [28]. It is possible that SCD could cause Fanconi Syndrome. No patient in our cohort was using deferoxamine, so if they had Fanconi Syndrome, it could be attributable to SCD itself. A distal tubule defect could also be responsible for FE\textsubscript{Na} increase in our patients. Since we have no data on glycosuria, hypophosphatemia and hypouricemia we cannot state that these patients have a proximal tubule defect.

Impaired reabsorption of solute free water in the distal convoluted tubules and collecting ducts is also supposed to occur in SCD, as suggested by Crosley Jr. & Strickland [29] in one of the first reported cases of renal concentration defect associated with SCD. It is believed that the kidney failure to acidify the urine to a normal extent implies a disturbed exchange of H\textsuperscript{+} ions for Na\textsuperscript{+}, so it is expected that abnormal acidification in SCD is accompanied by impairment in the sodium conservation [10]. Further studies are required to better comprehend proximal tubular dysfunction in SCD. The higher TTKG observed in SCD patients evidence an increased potassium transport in distal tubules, despite serum potassium was normal in all cases. A high TTKG is suggestive of inappropriate renal loss of potassium, if serum levels are normal [30]. Distal tubule function is often impaired in SCD, leading to reduced potassium and hydrogen excretion and an incomplete renal tubular acidosis type IV [5]. Higher TTKG is described in the setting of hyperaldosteronism [31], which is another possible explanation to our findings, although it is unlikely. It is known that plasma renin and aldosterone production can be increased in the presence of medullary fibrosis in patients with SCD [3], which could be responsible for some of the abnormalities found in our cohort. Unfortunately it was not possible to dose these hormones levels in our patients, due to technical institutional difficulties. Impaired concentrating defect could explain TTKG difference. Diuresis was also higher among SCD patients, which could be due to concentrating deficit and could also impact on potassium transport.

Abnormal urinary concentrating ability was present in all studied cases, and this is the most common tubular abnormality in SCD [3]. Urinary osmolality was significantly lower in SCD patients than in controls. The inability to concentrate urine under conditions of water deprivation (hyposthenuria) is a very frequent event in SCD, and this begins in childhood. Enuresis is a common finding in children with SCD, which is described in more than 60% of patients, reflecting urinary concentration defect [32]. It is described that patients with SCD can concentrate urine only to a maximum of 400–450 mOsm/kg after 8–10 h of water
deprivation, in comparison with normal subjects [33, 34], and this inability seem to be associated with age [33].

Our patients had a very low urine osmolality (mean 355±60mOsm/Kg after 12-hour water deprivation period, which points to a severe urinary concentration inability. All of them had no symptom, but are at high risk of dehydrating when facing long periods of water deprivation and if they were under extreme heat conditions. Patients with higher levels of HbF have a greater ability to concentrate urine [35]. The mean fetal hemoglobin in our patients was 10.9%, which is similar to previous studies describing renal abnormalities in SCD [22], and this could not be identified as a protective factor, since the majority of patients had low HbF levels (only 5 patients had HbF >10%, median was 8%). A possible action to do would be to administrate hydroxyurea to all these patients, in order to increase HbF levels and maybe improve renal function, but long-term studies would be necessary to assess this possible benefit.

A recent study with 160 children with different renal diseases found a significant association between the inability to concentrate urine and glomerular filtration rate [36], but we did not found this in our cohort, since all patients had urinary concentration defect and the majority of them had normal GFR. The urinary concentration deficit in SCD is associated with red blood cells sickling and sickle cell crisis, with a possible reversion being described with repeated blood transfusions [37]. Urinary concentration process requires an intact collecting duct. The juxtamedullary nephron collecting ducts extend deepest into the medulla and are capable of generating the highest urine concentrations. If reabsorbed sodium is not removed efficiently, as a result of sluggish blood flow due to sickling, sodium reabsorption in the collecting ducts is reduced. The normal medullary concentration gradient necessary for water reabsorption is lost, low-grade sickling persists and medullary congestion develops [3].

We found urinary acidification defect in 38.4% of the studied patients. This abnormality is less frequent than urinary concentration defect, and is described as a form of incomplete renal tubular acidosis. Ho & Alleyne [38] investigated the urinary acidification capacity 8 SCD adult patients by administrating ammonium chloride, as the first type of renal acidification capacity test described [39], and they found a mean urine pH of 5.42, which was lower than in controls (mean 4.85). These authors, however, did not state how many patients presented pH<5.5, which could be considered normal after an acid load. Goossens et al. [10] also found urinary acidification deficit in patients with SCD, and the prevalence of this defect was higher than the observed in the present study (75% among HbSC patients and 92% in HbSS).

Study limitations

Study limitations include the small number of patients (it was not possible to investigate all patients followed in our service). It was not possible to determine GFR through a gold-standard method such as inulin clearance or DTPA and no measurement of ammonium excretion nor titrable acid were performed due to technical limitations of our hospital. We also did not have data regarding \( P_{O_2} \) and \( P_{CO_2} \) to better characterize the acid-base disorders among the studied patients. The laboratory had only provided the values of pH and \( HCO_3^- \).

Conclusion

SCD is associated with important kidney dysfunction. The main abnormality found was urinary concentrating deficit, which was observed in all studied patients. Urinary acidification deficit was also frequent (found in almost 40% of cases). The higher \( F_{Na} \) points to a possible proximal tubular damage, while the increase in the potassium transport and decrease in water reabsorption evidences the occurrence of distal tubular dysfunction. Continued kidney function assessment is important for all SCD patients because the majority of them are symptomatic and there are possible measures that could be done to slow the progression.
of kidney disease, such as the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and hydroxyurea. Novel techniques are important to elucidate some aspects of the pathophysiology of sickle cell nephropathy.

**Conflict of Interests**

There is no conflict of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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