

Journal of Clinical and Biomedical Sciences

Journal homepage: www.jcbsonline.ac.in

Review Article

# Renal abnormalities in sickle cell disease.

Srinivasa Jayachandra[1]*, Gopinath Agnihotram[2], Lincy K. Skaria[3]

*1. Department of Physiology, KMCT Medical College, Kozhikode, Kerala, India.*
*2. Department of Biochemistry, KMCT Medical College, Kozhikode, Kerala, India.*
*3. Department of Biochemistry, Govt. Dental College, Patan, Gujarat, India.*

Received: 05th April-2013 Accepted: 22nd June-2013 Published: 30th-September 2013

## Abstract

Many structural and functional abnormalities of the kidney are observed in patients with sickle cell anemia and the related hemoglobinopathies. The environment of the renal medulla is characterized by acidosis, hypertonicity and hypoxia. These factors tend to promote HB S polymerisation and red cell sickling, thereby making this part of the kidney susceptible to changes in oxygen delivery. So these patients exhibits numerous kidney structural and functional abnormalities, changes that are seen along the entire length of the nephron. Changes are most marked in patients with homozygous sickle cell anemia, but are also seen in those with compound heterozygous states and the sickle cell trait. The renal features of sickle cell disease include hematuria, proteinuria, tubular disturbances and chronic kidney disease. Therapy of these conditions requires specialized knowledge of their distinct pathogenic mechanisms.

**Key words:** Proteinuria, Renal failure, Renal features, Sickle cell disease.

## Introduction

Sickle cell disease (SCD) is expressed as chronic haemolytic anaemia and a large variety of vaso -occlusive phenomena and their consequences, proliferative vasculopathy, and a predisposition to infections, leading to very high early morbidity and mortality rates. This is therefore a chronic disease with severe economic and psychosocial implications. An early diagnosis of SCD allows the implementation of necessary preventative measures that reduce mortality and morbidity. Kidney abnormalities in SCD start in childhood, with haematuria being the most common manifestation, along with renal papillary necrosis and tubular function abnormalities, which are triggered by vaso -occlusive phenomena. The long-term consequences of this condition are sickle cell glomerulopathies (albuminuria in 68% of SCD adults), with evolution to chronic renal failure (CRF) in as many as 20% of homozygous patients[1]. Since the life expectancy of patients with SCD has increased in the last decade, the prevalence of CKD secondary to SCD has increased significantly, becoming an independent factor for mortality in these patients[2-5]. Renal medullary carcinomas are also associated with the sickle cell trait (HbAS) and, to a lesser degree, with SCD. In this review article, we have attempted to present an overview regarding kidney abnormalities occurring in sickle cell disease.

## Asymptomatic haematuria

This is the most common form of SCD. It can be microscopic, or more commonly, macroscopic and self-limiting. It is frequently unilateral, and is more often found in the left kidney, due to the longer left renal vein and its anatomical location, compressed between the aorta and the superior mesenteric artery. This subjects this vessel to a greater venous

*Corresponding Author
Srinivasa Jayachandra, Associate Professor, Department of Physiology, KMCT Medical College, Kozhikode, Kerala, India.
E mail : jayachandra.srinivasa@gmail.com

Quick access Code

pressure with relative hypoxia in the renal medulla that favours cell sickling. It can develop at any age, and has been primarily described in patients with sickle cell trait (HbAS) much more frequent than in the homozygous form (HbSS) [6-9].

**Renal papillary necrosis and renal infarction**

They are also common complications of SCD, with an estimated prevalence of 30%-40% in homozygous HbSS patients. The clinical presentation of this condition varies from asymptomatic macroscopic haematuria (not always present) to an acute condition involving pain, fever, and even obstructive acute renal failure (ARF). However, a similar frequency of renal papillary necrosis (RPN) has been described in symptomatic and asymptomatic individuals (65% and 62%, respectively) [10-11].This may be at times associated with urinary tract infections (61.5%), for which it is considered a favour factor or risk modifier. Haematuria is probably a consequence of cell sickling in the renal medulla combined with vascular obstruction and extravasation of erythrocytes. The medullary environment is by nature prone to producing sickle cells due to the partial pressure of $O_2$ at 35-40mm Hg, below the sickling threshold of 45mm Hg, along with high osmolarity that dehydrates erythrocytes and concentrates the HbS and the acidic pH that also increases the probability of sickling.

