Sickle cell nephropathy is now a well characterized entity with specific manifestations, risk factors, and prognosis. This review provides an approach to understanding the mechanisms involved in the development of the nephropathy, in order to provide rational treatment for the patients.

**Epidemiology**

The presence of renal failure in sickle cell disease (SCD) ranges from 5 to 18% of the total population of SCD patients (1). Powars et al. (2), in a prospective, case-control study of patients with SCD compared with sickle cell hemoglobin C patients, documented 31 (4.2%) patients affected by renal failure. The median age at the time of renal failure was 23.1 yr. Survival time was 4 yr with a median age of death of 27 yr after the diagnosis of end-stage renal disease (ESRD) in spite of dialysis treatment. Proteinuria, hypertension, severe anemia, and hematuria were reliable predictors of chronic renal failure (2). In this series, the presence of the inherited Central African Republic β-gene cluster haplotype in a patient with SCD increased significantly the risk of chronic renal failure (2).

Recently, in a prospective survival analysis of 964 patients with sickle cell anemia in adults, Platt et al. (3) observed an 18% overall mortality in adult SCD patients with 40% of these (7.6% of the total) manifesting overt renal failure. None received a kidney transplant. By multivariate regression analysis, renal failure was identified as the major risk factor for early mortality in adult patients with SCD.

Sklar et al. (4), in a population study of 368 patients, found chronic renal insufficiency in 4.6% of SCD patients that was significantly associated with proteinuria and increased age. In patients with SCD, priapism episodes (5), especially those with postpubertal presentation and tricorporal disease (corpora cavernosa and corpus spongiosa involvement), had increased risk of multiorgan failure, including kidney failure.

Although there is no gender predilection for renal failure in most series, Nissenson and Port (6) analyzed and reported a marked male predominance of sickle cell nephropathy (SCN) patients in the U.S. Renal Data System database, in which few patients were offered transplantation.

**Pathophysiology**

Chronic sickling underlies several mechanisms for kidney injury. The arterial side of the renal microvasculature has a low O$_2$ tension. The hypertonicity and low pH of the renal medulla promote the formation of hemoglobin polymers in the red cells with deformation of the sickled cells, resulting in an increase in the blood viscosity, functional venous engorgement, and interstitial edema, predisposing the renal microcirculation to ischemia and infarction (7). Obliteration of the medullary vasculature produces segmental scarring and interstitial fibrosis (structural papillectomy), resulting in the formation of dilated renal pelvic capillaries and veins. Hematuria may result from rupture of vessels from the early venous engorgement or from the dilated vessels that result from scarring. The development of collateral vessels and their abnormal orientation in the medulla interfere with the countercurrent exchange mechanism, culminating through the years in irreversible loss of medullary tonicity (7). Renal cortical blood flow and GFR are increased perhaps by the secretion of medullary vasodilator prostaglandins (Figure 1) (7).

Hyperfiltration coupled with glomerular hypertrophy can lead to glomerulosclerosis (1,7,8). Once progression of the glomerular damage is evident, GFR begins to decrease, likely with some contribution from the ingestion of analgesics that can independently induce interstitial nephropathy (1). Recently, Guasch et al. (9) documented a pattern of an increased dextran permeability in the glomerular basement membrane of SCD patients, with an incremental increase in the pore radius. This would cause a nonselective proteinuria rather than the microalbuminuria associated with hyperfiltration.

Bank et al. (10) showed that in a transgenic sickle cell mouse model, there is an induction of nitric oxide synthase II (NOS II) in the glomeruli and distal nephron. This enzyme may increase the synthesis of nitric oxide leading to vasodilation and contribute subsequently to hyperfiltration.

**Clinical Findings**

The clinical manifestations of these pathophysiologic processes in SCD are well defined (Figure 2). Hyposthenuria is the first clinical evidence of defective medullary tonicity. In SCD patients older than 10 yr, the maximal urinary concentration is often reduced to 400 mosmol/kg H$_2$O. This urine concentrating capacity can be restored with multiple transfusions of normal erythrocytes, showing the reversible nature of the defect. However, in patients older than 15 yr, the process is often irreversible. Both vasopressin generation and urinary diluting capacity in SCN patients remain unchanged (1). Hyposthenuria can...
produce a higher than usual obligatory urine output, thereby increasing the risk of dehydration.

