

# Renal Complications of Sickle Cell Syndrome in Southern Iran

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## Abstract

**Background:** In spite of many reports on sickle cell disease, to our knowledge frequencies of nephrologic complications are not well defined especially in sickle thalassemia. The aim of this study was to assess the nephrologic complications of sickle cell syndrome.

**Methods:** This is a cross sectional study, including all of the patients with sickle cell syndromes (97 cases) in hematology-oncology clinics of Shiraz University of Medical Sciences. A complete history taken and physical examination was performed. Blood and urine samples were sent for different tests including micro albuminuria and Cystatin C to measure glomerular filtration rate.

**Results:** Ninety seven patients with mean age of  $8.5 \pm 3.4$  years (55.4% males) were divided into three groups; 30 cases with sickle cell disease, 31 patients with sickle cell trait, and 36 cases with sickle thalassemia. Enuresis was present in 20 (22.9%) patients > 5 years. Significant proteinuria was not observed, but micro albuminuria was found in 14 (14.4%) patients. GFR was in normal range when calculated with creatinine clearance, but glomerular hyper filtration was present in 5.2% by Cystatin C formula. Mean serum creatinine was in low normal range ( $0.5 \pm 0.1$ ) but mean serum Cystatin C ( $0.9 \pm 0.1$ ) was higher than the normal range especially in S $\beta$  patients ( $P = 0.023$ ).

**Conclusions:** In contrast to other reports, at least in the first two decades of life significant renal complications including renal failure and proteinuria were unusual in our patients with sickle cell syndrome.

**Keywords:** Sickle Cell Anemia, Sickle Trait, Sickle Thalassemia, Micro-Albuminuria, Glomerular Filtration Rate

## 1. Background

Sickle cell disease (SCD) is one of the most common genetic causes of morbidity and mortality in the world, especially in the central regions of Africa with an estimated 1 out of 500 births in African Americans (1-5). It is usually caused by inheritance of the sickle  $\beta$  globin gene, either in homozygous form (hemoglobin SS), Sickle trait (SA) or in combination with hemoglobin C (SC),  $\beta$ -thalassemia (S $\beta$ -thalassemia) or several less common hemoglobin variants (1). Sickle cell anemia and the related hemoglobinopathies (including sickle  $\beta$  thalassemia which is common in southern Iran) causes micro vascular occlusion, which is manifested in most organ systems with a large spectrum of renal abnormalities (5). About 4% - 12% of these patients will progress to end-stage renal disease (ESRD) and survival is significantly decreased in sickle cell patients who develop renal failure (5, 6).

The genitourinary tract is most commonly affected by hematuria, urinary tract infection, and priapism but other more serious complications like testicular infarction and renal medullary carcinoma have also been identified (2).

The patients have impaired urinary concentrating ability, supra normal proximal tubular function, defects in urinary acidification and potassium excretion (5). Young SCD patients have supra normal renal hemodynamics with elevations in both effective renal plasma flow and glomerular filtration rate (GFR). These changes decrease with age as well as following the administration of prostaglandin inhibitors (5-7).

Micro albuminuria, an early manifestation, has been reported in 30% - 60% in SCD patients (5, 6). Also proteinuria, which begins early in life and is associated with severity of disease, was seen in 20% - 25% of SCD patients. It may progress to nephrotic syndrome as a rare condition in > 4% of SCD patients (3, 8). Early detection of proteinuria may allow therapy to prevent progressive renal insufficiency (4).

To our knowledge there is not enough information about frequency of proteinuria, micro albuminuria, and other renal manifestations in subtypes of SCD especially in S $\beta$ -thalassemia. Therefore this study was carried out in order to fill such a gap.

## 2. Methods

### 2.1. Study Population

This is a cross sectional analysis of all of the patients with sickle cell syndromes in hematology-oncology clinics affiliated to Shiraz University of Medical sciences with referral patients from most Southern provinces of Iran. From January 2013 till April 2014 ninety seven patients were enrolled in the study. The inclusion criteria were age < 18 years and documented sickle cell anemia, sickle- $\beta$ -Thalassemia or sickle trait. Excluding criteria were presence of any unrelated renal disease or non-compliance.

