Glomerular filtration rate is altered in children with sickle cell disease: a comparison between Hb SS and Hb SC

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Background: *Renal failure is common among older patients with sickle cell disease; this is preceded by subclinical glomerular hyperfiltration. Data about renal function of adults with sickle cell disease have been reported, but data on children is scarce, especially when comparing heterozygotic and homozygotic patients.*

Objective*: The goal of this study was to investigate the glomerular filtration rate of heterozygotic and homozygotic children with sickle cell disease.*

Methods*: The glomerular filtration rate of 11 children with sickle cell disease [7 homozygotic (SS) and 4 heterozygotic (SC)] with a mean age of 11 years (standard deviation: ± 5 years) was evaluated using standard laboratory techniques. Results are presented as descriptive analysis.*

Results*: Our results suggest that glomerular hyperfiltration is present in children with sickle cell disease; this is more evident in homozygotic than heterozygotic children.*

Conclusion*: There is evidence of a need to monitor the renal function of children with sickle cell disease when special attention should be paid to homozygotic patients.*

Keywords: *Anemia, sickle cell/complications; Kidney glomerulus; Glomerular filtration rate; Hemoglobin SC disease; Humans; Child*

Introduction

Sickle cell disease (SCD) is a common and serious inherited blood disorder affecting ~300,000 live births globally every year[1]. It is a monogenetic, chronic anemia syndrome that is caused by a point mutation in the β-globin gene. It may be classified as a multiorgan syndrome with involvement of the central nervous system (infarcts and strokes), eyes, heart, lungs (pulmonary hypertension), spleen (infarcts), muscle, bone (avascular necrosis) and kidneys (chronic kidney disease)[2-4]. Interestingly, renal impairment is a complication of SCD which affects 4-20% of patients. It seems that the genotype presented by people with SCD [i.e., Homozygous S (Hb SS) Disease or Heterozygous SC (Hb SC) Disease] is related to the severity of organ involvement[5].

Growing attention is being paid to complications of the kidneys owing to the financial burden related to treating patients with chronic kidney disease (CKD)[6]. The cost of renal support for patients with CKD represents a huge financial burden to governments worldwide. The identification of patients who are at greater risk of developing progressive disease may allow early referral to specialist services for appropriate and timely intervention and a modification of the risk profile[6]. Based on this statement, monitoring the renal function of people that are more susceptible to renal impairment, such as people with SCD, could be an interesting way to prevent the development of CKD and reduce the costs to treat these patients.

Since there is evidence of early changes (i.e., in childhood) of renal function in patients with SCD, the goal of this study was to investigate the glomerular filtration rate (GFR) of Brazilian Hb SC and Hb SS children.

Methods

Eleven children with SCD [7 homozygotic (SS) and 4 heterozygotic (SC)], residents in Jequie (Bahia, Brazil) with a mean age of 11 years (standard deviation: ± 5 years) and no history of renal disease or on hydroxyurea treatment were included in the current study. The study was approved by the local ethics committee and informed written parental consent was obtained.

Twelve-hour urine collections were used to estimate urine creatinine and creatinine clearance as proposed by Silva et al.[7]. Blood samples were drawn from the antecubital vein to determine the hematocrit, hemoglobin and plasma creatinine concentrations following standard laboratory techniques. The GFR was estimated using the Schwartz formula because it is adequate for children and adolescents. This is a descriptive study and results are presented as means ± standard deviation.

Conflict-of-interest disclosure:
The authors declare no competing financial interest

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Results

As expected SCD patients showed lower hematocrit (29 ± 5%; reference value: 37-44%) and hemoglobin levels (9.9 ± 1.6 g/dL; reference value: 12.0-16.0 g/dL) than reference values. Homozygous (Hb SS) SCD patients showed lower hematocrit (Hb SS: 26 ± 3%; Hb SC: 34 ± 4%) and hemoglobin (Hb SS: 9.1 ± 1.0 g/dL; Hb SC: 11.4 ± 1.3 g/dL) values than heterozygous children (Hb SC).

Serum creatinine was normal in all patients (0.3 to 0.68 mg/dL; reference value ≤ 1.3 mg/dL). Creatinine clearance values were normal in 75% of patients (reference values from 70 to 140 mL/min/1.73m^2) and lower than the reference value in 25% of patients.