**Hematuria**

Asymptomatic hematuria is one of the most prevalent features of the disease (1,7) and occurs either in heterozygous or homozygous patients at any age. Gross hematuria may also be observed in patients with sickle cell trait, either alone or in combination with von Willebrand disease, even in the absence of extrarenal bleeding (1,7). The hematuria is usually unilateral with the left kidney four times more frequently involved than the right. This may be explained by increased venous pressure due to the greater length of the left renal vein (7). Most of the episodes are self-limited, although dramatic and prolonged periods of gross hematuria may be seen (1,8).

**Renal Tubular Acidosis**

In sickle cell trait, renal acidification is normal (1,7,8). The distal tubule of homozygous hemoglobin S (Hb-SS) patients requires a greater acidic stimulus to reach a maximum urine-to-blood hydrogen ion gradient. The acidification defect is consistent with less than maximal generation of titratable acid (7). Usually, this defect does not cause systemic metabolic acidosis (1,7). There is no proximal loss of bicarbonate.

**Proteinuria**

Proteinuria is a frequent finding in SCD, and is present in 30% of patients during long-term follow-up (7). Both proteinuria and renal insufficiency increase with age in a parallel pattern (1,7,11).

Nephrotic syndrome is found in 40% of the patients with SCN (1,7). Falk and Jenette (12), summarizing the series of Falk (13), Bakir (14), Powars (2), and Sklar (4), suggested that the nephrotic syndrome in SCD is a predictor of progression to chronic renal failure.

It is believed that glomerular capillary hypertension, thought to be present in sickle cell nephropathy, mediates proteinuria. This concept is supported by the decrease in protein excretion that is observed with the administration of angiotensin-converting enzyme inhibitors (13).

**Renal Failure**

Renal failure occurs with either an acute or chronic presentation. Acute nonoliguric renal failure is present in 10% of patients hospitalized with SCD (15). Frequently, a concomitant infection or rhabdomyolysis is detected with the renal failure. Less often, renal vein thrombosis and intravascular hemolysis have been reported as causes of acute renal insufficiency in SCD patients (15). Despite the sparse literature, the prognosis seems to be favorable (15). Sklar et al. (15), in a retrospective case-control study of 12 SCD patients with acute renal failure, reported an 83% patient survival with recovery of function in all patients who survived, without progression to ESRD.

Usually, in sickle cell nephropathy the development of ESRD occurs between the third and fifth decades of life (1,11). However, the renal abnormalities begin at earlier ages (16).

Hyperfiltration is common in young patients with SCD (16), and is closely related to glomerular hypertrophy. Proteinuria in sickle cell nephropathy is associated with glomerulosclerosis on renal biopsy, which often progresses to renal failure. The presence of the nephrotic syndrome in patients with SCN is a clinical marker for ESRD, evolving from the progression of glomerulosclerosis. It is reasonable to argue that chronic renal failure is almost always the consequence of the progression of this mechanism of renal injury in SCN, clinically manifested by proteinuria and pathologically represented by glomerular hypertrophy and focal segmental glomerulosclerosis.

**Hypertension**

The incidence of hypertension in patients with Hb-SS ranges between 2 and 6% (7) compared with the published incidence for the black population in the United States of 28%. A renal salt-losing state has been suggested to explain the rather low
incidence of hypertension in patients with SCD (7), although this would suggest chronic volume depletion. A defect in vascular tone has also been suggested (17). Recently, data from the Cooperative Study of Sickle Cell Disease demonstrated that individuals with SCD have BP levels that are significantly lower than in the general population. Predictive variables of BP by a multiple regression analysis showed that in males under 18 yr, there was a positive correlation between diastolic BP and blood urea nitrogen, and a negative correlation with the estimated creatinine clearance. Systolic BP correlated with blood urea nitrogen in females over 17 yr of age. Alarming, values that could be considered normal or that represent mild hypertension in healthy individuals should be considered a risk for important cardiovascular complications in patients with SCD. Also, there was a positive association between BP, stroke, and increased mortality in SCD (18).