### 2.2. Data Collection

A complete history was taken and physical examination performed in all the patients. Questions were asked about different urinary symptoms including; dysuria, polyuria (> 4mL/kg/hr), frequency, edema, stone passing, nocturia, enuresis, and history of hospital admission. Complete physical examinations including measurement of weight, height, blood pressure level was done. Polyuria and urinary frequency were reported by the parents. For every patient urine samples were taken for microalbuminuria, specific gravity, and urinalysis (U/A). Also a blood sample for complete blood count (CBC), Cr, and cystatin C was taken.

CBC was done on an oxalated 2 mL blood sample by a (Sysmex- K 21 model), serum Cr was measured from clot sample by Jaffe method, serum cystatin C was measured in clot sample by ELISA method. Urine micro albumin was checked with Minineph by nephelometric method using Binding site kit.

### 2.3. Definitions

Enuresis was defined as nocturnal or diurnal urinary incontinence at least 2 times/week after age of 5 years. Height was measured in standing position by Seca instrument and weight by Balas Digital instrument. Blood pressure was checked twice with a 10-minute interval and by one physician, using mercury sphygmomanometer and the mean value was recorded. Prehypertension (preHTN) was defined as systolic or diastolic pressure between 90 to 95 percentile for age and sex of the patients. Hypertension (HTN) was defined as systolic or diastolic pressure over 95 percentile for age and sex of the patients. Microalbuminuria was described to be abnormal if it was > 30 mg/dL. Glomerular filtration rate (GFR) was measured by Cystatin C formula as the following  $GFR = -4.32 + (80.35/Cystatin\ C)$ .

### 2.4. Ethical Consideration

All procedures performed in this study were in accordance with the ethical standards of Shiraz University of Medical Sciences research ethics committee; and with the Helsinki declaration standards. Informed consent was obtained from parents of all patients included in this study.

### 2.5. Statistical Analysis

The statistical analysis of the data was performed using statistical package for social sciences version 18 (SPSS Inc, Chicago, IL, USA). The results related to the continuous variables are presented as mean  $\pm$  SD and those related to the quantitative or categorical data are shown as percentage and frequency. Statistical analyses were performed by Chi-square analysis (for categorical variables in different three groups as sex, blood pressure status, and some symptoms), t-test (for continuous variables in two groups as difference of mean age of the patients with microalbuminuria and in those without microalbuminuria, also in patients with enuresis and in those with no enuresis), Pearson coefficient (for relation of two continuous variables as microalbuminuria and serum Cr, also microalbuminuria and Cystatin C levels), and ANOVA test (for continuous variables in three different groups as age, height, weight, disease duration, and some symptoms). P value < 0.05 was considered significant.

## 3. Results

Overall 97 patients with age range of 3 to 18 years (mean age  $8.8 \pm 3.4$  years) were included in the study of whom 54 patients (55.4%) were male with male/female ratio 5.5:4.5. Thirty six patients had sickle thalassemia ( $S\beta$  group), 31 patients had sickle trait (SA group), and 30 cases had sickle cell anemia (SS group). Height for age percentile was in normal range for 84.5% while weight for age percentile was in normal range of 79.4%. There was no significant difference within groups in variables ( $P > 0.05$ , Table 1) except in disease duration; it was  $5.4 \pm 3.5$ , that was lower in sickle trait group versus  $S\beta$  and SS groups;  $3.9 \pm 2.3$  vs  $5.7 \pm 3.9$  and  $6.4 \pm 3.8$  ( $P = 0.018$ ).