The GFR was higher than reference rates for children and adolescents (104 mL/min/1.73m^2 as proposed by Aygun et al.[8]). The mean GFR of patients was 158.22 mL/min/1.73m^2 indicating a hyperfiltration state. The maximum and minimum values obtained were 237.42 and 97.4 mL/min/1.73m^2, respectively. The stratification of the sample as Hb SS or Hb SC patients identified a trend of higher GFR for Hb SS (mean GFR = 168.52 mL/min/1.73m^2; highest GFR = 237.00 mL/min/1.73m^2; lowest GFR = 107.00 mL/min/1.73m^2) compared to Hb SC patients (mean GFR = 140.20 mL/min/1.73m^2; highest GFR = 167.50 mL/min/1.73m^2; lowest GFR = 97.40 mL/min/1.73m^2). The results of creatinine clearance and GFR are summarized in Table 1.

Table 1 - Mean, standard deviation, maximum and minimum values of creatinine clearance and glomerular filtration rate (GFR) from homozygous (Hb SS) and heterozygous (Hb SC) SCD patients

		Creatinine clearance (mL/min/1.73m^2)	GFR (mL/min/1.73m^2)
Hb SS (n = 7)	Reference values	55-85	≤104.00**
	Mean	139.43	168.52*
	Standard Deviation	55.13	43.56
	Maximum	228.00	237.00*
	Minimum	61.00	107.00*
Hb SC (n = 4)	Mean	100.74	140.20*
	Standard Deviation	25.13	30.98
	Maximum	125.82	167.50*
	Minimum	68.12	97.40

* = higher than reference values; (**) reference value as proposed by Aygun et al.[8]

Discussion

The purpose of this study was to investigate the GFR of Brazilian Hb SC and Hb SS children. The results of this study suggest that glomerular hyperfiltration is present in this population, more evidently in Hb SS than Hb SC patients.

The pathogenesis of glomerular damage in SCD is not well understood, but renal hemodynamic alterations in patients with SCD are probably related to renal vasodilation associated with chronic anemia, which results in renal hyperperfusion and glomerular hyperfiltration[5]. Our results corroborate previous reports that young patients with SCD have supranormal renal hemodynamics with elevations in GFR[9].

Guasch et al.[5] suggested that the genotype presented by people with SCD (i.e., Hb SS Disease or Hb SC Disease) seems to be related to the severity of organ involvement; the results reported here corroborate this statement and add the hypothesis that renal involvement of people with Hb SS SCD could be more severe since childhood. However, further studies should be conducted with large samples to confirm these findings.

The assessment of the GFR is key to identifying opportunities to prevent or provide early interventions to patients with SCD[10]. Knowledge of factors that impose higher risk is an important way to guide prevention and early intervention.

Aygun et al.[11] developed a prospective observational study where 23 children with sickle cell hemoglobinopathies (20 with Hb SS and three with Hb S/b0thalassemia) were monitored for three years and received hydroxyurea treatment, an approach suggested to diminish renal involvement in SCD patients. They found an elevated GFR (167 ± 46 mL/min/1.73 m^2 at baseline) as we found (Table 1) and a significant reduction in GFR (145 ± 27 mL/min/1.73 m^2) after 3 years of hydroxyurea treatment.

It is important to note that the cited study included only patients with Hb SS and Hb S/b0thalassemia, which have similar clinical presentations. On comparing the results of Aygun et al.[11] and those shown in Table 1, hydroxyurea treatment reduces the GFR of Hb SS patients to rates similar to Hb SC patients. Thus, treatment with hydroxyurea should be considered in children with Hb SS in order to diminish renal involvement. This provides evidence to the Brazilian Ministry of Health that recommends hydroxyurea treatment for adults, but claims a lack of evidence, especially in respect to safety aspects, for the use of hydroxyurea in children with SCD[12].

Homozygous SCD patients (i.e., Hb SS) have a higher Hb S content, which leads to greater sickling of the red blood cells compared to Hb SC patients and the acidic, hypoxic and hypertonic environment of the renal medulla leads to vaso-occlusion and consequently to injuries of the vasa recta[9,11]. To avoid renal injuries, the levels of vasodilating agents such as prostaglandins and nitric oxide increase and augment the blood flow to the glomerulus resulting in hyperfiltration[11].

As proposed by Aygun et al.[11], hydroxyurea might prevent renal damage in SCD patients, especially Hb SS patients, but the mechanisms by which hydroxyurea prevents renal damage are not clear but may involve increases in Hb and fetal hemoglobin (Hb F) levels, lowering white blood cell counts and reducing hemolysis[11-13].

Conclusion

In summary, the results in this study confirm previous reports that glomerular hyperfiltration is present in children with SCD, and expand this, since it was found that this is more evident in Hb SS than Hb SC patients. Thus, there is evidence supporting the need to monitor renal function from childhood of patients with SCD, especially those with Hb SS disease. Further studies are necessary focusing in other renal protective strategies for children with Hb SS disease.

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