The Kidney in Sickle Cell Disease: Pathophysiology and Clinical Review

Ibrahiem Saeed Abdulrahman

Sickle cell disease is a major health problem in many countries. Sickled erythrocytes in the renal medullary vessels are the hallmark of the disease, and are associated with a variety of renal complications. Renal ischemia, microinfarcts and papillary necrosis occur, and renal tubular abnormalities follow. Glomerular disease with proteinuria may be observed. Renal failure, both acute and chronic, is the expected outcome of the disease. Hematuria, electrolyte and acid base disturbances are common throughout the course of the disease. End-stage renal disease as a complication of aggressive sickle cell disease should be treated with dialysis or kidney transplantation; both are effective. There is a tendency towards better survival in sickle cell nephropathy patients undergoing transplantation than in those treated with hemodialysis alone. Whether bone marrow transplantation in the early stage of the disease can halt the progression of sickle cell nephropathy is unknown and awaits clinical studies. [Hong Kong J Nephrol 2004;6(1):2–13]

Key words: sickle cell, tubular, glomerular disease, papillary necrosis, renal failure, ESRD

INTRODUCTION

Sickle cell disease is a major public health problem in the Eastern Province of Saudi Arabia. It is said to be present in individuals heterozygous (Hb-S) or homozygous (Hb-SS) for the hemoglobin S (HbS) gene. The term sickle cell disease applies to homozygous patients; heterozygotes are said to have sickle cell trait. Sickle cell nephropathy is indicated by sickled erythrocytes and is characterized by decreased medullary blood flow, ischemia, microinfarcts, and papillary necrosis. Tubular function, glomerular filtration, blood pressure regulation, and water and electrolyte metabolism are all disturbed (Table 1). Although there are many studies showing that proteinuria, nephritic syndrome, chronic progressive renal failure, and acute renal failure syndromes are the outcome of sickle cell nephropathy, the pathogenic mechanisms and potential therapies remain to be elucidated. Platt et al provide the most comprehensive analysis of life expectancy and risk factors for early death in sickle cell disease; 18% of deaths are ascribed to chronic end-organ involvement, predominantly renal [1]. Patients with sickle cell nephropathy who progress to end-stage renal disease (ESRD) have similar survival to those with non-diabetic ESRD [2]. This article pre-
sent a review of the glomerular and tubular disorders associated with sickle cell disease and points to relevant pathophysiologic and clinical implications.

**RENAL TUBULAR ABNORMALITIES**

An inability to achieve maximally concentrated urine is the most consistent feature of sickle cell nephropathy. This inability has now been documented in both homozygotes and heterozygotes [3–9]. It seems that there is a relationship between concentrating capacity and age. In Hb-SS patients more than 10 years old, the maximal urinary concentration is reduced to about 400 mOsm/kg H₂O and does not decrease further with advancing age. In very young children with sickle cell disease, a concentrating defect is present, but normal concentrating ability can be restored by multiple transfusions of Hb-A erythrocytes [4,7]. This capacity for improvement is progressively lost with age, and in patients older than 15 years, impaired concentrating capacity is irreversible [7]. This is due to repeated sludging that causes thrombosis, progressive infarction of the inner medulla, and papillary necrosis [10,11]. In heterozygotes, more gradual and smaller degrees of impairment are seen [10,11].

The hypoxic, acidotic, and hyperosmolar environment of the inner medulla is known to promote sickling of erythrocytes with resultant impairment of tubular function (Figure 1). Patients with sickle cell disease have a significantly reduced number of vasa recta and obliteration of the remaining medullary capillaries with consequent disturbance in the countercurrent multiplication and exchange system of the inner medulla [10,12]. Defects in urinary diluting capacity also occur. Patients with sickle cell disease are capable of normal urine dilution [6,7,9]. Under conditions of water diuresis, the fall in urinary osmolality is the same in control subjects and Hb-SS patients; this combination of a defect in renal concentrating capacity and normal diluting capacity is characteristic of sickle cell disease [5,12].