Mean systolic blood pressure in all study groups was  $95.0 \pm 9.9$  (range = 80 - 130) mmHg and mean diastolic blood pressure was  $66.7 \pm 7.5$  (range = 55 - 80) mmHg. There was no significant difference between different groups ( $P = 0.758$  for systolic blood pressure and  $P = 0.192$  for diastolic blood pressure). There was a significant positive correlation between age and systolic blood pressure ( $P = 0.002$ ,  $r = 0.317$ ). PreHTN was detected in 18.6% of our patients (18 cases) and 11.3% of all patients (11 cases) had HTN. As shown in Table 2 the prevalence of preHTN and

**Table 1.** Distribution of the Base Line Characteristics in Patients with Sickle Syndrome

Characteristics	Total, n = 97	Study Groups			P Value
		Sickle Thalassemia, n = 36	Sickle Trait, n = 31	Sickle Cell Disease, n = 30	
Age (Years), Mean $\pm$ SD	8.8 $\pm$ 3.4	8.6 $\pm$ 3.9	8.3 $\pm$ 2.3	9.6 $\pm$ 3.8	0.277
Sex (Male), n (%)	54 (55.7)	21 (58.3)	19 (61.3)	14 (46.7)	0.521
Height (cm), Mean $\pm$ SD	126.7 $\pm$ 17.0	124.7 $\pm$ 17.4	127.2 $\pm$ 14.8	129.4 $\pm$ 18.9	0.535
Weight (Kg), Mean $\pm$ SD	25.8 $\pm$ 9.1	24.9 $\pm$ 8.8	26.7 $\pm$ 9.9	26.1 $\pm$ 8.8	0.711
Disease duration (Years), Mean $\pm$ SD	5.4 $\pm$ 3.5	5.7 $\pm$ 3.9	3.9 $\pm$ 2.3	6.4 $\pm$ 3.8	0.018 <sup>a</sup>

<sup>a</sup>LST test as a post hoc test showed: sickle trait group had lower disease duration than the other groups (P = 0.007, P = 0.036).

HTN had no significant differences between groups (P > 0.05).

Frequency of urinary and renal characteristics is shown in Tables 3 and 4, with no significant change in urinary symptoms between groups (P = 0.05). Hypercalciuria was detected in 16.5% (16 cases), and 2.1% (2 S $\beta$  patients) reported the history of renal stone. Hematuria was detected in only one SS group patient (1% of all patients). Polydipsia, polyuria, frequency, and dysuria were seen in 19 (19.8%) patients, 41 (42.3%) patients, 5 (5.2%) patients, and 5 (5.2%) patients, respectively. And also nocturia was reported in 30.9% (30 cases) of our patients. All variables mentioned above, had no significant relation with age (P = 0.05). But enuresis was present in 20 out of 87 (23%) patients who were > 5 years old. Mean age of the patients with enuresis was 7.8  $\pm$  2.2 years while it was 9.9  $\pm$  3.2 years in those with no enuresis (P = 0.007).

Glomerular hypofiltration (GFR by Cystatin C < 60) was present in 5.2% of the patients. Mean serum Cr in our patients was in low normal range (0.5  $\pm$  0.1) but mean serum Cystatin C (0.9  $\pm$  0.1) was higher than normal range especially in S $\beta$  patients (P = 0.023).

Proteinuria was not found by dipstick, but mean of the urine microalbumin in all patients was 27.7  $\pm$  7.6 (range = 0 - 235). It was 11.1  $\pm$  4.4 (range = 0 - 48.9) in SS group, 46.1  $\pm$  15.2 (range = 0 - 235) in SA group, and 10.2  $\pm$  3.8 (range = 0 - 46) in S $\beta$  group, (P = 0.901). Four of 29 (13.3%) patients in SS group; 5/32 (16.6%) of SA group; and 5/32 (15.6%) in S $\beta$  group had microalbuminuria. Mean age of the patients with microalbuminuria was 7.95  $\pm$  3.2 years as compared to 8.9  $\pm$  3.5 years in those without microalbuminuria (P = 0.464). There was no significant correlation between microalbuminuria and serum Cr levels (P = 0.594); and also microalbuminuria and Cystatin C levels (P = 0.07)

#### 4. Discussion

To our knowledge this is the first study that compares renal function and different aspects of renal involvement in the S $\beta$ , SA, and SS anemia. There are different renal manifestations in SCD patients, from painless hematuria to renal failure (5). Due to improvement in the management of SCD in recent decades, which led to a significant increase in the life expectancy of patients, a greater rate of genitourinary complications, is expected (3, 5). Bakir et al reported that 5-year mortality in the general population of sickle cell anemia is 3.7%, and 75% of patients aged 15 years or older survive 18 years or longer (9).