**Diagnosis**

**Proteinuria**

Once proteinuria is detected by dipstick, it should be quantified and renal function should be assessed (1). Diseases other than sickle cell nephropathy should be considered. Sudden edema or massive proteinuria (>3 g/24 h) may initially suggest idiopathic nephrotic syndrome, although renal vein thrombosis should always be ruled out, due to the predisposition of patients with Hb-SS to experience venous thrombosis (1,7).

**Hematuria**

Before considering the diagnosis of sickle cell nephropathy, other causes of hematuria must be excluded. Renal and bladder ultrasound can identify bleeding from a stone or tumor (1). Increased echogenicity of the renal pyramids or calyceal clubbing by urography, in the absence of hypercalciuria or nephrocalcinosis, may suggest sickle cell disease (1). In patients with gross hematuria, the use of cystoscopy may identify the source of bleeding. Coagulation tests are useful to rule out the coexistent appearance of von Willebrand disease in sickle trait patients.

**Hyperfiltration**

The upper limit for a normal GFR is not certain even with inulin clearance (1). Simplified methods for nonisotopic iothalamate and para-aminohippurate measurement are now available (1), although for most clinical purposes an accurate measure of GFR is not necessary. A decrease in GFR over time in a patient with sickle cell disease, especially when accompanied by proteinuria, requires a careful follow-up (1).

**Pathology**

Glomerular enlargement was described as part of SCD in 1960 (1). In children, the finding has been reported more frequently beyond 2 yr of age (19). This pattern is more obvious in the juxtamedullary glomeruli. A difference in size has been shown when glomeruli from SCD children are compared with healthy children (19). In adults with Hb-SS, the average diameter of the glomeruli (186 ± 14.5 μm) has been found to be greater than that in glomeruli from control biopsies (137.9 ± 19.3 μm) (13). In older patients with renal involvement, progressive ischemia and fibrosis lead to obliteration of the glomeruli (1).

Falk et al. (13) observed perihilar focal and segmental glomerulosclerosis in eight of 10 biopsy specimens. The sclerotic segments were adherent to Bowman’s capsule with areas of hyalinosis, lipid vacuolation, and foam cells. Adjacent to the glomeruli, focal interstitial fibrosis and tubular atrophy were noted. Immunofluorescence microscopy revealed only irregular staining for IgM, C3, and C1q in sclerotic areas. No electron-dense immune complex-type deposits were seen. Some areas of subendothelial rarefaction had the appearance of basement membrane duplication.

Bhathena and Sondheimer (20) in their analysis of kidney biopsies from six nephrotic patients with Hb-SS described both collapse of the capillaries and mesangial atrophy and expansion of the obliterated tuft segment by mesangial matrix in maximally hypertrophied glomeruli in focal segmental glomerulosclerosis. The mean glomerular diameter was enlarged in nephritic Hb-SS (233.6 ± 25.3 μm) and non-SCD nephrotic patients (243.0 ± 12.5 μm) compared with control subjects (158.0 ± 12.7 μm). Some peripheral capillary loops had the appearance of duplication, others a wrinkling appearance.

Bakir et al. (14) analyzed 240 patients with SCD. Twelve had the nephrotic syndrome. In nine, the glomerular lesion consisted of mesangial expansion and basement membrane duplication (nonimmune membranoproliferative glomerulonephritis [MPGN]-like lesion), and global or focal segmental glomerulosclerosis.

Immunofluorescence studies in one series of four young patients with Hb-SS (1975) and glomerular disease revealed MPGN like lesions associated with Ig and complement deposition (four patients), and renal tubular epithelial antigen deposition (two patients) in a granular pattern along the glomerular basement membrane (21). In the circulation of some patients, tubular epithelial antigens and cryoprecipitable renal tubular antigen-antibody complexes were detected (21). It is uncertain whether these were attributable to SCD.

The composite picture of sickle cell glomerulopathy is one of glomerular hypertrophy and focal glomerulosclerosis (13), with either an expansive or collapsing pattern (20). The basement membrane lucencies and areas of apparent duplication present a variable nonimmune MPGN-like picture (14), without the lobular appearance of immune MPGN. In a few cases, an immune complex nephropathy has been reported (21,22), although it is uncertain whether this is part of sickle nephropathy or an unusual appearance of an immune complex nephropathy modified by the presence of sickle cell disease.