The diagnosis of this is presence of c ontinuous or persistent macroscopic haematuria in a patient with SCD or sickle cell trait (HbAS) indicates a renal sickle cell crisis. However, other more severe and treatable causes of haematuria, such as renal medullary carcinoma, must first be ruled out. The presence of intense pain widens the potential differential diagnosis, especially in the presence of a renoureteral crisis (lithiasis or renal papilla) or renal infarction. Haematuria may be asymptomatic or produce a moderate lumbar pain, which, if unilateral, can indicate the location of bleeding. Clinical suspicion is very important for the diagnosis of RPN. Renal ultrasound is the technique of choice for the detection and differential diagnosis against lithiasis and renal medullary carcinoma. The earliest finding in RPN is increased echogenicity in the medullary pyramids (the innermost region of the medulla), which, in the absence of hypercalciuria in a patient with SCD and haematuria suggests RPN. In later stages, calcification may appear in the medullary pyramids with a typical 'garland pattern' surrounding the renal pelvis, or a defect in echogenicity in the pyramids due to detachment of the papilla. Intravenous pyelogram, which should be avoided in these patients due to the elevated risk of nephrotoxicity from iodinated contrast solutions, was used in initial studies of SCD and showed a 39% calyceal clubbing deformity or swelling, which is not accompanied by the cortical scarring characteristic of chronic pyelonephritis. In cases of uncertainty, helical CT scans are more sensitive than ultrasound for early detection of RPN, as well as for renal medullary carcinoma, although prophylactic measures must always be taken to prevent nephrotoxicity from iodinated contrast solutions, and especially volume expansion [11].

**Tubular Function Abnormality**

Defective urinary acidification also is well described in SCD [11-12]. Typically, however, patients have normal aldosterone and renin responses [13]. The primary abnormality is an incomplete distal renal tubular acidosis (RTA), and the severity of the acidification defect is related, at least in part, to the severity of the hyposthenuria. Defects in potassium excretion are also seen in SCD. Although not clinically apparent under normal circumstances, hyperkalemia does become manifest as overall renal function deteriorates. In addition, even SCD patients with normal renal function are at risk for hyperkalemia following administration of drugs such as ACE inhibitors, beta-blockers, and potassium-sparing diuretics [11].Increased creatinine secretion causes a lower serum creatinine level and thus an overestimation of the glomerular filtration rate (GFR) in SCD-SS patients. Differences of up to 30 percent have been reported when creatinine clearance is compared to inulin clearance [12-13]. The significance of this enhanced proximal tubular function in the pharmacokinetics of drugs in which tubular secretion is a major pathway of elimination is uncertain. Despite increased secretion of uric acid, patients with SCD often have hyperuricemia and are vulnerable to secondary gout [14].

**Glomerular Abnormalities and Chronic Renal Failure**

Proteinuria, which can progress to the nephrotic syndrome, is the most common manifestation of glomerular injury in SCD patients. Moreover, as many as 40 percent of SCD-SS patients with nephrotic syndrome may go on to develop end-stage renal disease (ESRD). Therefore, patients with persistent proteinuria should have a urine collection obtained for the determination of 24-hour protein excretion, and a nephrology consultation should be requested for consideration of other, nonsickling causes of proteinuria and possible renal biopsy [15-17]. ACE inhibitors ameliorate pathological changes such as peripheral focal and segmental

glomerulosclerosis. They also decrease urinary protein excretion in patients with early manifestations of sickle cell nephropathy [18]. Renal insufficiency occurs earlier in SCD-SS patients than it does in SCD-SC patients. Factors that appear to predict renal failure in SCD-SS patients include hypertension, proteinuria, increasingly severe anemia, and hematuria [19-20]. Finally, the risk of renal failure is increased in those SCD-SS patients with the Central African Republic (CAR) s-gene cluster haplotype.