Renal acidification and potassium excretion are also impaired in patients with sickle cell disease, and many
individuals may show a form of incomplete distal renal tubular acidosis. Sickle cell disease patients are unable to lower their urine pH to less than 5.3 following standard ammonium chloride loading [13,14], which is not seen in patients with sickle cell trait [15]. Under normal conditions, patients with sickle cell disease do not manifest acidosis unless the glomerular filtration rate (GFR) is reduced to less than one-half of normal [16]. Other points that differentiate it from classic renal tubular acidosis type I include the absence of hypo-kalemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis [16].

In addition to the defect in hydrogen ion excretion, potassium excretion is also impaired in sickle cell disease patients [13,16,17]. After administration of potassium chloride, sodium sulfate, or furosemide, potassium excretion is subnormal in patients with sickle cell disease; however, hyperkalemia has not been reported in sickle cell disease patients unless there is impairment of renal function or conditions of stress [13,16]. Plasma renin activity and plasma aldosterone concentrations in these patients are normal, both with normovolemia and after volume contraction, so the defect cannot be explained by hypoaldosteronism [16,18]. DeFronzo et al suggest the presence of a primary defect in the renal tubular secretion of potassium, which is probably caused by ischemic injuries in the collecting ducts [13]. Despite impaired potassium excretion, the serum potassium concentration does not increase during potassium loading, which suggests an increased intra-
cellular shift of potassium, probably caused by β, adrenergic stimulation [19]. Potassium excretion in sickle cell trait is normal [20]. Few reports have described hyporeninemic hypoaldosteronism in patients with sickle cell disease [17,18]. In these cases, an impaired renin-secreting apparatus may result in impaired function of the adrenal glomerulosa cells, diminished aldosterone secretion, and an impaired ability to excrete potassium loads. In such cases, the hyperkalemia responds favorably to treatment with mineralocorticosteroids.

In spite of the severe disturbances in medullary transport in patients with sickle cell disease, proximal tubular activity, both secretory and reabsorptive, appears to be supernormal. With increased red blood cell (RBC) turnover and consequent uric acid overproduction, most patients with sickle cell disease are normouricemic. Uric acid clearance is greater in these patients [21,22]. Urate clearance, however, decreases with age and the incidence of hyperuricemia increases as renal function deteriorates [23]. In addition, the tubular secretion of creatinine is increased in Hb-SS patients compared to control subjects [24,25]. One should realize, therefore, that creatinine clearance in sickle cell disease overestimates GFR considerably. Maximum tubular reabsorption of phosphate is also increased in patients with sickle cell disease, so serum phosphate is elevated in these patients [26,27]. It has been postulated that the high phosphate reabsorption reflects an increased reabsorptive activity in the proximal tubules [26]. There is also increased sodium reabsorption, which parallels phosphate reabsorption. Some studies report an increased plasma volume in the non-crisis steady state in sickle cell disease [28–30]. Increased reabsorption of β-microglobulins has also been described [31].

**Figure 1.** Renal medullary changes that lead to hyposthenuria, papillary necrosis, and hematuria. RBCs = red blood cells.

**GLOMERULAR FILTRATION AND RENAL BLOOD FLOW**

GFR and renal blood flow (RBF) are increased by as much as 50% in patients with sickle cell disease [24,32]. This is probably related to compensatory hypersecretion of vasodilator prostaglandins during the process of sickling. The filtration fraction is usually decreased, indicating that increases in GFR are not proportional to increases in RBF. Anemia per se probably has some influence on these abnormalities since similar changes have been observed in children with β-thalassemia [4]. However, other factors must be involved since transfusion-associated increases in hematocrit do not cause the renal hemodynamic parameters to revert to normal [4].

Bank et al recently studied the mechanism of hyperfiltration in a transgenic sickle cell mouse model
and concluded that renal synthesis of nitric oxide by the L-arginine pathway was increased in the transgenic mice and that this increase correlated positively with the GFR [33]. In a more recent study, the exposure of transgenic sickle cell mice to chronic hypoxia resulted in activation of inducible nitric oxide synthase and superoxide radical and peroxynitrite formation; the consequences of these reactions enhanced apoptosis, ultimately leading to structural damage [34]. Whether these mechanisms are operative in humans remains to be proved.