Significant renal involvement was not common, but microalbuminuria, enuresis and polyuria were the most common findings in our patients.

The development of chronic azotemia correlates strongly with poor prognosis and early mortality as compared to the general population of sickle cell anemia (9). GFR < 60 was present in 5.2% of our patients while end stage renal disease was not present. GFR is usually increased in younger patients with sickle cell but it is typically reduced in older patients (5). A reversible renal concentrating defect in younger age groups can become irreversible in older patients. Vardaman et al stated increased total renal blood flow while medullary blood flow was probably decreased among young patients with sickle cell anemia (8). Also, Aygun reported that GFR was increased in SCD patients (10). In the patients > 16 years, GFR decreased toward normal. In that study mean serum Cr was 0.3 mg/100 mL while serum Cystatin C was normal. Moreover Cystatin C was higher in those with lower GFR and higher levels of proteinuria. This is consistent with our findings (6). In contrast to defects in distal nephron abnormalities, proximal tubular functions were found to be supernormal. This is evidenced by an increased reabsorption of phosphorus and beta2-microglobulins and increased secretion of uric acid and Cr. Alterations in renal hemodynamics were noted in SCD and S $\beta$  patients; but not

**Table 2.** Frequency of Prehypertension and Hypertension in Patients with Sickle Syndrome

Blood Pressure Status, n (%)	Total, n = 97	Study Groups			P Value
		Sickle Thalassemia, n = 36	Sickle Trait, n = 31	Sickle Cell Disease, n = 30	
Systolic prehypertension	2 (2.1)	1 (2.8)	0 (0.0)	1 (3.3)	0.621
Systolic hypertension	5 (5.2)	1 (2.8)	4 (12.9)	0 (0.0)	0.758
Diastolic prehypertension	16 (16.5)	7 (19.4)	6 (19.4)	3 (10.0)	0.756
Diastolic hypertension	6 (6.3)	4 (11.1)	0 (0.0)	2 (6.7)	0.192

**Table 3.** Frequency of Urinary Symptoms in Patients with Sickle Syndrome

Symptoms, n (%)	Total, n = 97	Study Groups			P Value
		Sickle Thalassemia, n = 36	Sickle Trait, n = 31	Sickle Cell Disease, n = 30	
Hematuria	1 (1.0)	0 (0.0)	0 (0.0)	1 (3.3)	0.309 <sup>a</sup>
Polydipsia	41 (42.3)	18 (50.0)	12 (38.3)	11 (36.7)	0.490
Polyuria	19 (19.6)	6 (16.7)	6 (20.0)	7 (23.0)	0.795
Frequency	5 (5.2)	1 (2.8)	2 (6.5)	2 (6.7)	0.605
Enuresis	20 (20.6)	5 (15.6)	7 (24.1)	8 (30.8)	0.389
Nocturia	30 (30.9)	10 (31.3)	9 (31.0)	11 (42.3)	0.732
Dysuria	5 (5.2)	0 (0.0)	1 (3.2)	4 (13.3)	0.832

<sup>a</sup>Fisher exact test

in subjects with the SA. Mechanism of increased GFR and renal plasma flow in patients with SCD is related to compensatory hypersecretion of vasodilator prostaglandins in response to sickling (5, 11, 12). During adolescence both GFR and RPF are normal, but are frequently subnormal after the age of 40. Progressive renal insufficiency in these patients has been ascribed to hyperfiltration-mediated sclerosis of the glomerular capillaries (13). In a more recent study, Schmitt et al, found enhanced macromolecule trafficking, decreased glomerular size selectivity, and at later stages, the reversible changes are no longer detected, and even a decrease in Kf may contribute to the decrease in GFR (14).

Significant proteinuria in the form of nephrotic syndrome, most often caused by sickle glomerulopathy, occurs in 4% of patients with sickle cell anemia, leading to renal failure in 2/3 and death during 2 years in half of the patients (5). However, in the present study proteinuria was not found. The rate of microalbuminuria was similar to the reports of Becton et al (9), but less than reports of Imuetiyan et al, Lenensburger et al, and King (15-17). It is expected that micro-albuminuria is increased by aging and decreasing GFR (10, 18).