The amount of proteinuria can be decreased by the administration of ACE inhibitors, and it is conceivable that the progression of sickle cell nephropathy may be slowed by a prolonged course of these drugs. Patients should avoid non-steroidal anti-inflammatory drugs (NSAIDs), because NSAIDs have been shown to produce significant declines in the rates of glomerular filtration and renal blood flow in patients with SCD [20-21]. Effective control of blood pressure has been reported to slow the progression of ESRD in patients with SCD; they should be treated with standard approaches. Optimum target blood pressure has not been defined [22]. Because dehydration can precipitate vasoocclusive events, caution should be exercised in the use of diuretic agents in an individual with obligate hyposthenuria. Every effort must be made to avoid additional renal damage due to urinary tract infection. Infection must be recognized and treated vigorously. Follow-up should be maintained longer than for patients without SCD.

Although erythropoietin levels are generally high in steady-state SCD-SS patients, they are not increased to the level that would be expected for the degree of anemia [23]. One explanation for the relatively decreased erythropoietin levels is the right-shifted hemoglobin-oxygen dissociation curve seen in SCD patients [24]. Erythropoietin levels in SCD patients fall still further as renal function worsens, and these patients may require substantially higher doses of erythropoietin than are required for patients with other forms of ESRD . If erythropoietin is ineffective, transfusions can be given; they must be done carefully, however, to avoid volume overload . As with all patients who develop ESRD, SCD patients can be treated with both hemodialysis and peritoneal dialysis, and they can undergo renal transplantation. Although early reports suggested poor allograft survival and other disease-specific problems in SCD patients, others have reported graft and patient survival rates comparable to those of other non diabetic patients . A recent study of renal transplantation in SCD reported short-term patient and allograft outcomes comparable to other age-matched African Americans [19-22].

However, there was a shorter cadaveric graft survival and high risk of graft loss with longer follow up in the SCD patient group. There was a trend toward improved survival in those SCD patients who received transplants compared to those on chronic dialysis. Although many SCD patients have done well after renal transplantation, several unique complications have been described. Patients may experience a resumption of frequent vaso-occlusive events which presumably are related to an increase in whole blood viscosity accompanying a higher hemoglobin level [23-24]. Renal infarction, a probable secondary consequence of Hb S polymerization, cell sickling, and vaso-occlusion, has been reported to occur as early as 6 days following transplantation. The reappearance of sickle cell nephropathy in the donor kidney has also been reported [22-25]. It is possible that the availability of new immunosuppressive drugs may further improve the outcome renal transplantation in SCD patients. Hydroxyurea is excreted by the kidney and thus its use in patients with renal failure requires careful monitoring. SCD patients receiving renal transplants may benefit from exchange transfusion or even from periodic phlebotomy, particularly when hemoglobin level is high.

**Acute Renal Failure**

Acute renal failure (ARF) is not uncommon in SCD. An estimated 10% of patients that require hospitalisation have at least doubled values of serum creatinine , which may be due to various causes that often coexist. The most commonly observed precipitating factor is depleted volume. The use of NSAIDs is probably at least partially responsible for many cases of acute renal failure by inhibiting the previously mentioned renal compensatory mechanisms mediated by prostaglandins. It is usually associated with infections, rhabdomyolysis, and anemia.

The incidence of ARF during acute vaso-occlusive crises is low (4.3%) and appears to be related to the severity of the crisis, 13.6% in severe acute chest syndrome. It appears to be limited to patients with pulmonary hypertension (PHT); therefore, venous congestion may be implicated as the pathogenic phenomenon. Acute failure of at least two major organ systems (kidneys, heart, lungs, etc.), during an acute painful vaso-occlusive crisis is considered to be a multi-organ failure. In these cases, individualized erythrocyte exchange may be indicated, according to the USA guidelines for apheresis. Obstructive ARF may be produced due to papillary necrosis or macroscopic haematuria [26-28]. ARF has also been described in subjects with sickle cell trait (HbAS) associated

clotting after rigorous military training.

**Arterial Hypertension**

Patients with sickle cell disease have lower blood pressure (BP) than healthy African American controls adjusting for age, but this is not the case for patients with sickle cell trait, who have similar BP values. The prevalence of arterial hypertension (AHT) is estimated to be lower than in the general population (2%-6% vs 28%, respectively). The potential aetiopathogenic mechanisms are obstruction of the vasa recta and repeated ischaemia in the renal medulla, which are involved in hyposthenuria, as well as the lower body mass index and reduced arterial rigidity described in these patients. Recent studies have also suggested that endothelial dysfunction and systemic vasculopathy are associated with a decreased bioavailability of nitric oxide in SCD patients. Even within the normal range of BP, the occurrence of stroke has been associated with systolic BP of 120-139mm Hg or diastolic BP of 70-89mm Hg, defining the category of relative systemic AHT in SCD patients, also associated with a higher risk of PHT and renal dysfunction [29-31].