Both GFR and RBF are normal during adolescence but are frequently subnormal after the age of 40 [35, 36]. On the other hand, some patients with Hb-SS in their 40s or even older may have completely normal or even supernormal GFR and RBF [12]. Renal pathologic findings in young patients with sickle cell disease include glomerular enlargement as well as increased numbers of capillary lumens and epithelial, endothelial, and mesangial cells [37]. Other findings may include congestion of capillary loops with sickled erythrocytes and hemosiderin (Figures 2 and 3). Fractional creatinine excretion is increased [24]. It is therefore advisable to employ inulin clearance when investigating GFR. In sickle cell trait, sickle cell-hemoglobin C disease, homozygote-hemoglobin C disease, hemoglobin C trait, and sickle cell ß-thalassemia, GFR and RBF are within the normal range [3].

There is speculation on the possible mechanisms responsible for the decline in renal hemodynamics with age, sometimes ending in renal failure with shrunken end-stage kidneys. Progressive renal insufficiency in these patients has been ascribed to hyperfiltration-mediated sclerosis of the glomerular capillaries [38,39]. In a recent study to determine the cause of progressive renal insufficiency in patients with sickle cell disease, Guasch et al found an association between renal insufficiency and a decrease in the ultrafiltration coefficient [40]. The ultrafiltration coefficient was also reduced in albuminuric patients with normal GFR [40]. This latter finding supports the observation of Powars et al that proteinuria and nephrotic syndrome are significant preazotemic predictors of chronic renal failure [41]. The results of another recent study by Schmitt et al seem to contradict those of Guasch et al [42]. However, we can speculate that proteinuria with an increase in the ultrafiltration coefficient may represent very early changes that act significantly to trigger the development of glomerulosclerosis; these early changes may no longer be detected at later stages, and a decrease in the ultrafiltration coefficient may contribute to the decrease in GFR. Remuzzi and Bertani suggest that filtered plasma proteins taken up by tubular epithelium stimulate inflammatory genes and release inflammatory and vasoactive substances into the renal interstitium that induce scarring and sclerosis [43].

Papillary Necrosis

Renal papillary necrosis is a frequent occurrence in both sickle cell disease and sickle cell trait. As a complication of sickle cell nephropathy, papillary necrosis has an incidence of 15% to 36% [44]. Papillary necrosis in sickle cell disease is mediated by blood vessel occlusion, specifically of the vasa recta and medullary vessels, that causes infarction and necrosis of papillary tissue [45] (Figure 1). In most patients with sickle cell disease, the infarcted areas are small, and renal function, as measured clinically, is not usually immediately affected [44]. Less commonly, sickle cell disease patients have more widespread necrosis of the papillae due to more extensive infarction [2]. Given that these patients all have the same SS genotype, these data suggest that

**Figure 2.** Sickle cell nephropathy. Sickled erythrocytes in capillary loops. (Jones’ silver stain with hematoxylin and eosin counter stain.)

**Figure 3.** Electron microscopic features of a large, congested glomerulus. The capillary lumina are distended by sickled erythrocytes. (Uranyl acetate and lead citrate, × 6,380.)
individual variability in non-sickle cell disease genes helps to determine the degree of blood vessel occlusion with infarction. Thus, while HbS is caused by a single mutation, sickle cell disease could be a multigene disease [46]. This concept helps to account for the variable severity of disease, including the degree of papillary necrosis, among sickle cell disease patients.

Vessel occlusion is also affected by local production of cytokines that alter local factors in a way that augments vascular occlusion [47]. Sickle cell disease patients with higher levels of fetal hemoglobin (HbF) or of hemoglobin A2 have a lower risk for SS hemoglobin polymerization and, hence, a lower risk for infarction of papillary tissue with subsequent papillary necrosis [48]. In addition to HbS polymerization, the degree to which sickled RBCs adhere to vascular endothelium is an important component of the cascade leading to blood vessel occlusion in sickle cell disease [47]. Furthermore, immature and larger RBCs are more likely than mature ones to adhere to vascular endothelium [47]. There is individual variability among sickle cell disease patients in their marrow response to the increased RBC destruction that characterizes sickle cell disease [49]; thus, variability in the release of immature RBCs might contribute to individual variability in the degree of vaso-occlusive disease, including papillary necrosis, among these patients.