Medullary lesions consist of edema, focal scarring, and interstitial fibrosis with consequent atrophy and mononuclear infiltration. Renal papillary necrosis appears focaly, with a few collecting ducts surrounded by an extensive area of fibrosis (1,7).

Tubular hemosiderin deposits observed in biopsy specimens may play a role in the progression of the nephropathy. Magnetic resonance imaging in SCD patients shows a decrease in the renal cortical spin echo signal, suggesting defective renal
cortical iron metabolism (23). In experimental models using rabbits, saccharated-iron complexes can produce the nephrotic syndrome (24).

**Renal Medullary Carcinoma**

The incidence of cancer in the sickle cell disease population is 1.74 per 1000 patient years with a mortality rate of 1.04 cases per 1000 patient years (25). This is comparable to the cancer incidence rate of 1.9 per 1000 patient years for African-Americans between 35 and 44 yr of age in 1990 (26). The existence of renal cell carcinoma in some patients with sickle cell disease was first suspected by Baron et al. (27), and later confirmed by Davis et al. (28). In their original description of 33 patients, Davis et al. (28) observed a cohort with male predominance under 25 yr of age, although both sexes were equally affected after 25 yr of age. In 25 patients in whom ethnic group data were provided, all were black. Gross hematuria and abdominal flank pain were frequent clinical symptoms. Less frequently, weight loss and a palpable mass were found. In 13 patients, the mean duration of the symptoms was 8 wk. Data available on 19 patients showed survival from the time of surgery of only 15 wk, evidence of the aggressive nature of the tumor. Gross pathology revealed involvement of the right kidney in 23 of the 33 patients. Most of the tissue sections had satellite nodules in the renal cortex with extension to the perinephric and peripelvic soft tissue, characteristics that have been used to detect the presence of tumor in radiologic studies (29). A composite description is that of a lobulated pattern with the tumor located in the renal medulla, which is firm with variable areas of necrosis and hemorrhage (30). Microscopically, the tumor presents a reticular or adenoid cystic pattern with regions of poor differentiation in a stroma with a mucinoid, myxoid, or edematous appearance.

Due to the young age of most of the patients with SCD and renal cell carcinoma, it has been suggested that genetic factors may play a role (30). Avery et al. (30) performed cytogenetic testing in a sample of renal tumor tissue from a 30-yr-old black man with SCD. In the abnormal cells that were successfully karyotyped \( n = 4 \), all had chromosome 11 monosomy and two contained anomalies on chromosome 3 (one monosomy and one translocation). The authors suggested a potential role of a chromosome 11 anomaly in patients with SCD and medullary carcinoma, due to the known location of the gene for beta globin in the terminal portion of the short arm of chromosome 11. Interestingly, allelic loss in chromosome 11 has been associated with other types of neoplasias (31). On the other hand, some familial cases of renal cell carcinoma and younger patients with Hippel-Lindau syndrome and renal cell carcinoma have an association with chromosome 3 abnormalities (32,33). Patients with SCD and medullary carcinoma then share special clinical, demographic, and radiologic findings that may be used for a more prompt detection of the tumor. Medullary carcinoma is an aggressive neoplasm, and the course of the disease has not been modified with different immuno- and chemotherapies (30).

**Treatment of SCN**

Treatment is directed toward the prevention of vaso-occlusive crises and control of infections that can worsen renal function, as well as toward adequate identification and management of renal complications. Neonatal screening for detection of the disease has increased the survival of SCD patients (34).

Altitudes above 2500 m without the use of supplementary oxygen should be avoided by SCD patients (7). Heavy exercise may be dangerous to the patient because of the risk of lactic acidosis. Sudden death has rarely been reported, but occurs even in sickle trait patients. Before elective surgery, it is recommended that transfusions with filtered normal red blood cells be performed.