The relationship between PHT and higher BP values in adults with SCD supports the possibility of a pathophysiological mechanism acting in both conditions. Additionally, AHT contributes to left ventricular diastolic dysfunction, which has been shown to be an independent predictive factor for SCD patient death. Even mild increases in pulmonary arterial pressure are poorly tolerated by SCD patients, which could be extrapolated to AHT. Given this evidence, antihypertensive treatment may be indicated in the category of prehypertension (systolic BP: 130- 139mm Hg; diastolic: 80-89mm Hg) or even earlier in SCD patients due to the risk of target organ damage (heart, lungs, and kidneys). This condition would be a new component to be added to the six situations enumerated in the seventh report by the Joint National Committee [31] with indications for antihypertensive treatment for patients in the prehypertension phase: heart failure, post-myocardial infarction, high risk of coronary disease, diabetes mellitus, CKD, and the prevention of stroke recurrence. Nevertheless, more clinical trials are needed in order to establish the guidelines for treatment and objectives of BP in SCD patients. Given the aetiopathogenic mechanisms established in SCD related CKD and their extrapolation to other glomerulopathies, renin-angiotensin-aldosterone system inhibitors would be the treatment of choice for pre-AHT in SCD with albuminuria or PHT. In the case of AHT, this recommendation remains valid along with measures for avoiding hyperkalemia, especially with regard to potassium-sparing drugs, as previously mentioned. We do recommend special precaution when using diuretics, since dehydration may precipitate vaso-occlusive crises, and we must also remember that these patients are predisposed to these crises due to the almost universal hyposthenuria observed in SCD patients.

**Renal Medullary Carcinoma**

Renal medullary carcinomas are rare, with an extremely poor prognosis, and are described almost exclusively in the black population with sickle cell trait, and less frequently with SCD. It appears in the majority of cases before the patient has reached 20 years of age, with a higher incidence in men. A genetic predisposition has been suggested, and this disease is distinguished from carcinoma of the collecting tubules by certain markers, including a factor that is inducible by hypoxia. Medullary hypoxia in SCD can promote its development. Its most common clinical presentation is macroscopic haematuria, lumbar pain, and abdominal mass and/or constitutional syndrome. By the time the carcinoma is diagnosed, usually it has already metastasized, making extirpation of the tumour a non-curative approach. Survival after diagnosis does not surpass 5-12 months. The diagnosis should be confirmed by a CT scan [9-11].

**Urinary Tract Infections**

Patients with SCD have reduced humoral immune response due to splenic infarctions, which predisposes them to encapsulated bacterial infections, including urinary tract infections (UTI). Special attention must be given to its appearance during gestation, and we have already mentioned that it can contribute to RPN. The present overview concludes that as in other infections, UTI can cause sickle cell crises, which should be taken into consideration in children due to the higher frequency of asymptomatic UTI.

**Conclusion**

Sickle cell nephropathy is a complication with high prevalence, after hepatobiliary and pulmonary hypertension complications. Chronic sickling promotes different mechanism of kidney injury: structural papillectomy, urine concentration defects, hyperfiltration and glomerular enlargement with scelerosis. kidney injury in SCD, channeled through the vasculature or tubular or glomerular or papillary damage may thereby contribute to the morbidity of SCD. So, therapy for these renal damage requires specialized knowledge of their distinct pathogenic mechanisms.