Papillary necrosis is most frequently found incidentally during renal imaging procedures, formerly intravenous pyelography (Figures 4 and 5) but now more commonly ultrasound, computerized axial tomography scan, or magnetic resonance imaging. The most detailed analysis of reported series found 131 cases of papillary necrosis in 334 patients with sickle cell disease (39%), with the incidence ranging from 23% to 67% in the individual series [44]. The true incidence of this complication is probably higher, since many cases will be asymptomatic or have only microscopic hematuria that is not evident using imaging procedures [50]. The mean age at discovery was 21 ± 1 years (range, 4–68 years) [44]. Papillary necrosis in sickle cell disease may have a protracted course of months to years, interrupted by recurring episodes of gross hematuria and/or urinary tract infection [45]. Less commonly, it may present dramatically with renal colic, gross hematuria, and acute renal failure with or without urinary tract obstruction [44,45,51]. Patients with sickle cell disease who develop symptomatic papillary necrosis sometimes have blood clots and/or sloughed papillary tissue in their urine, although this finding was infrequent in one large series, and acute urinary tract obstruction was even less frequent [44]. Papillary necrosis is categorized according to severity. The less severe variety is referred to as the medullary or partial papillary form and is usually confined to the tip of the papilla. When more advanced, the forniceal architecture is preserved but types of involvement may include the ring sign, sinus tract formation, and cavity formation involving loss of part or all of the papilla. Further progression to the total papillary stage includes sinus tract formation at the fornice, larger ring shadows indicative of larger sequestered papillae, and amputated calyces (Figure 6). Totally sloughed papillae may be seen as filling defects in the renal pelvis, ureters, or bladder [44].
HEMATURIA

In 1984, Abel and Brown discovered a relationship between sickle cell disease and hematuria [52]. Hematuria is a major alteration detected in individuals with sickle cell disease and sickle cell trait. It is usually described as painless, symptomless, benign, and self-limited, but it may also be hemorrhagic and difficult to control. The pathogenesis of hematuria seems to be explained by vascular obstruction in the renal medulla by sickled RBCs, with consequent extravasation of blood cells [53,54] (Figure 1). In 80% to 90% of cases, the bleeding is unilateral and originates from the left kidney, probably because of anatomic differences in kidney venous drainage [55].

Mostofi and associates studied 21 kidneys from patients with sickle cell disease that were removed because of massive blood loss and the possibility of renal neoplasm [56]. The absence of gross alterations in most of these kidneys emphasizes the fact that the lesions are inconspicuous and may be easily missed. The most striking change was severe stasis in the peritubular capillaries of both the cortex and the medulla. Changes were most marked in the medulla. Extravasation of blood was observed, mainly into the collecting tubules. In 1990, Osegbe described 12 individuals (six with sickle cell disease) aged between 12 and 32 years with renal papillary necrosis diagnosed by suggestive findings on excretory urography and manifested by hematuria of 3 days’ to 5 months’ duration [57]. Bleeding was intense in four patients and moderate in eight. Mild lumbar pain and fever occurred at low frequency. Hematuria originated exclusively from the left side in 10 of these patients.

Renal medullary carcinoma, of which the most frequent symptom is massive hematuria, is a rare and extremely aggressive tumor detected in association with sickle cell trait, and more rarely with sickle cell hemoglobinopathy. This tumor has not been reported in homozygotes, a fact that remains unexplained. Curiously, most of the bleeding occurring in this tumor comes from the right kidney [58]. Renal medullary carcinoma, although rare, should always be kept in mind in the differential diagnosis of benign hematuria, especially when the patient is a child or young adult with sickle cell trait; renal imaging and urine cytology should be performed in these patients [58,59].