In spite of the fact that these patients are prone to recurrent severe infections, dehydration and exposure to

potential nephrotoxic agents, similar to our finding the reported incidence of severe kidney injury in patients with SCD requiring renal replacement therapy is surprisingly low (1, 2). Papillary necrosis and infarction are well-recognized findings in patients with SCD, as the risk of sickling is increased by the milieu of vascular congestion, relative sickle cell kidney hypoxia, hypertonicity and low pH in the renal medulla (19).

Due to the hypoxic, acidotic, and hyperosmolar environment of the inner medulla, sickling of erythrocytes with resultant impairment in renal medullary blood flow, ischemia, micro infarct, and papillary necrosis is promoted. Clinically, patients demonstrate an inability to concentrate urine (5, 20). In our study the rate of enuresis and nocturia was high. The rate of enuresis was high in the sickle cell anemia (30.8%); moderate in SA (24.1%); and lower in S $\beta$  patients (15.6%). Rate of nocturia was higher in patients with sickle cell anemia (42.3%) but similar in SA and S $\beta$  patients (31%). This was expected by considering the above explained pathophysiologic changes. It has been shown in the previous studies that in young children with sickle cell anemia, maximal urine osmolality can be increased by multiple blood transfusions (21). However, with repeated thrombosis, progressive infarction, and necrosis of the papillae and inner medulla, the capacity to improve

**Table 4.** Distribution of Some Renal Characteristics in Patients with Sickle Syndrome

Symptoms, n (%)	Total, n = 97	Study Groups			P Value
		Sickle Thalassemia, n = 36	Sickle Trait, n = 31	Sickle Cell Disease, n = 30	
Specific gravity	1.013 ± 0.04	1.013 ± 0.04	1.014 ± 0.05	1.012 ± 0.004	0.178
Serum cratinine	0.5 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.2	0.016 <sup>a</sup>
Serum Cystatine C	0.9 ± 0.2	1.0 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	0.007 <sup>b</sup>
GFR by Cystatine C	86.9 ± 21.5	77.2 ± 12.8	91.3 ± 22.3	94.1 ± 24.9	0.002 <sup>+</sup>
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Microalbuminuria	14 (14.4)	5 (13.9)	5 (13.9)	4 (13.3)	0.946
Hypercalciuria	16 (16.5)	6 (16.7)	2 (6.5)	8 (26.7)	0.104

<sup>a</sup>LST test as a post hoc test showed: sickle trait group had higher cratinine than the other groups (P < 0.003).

<sup>b</sup>LST test as a post hoc test showed: sickle trait group had higher Cystatine C than the other groups (P < 0.004). +LST test as a post hoc test showed: sickle trait group had higher GFR than the other groups (P < 0.001).

renal concentrating ability is progressively lost with age, and the defect is irreversible after the age of 15 (21). Unexpectedly in our patients there was a significant negative correlation between age and urine concentration, so that mean age of 8 patients who had urine specific gravity < 1.005 was 6.05 ± 1.8 years; while it was 8.97 ± 3.45 in patients who had urine specific gravity > 1.005. This was against the expected progressive loss of urine concentrating ability with increasing age. It may be in part explained by physicians encouraging the patients for increasing water intake in smaller children and their compliance may be better than teenagers.

Idiopathic hypercalciuria was not previously reported in sickle syndrome. Hypercalciuria predisposes the patients to renal stone and may be the cause of different urinary symptoms (22), including vasopressin resistant diabetes insipidus (23). Hypercalciuria was detected in 16.5% of our patients and only 2% had history of renal stone. Hematuria which is more prevalent in thalassemia major patients in this center (24) was unexpectedly infrequent in our patients with sickle syndrome. Susceptibility to malignancy in cases of hemoglobinopathy which was previously reported in sickle cell anemia (25, 26) was not detected in our patients.

These findings need to be the subject of more detailed study in future and preferably within a cohort study.

#### 4.1. Conclusion

In contrast to other reports, significant renal complications including renal failure and proteinuria were unusual in our patients with sickle cell syndrome at least in the first two decades of life.

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