**Fluid Intake**

Close monitoring of fluid intake and output should be performed. Fluid deprivation, excessive fluid loss, and inability to ingest fluids can induce dehydration in Hb-SS more rapidly than in a normal population, thus exposing the patient to the additional risk of a potential sickle-cell crisis (7,11). Urine output usually should be maintained above 2000 ml/d in adults and in children in proportion to their size (7) to ensure adequate hydration. In states of circulatory overload in critically ill patients due to multiple transfusions, the use of furosemide is recommended (1).

**Hematuria**

Most of the episodes of gross hematuria in patients with SCD subside spontaneously. However, in a few patients hematuria may be massive. Bed rest is recommended to avoid dislodging clots. The use of hypotonic solutions (4 L/1.73 m² per d) in conjunction with diuretics (furosemide or thiazide) can efficiently eliminate clots from the bladder and concomitantly alleviate sickling and possibly prevent renal papillary necrosis (1). Transfusions may be necessary for excessive blood loss. The use of epsilon-aminocaproic acid for fibrinolysis may be necessary. To control hematuria, low doses may be adequate, starting from 1 g per 1.73 m² body surface area orally 3 times daily with a subsequent incremental increase until bleeding subsides (1).

Arteriographic localization and local embolization of the affected renal segment are indicated in patients with uncontrolled bleeding (1). Rarely, nephrectomy is required.

**Proteinuria**

The avoidance of a high protein intake (greater than the recommended dietary allowance) may prevent further deterioration of the nephropathy. However, protein restriction is not recommended due to preexistent growth failure and the low energy state of many Hb-SS patients (35).

The use of angiotensin-converting enzyme inhibitors potentially can diminish the degree proteinuria in SCD patients with nephropathy (Table 1). In a 2-wk trial with enalapril therapy involving 10 patients with mild nephropathy, Falk et al. (13) showed that proteinuria decreased by 57%, but returned to high
levels after treatment withdrawal. BP, GFR, and effective renal plasma flow did not change significantly (13).

**Chronic Renal Insufficiency**

The U.S. Renal Data System study reported 345 SCD patients with renal failure of 332,459 patients treated for renal insufficiency from 1992–1996 (36). Compared with the entire population, fewer SCD patients with ESRD received a kidney transplant (36). It is possible that physicians do not offer treatment to many SCD patients with chronic renal insufficiency, assuming there is a poor chance for successful therapy (1).

Hemodialysis is selected by most SCD patients with ESRD. Interestingly, they do not have more complications than the rest of the dialysis population (1,7,11). There may be an underuse of peritoneal dialysis reflected by the low frequency of selection of the modality by SCD patients when compared to other groups with ESRD (11).

Renal transplantation can be successfully performed in patients with SCD and chronic renal failure. A national registry of renal allografts in recipients with SCD was developed in 1980 (37). Thirty-four transplants were performed in 30 patients. Twenty-three (67%) were functioning at 1 yr, with a 13% patient mortality. In an update of the series in 1987 (38), 45 transplants were performed in 40 recipients. There was a 1-yr graft survival of 82% in living related donors and 62% in those receiving cadaveric kidneys. These data are similar to the graft survival in the general transplant population at 1 yr (37–39). Of particular importance was the fact that sickle cell crises were most frequent in the first year after the transplantation. This is associated with the concurrent elevation in the hematocrit and plasma viscosity (7). As early as 5 mo after transplantation, disturbances in urine concentrating ability can be observed (7). In one case report, recurrence of sickle cell nephropathy was suggested in a transplanted kidney 3½ yr after transplantation (40).

Adequate preparation of the patient before surgery with multiple transfusions of normal blood and the concurrent use of hydroxyurea to increase hemoglobin F production while decreasing the hematocrit may reduce the frequency of crises (7,41).

In summary, sickle cell nephropathy is an important cause of mortality in SCD patients, with specific genetic and clinical markers that can indicate further progression to ESRD. Chronic sickling promotes different mechanisms of kidney injury: structural papillectomy, urine concentration defects, hyperfiltration, and glomerular enlargement and sclerosis. Clinical detection of the manifestations of these processes, as well as detection of risk factors for medullary carcinoma, can permit the clinician to offer a rational treatment to the SCD patient.

Chronic dialysis and transplantation represent reasonable options for those patients who reach ESRD.

**References**

5. Sharpsteen JR, Powars D, Johnson C, Rogers ZR, Williams WD,