## References


1. Guasch A, Navarrete J, Nass K, et al. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlations of progressive renal failure. J Am Soc Nephrol 2006; 17:2228-35.
2. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994; 330:1639-44.
3. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a decade observational study of 1056 patients. Medicine 2005; 84:363-76.
4. Powars DR, Elliot-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, et al. Chronical renal failure in sickle cell disease: risk factors, clinical course and mortality. Ann Intern Med 1991; 115:614-20.
5. Weatherall DJ. Inherited haemoglobin disorders: an increasing global health problem. Bulletin of the World Health Organization 2001; 79:704-12.
6. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood 2010; 115:4331-36.
7. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bulletin of the World Health Organization 2008; 86:480-87.
8. Odita JC, Ugbodaga CI, Okafor LA, Ojogwu LI, Ogisi OA. Urographic changes in homozygous sickle cell disease. Diagn Imaging 1983; 52:259-63.
9. Pandya KK, Koshy M, Brown N, Presman D. Renal papillary necrosis in sickle cell hemoglobinopathies. J Urol 1976;115:497–501.
10. Van Eps S, De Jong PE. Sickle cell disease. In Schrier RW, Gottschalk CW (eds.). Boston: Little, Brown and Company, 1988;2561-81.
11. Allon M. Renal abnormalities in sickle cell disease. Arch Intern Med 1990; 150:501-04.
12. Kontessis P, Mayopoulou-Symvoulidis D,Symvouli -dis A, et al. Renal involvement in sickle cell thalassemia. Nephron 1992; 61:10-05.
13. DeFronzo RA, Taufield PA, Black H, et al. Impaired renal tubular potassium secretion in sickle cell disease. Ann Intern Med 1979; 90:310-06.
14. Allon M, Lawson L, Eckman JR, et al. Effects of nonsteroidal anti-inflammatory drugs on renal function in sickle cell anemia. Kidney Int1988; 34:500-06.
15. Foucan L, Bourhis V, Bangou J, et al. A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia. AmJ Med 1998; 104(4):339-42.
16. Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern-Med 1991; 115:614-20.
17. De Jong PE, de Jong-van den Berg TW, Sewrajsingh GS, et al. The influence of indomethacin on renal hemodynamics in sickle cell anemia. Clin Sci 1980; 59:245-50.
18. Nissenson AR, Port FK. Outcome of end-stage renal disease in patients with rare causes of renal failure. I. Inherited and metabolic disorders. Quart J Med 1989;271:1055.
19. Sherwood JB, Goldwasser E, Chilcote R, et al. Sickle cell anemia patients have low erythropoietin levels for their degree of anemia. Blood 1986; 67:46-49.
20. Morris J, Dunn D, Beckford M, et al. The haematology of homozygous sickle cell disease after the age 40. Br J Haematol 1991; 77:382-85.
21. Steinberg MH. Erythropoietin for the anemia of renal failure in sickle cell disease. N Engl J Med 1991; 324:1369-70.
22. Chatterjee SN. National study in natural history of renal allografts in sickle cell disease or trait: A second report. Transplant Proc 1987; 19(2 Suppl 2):33-35.
23. Ojo AO, Govaerts TC, Schmouder RL, et al. Renal transplantation in end-stage sickle cell nephropathy. Transplantation 1999; 67:291-95.
24. Donnelly PK, Edmunds ME, O'Reilly K. Renal transplantation in sickle cell disease. Lancet (letter) 1988; 2:229.
25. Miner DJ, Jorkasky DK, Perloff LJ, et al. Recurrent sickle cell nephropathy in a transplanted kidney. Am J Kidney Dis 1987; 10:306-13.
26. Sklar AH, Perez JC, Harp RJ, Caruana RJ. Acute renal failure in sickle cell anemia. Int J Artif Organs 1990; 13(6):347-51.
27. Audard V, Homs S, Habibi A, Galacteros F, Bartolucci P, GodeauB, et al. Acute Kidney injury in sickle patients with painful crisis or acute chest syndrome and its relation to pulmonary hypertension. Nephrol Dial Transplant 2010; 25:2524-29.
28. Szczepiorkowxki ZM, W inters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, et al. Guidelines on the use os Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Apheresis Applications Comittee of the American Society of Apheresis. J Clin Apheresis 2010; 25(83):177.
29. Pegelou CH, Colangelo L, Steinberg M. Natural history of blood pressure in sickle cell disease:

Risks of stroke and death associated with relative hypertension in sickle cell anemia. Am J Med 1997; 102:171-77.

30. Gordeuk VR, Sachdev V, Taylor JG, Gladwin MT, Kato G, Castro OL. Relative systemic Hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. Am J Hematol 2008; 83:15-18.
31. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al., National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289(19):2560 -72.