More commonly, gross hematuria occurs in patients who have heterozygous sickle hemoglobin (Hb-AS, Hb-SC), as well as in those who have homozygous disease [60–65]. The relative rarity of hematuria in patients with HB-SS is more apparent than real, as sickle cell trait is approximately 40 times more common than the homozygous state. Gross hematuria in affected patients may occur at any age, including young children, and appears to be more common in males than in females [65,66].

GLOMERULAR ABNORMALITIES AND PROTEINURIA

The major pathologies in sickle cell disease-associated renal failure are papillary necrosis, focal segmental glomerulosclerosis (FSGS), and type 1 membranoproliferative glomerulonephritis (MPGN) [52]. Renal biopsies in patients [37,38,45,67], as well as autopsy studies, show that FSGS is the most common cause of renal failure in sickle cell disease. Moreover, clinicopathologic studies show that the early lesion of most forms of sickle cell nephropathy is glomerular enlargement with progressive development of perihilar FSGS [38,45]. These data support the hypothesis that FSGS is the major cause of sickle cell nephropathy (Figure 7).

Recent data suggest that sickle cell disease is a state of oxidative stress [68]. It seems that initiation, progression, and resolution of the vaso-occlusive episodes comprise features of ischemia-perfusion injury with the associated chronic inflammatory response that includes activation of white blood cells and a local increase in the oxidative state [69]. Activated monocytes/macrophages of bone marrow origin play an important role in the pathogenesis of glomerulosclerosis in humans [70]. In addition, oxidized plasma lipoproteins are implicated in the pathogenesis of glomerulosclerosis in experimental animals and in humans [69,71]. Factors that probably cause FSGS in sickle cell disease are summarized in Table 2.
Although MPGN in sickle cell disease is morphologically similar to the classic variety of this disease, few cases have the characteristic immune deposits, particularly in the early stages [38,45]. Type 1 MPGN with immune complex deposits has been documented in a small number of patients [2]. The etiology of MPGN in sickle cell disease is poorly understood, but it is not the major cause of renal failure in sickle cell disease [45].

In sickle cell disease, glomerular size tends to increase with age. Glomerular enlargement and congestion are present in children more than 2 years old [2,67]. Proteinuria has been detected by the dipstick method in 17% to 33% of patients with sickle cell disease, and seems to be associated with reduced creatinine clearance in patients older than 40 years [67, 72]. Wigfall et al followed 442 patients with sickle cell disease for 10 years; proteinuria lasting at least 6 months was detected in 6% of children and 12% of adolescents [73]. Proteinuria was associated with disease severity.

The mechanisms whereby nephrotic syndrome, renal insufficiency, and glomerular lesions interrelate in patients with sickle cell nephropathy remain unclear [74]. Possible mechanisms include fortuitous occurrence, iron overload and subsequent deposition in the kidneys, mesangial phagocytosis of sickled cells, immune complex glomerulonephritis due to auto-antigens released from ischemic tubules, FSGS associated with glomerular hyperfiltration, glomerular hypertrophy, and endothelial damage [74,75]. Some authors suggest that there must be a specific mechanism associated with hemodynamic alteration in the pathogenesis of sickle cell nephropathy, probably a change in the glomerular capillary wall that leads to an altered pore size [2,76]. It is also possible that the glomeruli are sensitive to a common stimulus provoked by growth hormone or cytokines [77–79].

Falk and colleagues found proteinuria of at least +1 in 101 of 381 (26.5%) patients with sickle cell disease [67]. Among the 44 patients for whom there was complete 24-hour urine collection, protein excretion ranged from 0.028 to 10.8 g/24 hours (mean, 1.7 g/24 hours; standard deviation, SD, 2.4 g/24 hours). Twelve patients excreted more than 2.5 g/24 hours, associated with other features of the nephrotic syndrome. Sklar and coworkers reviewed the records of 368 patients with sickle cell disease [80]. Seventy-eight patients (20.6%) had proteinuria and 17 patients (4.6%) had renal insufficiency. Both renal insufficiency and proteinuria increased with age. Renal vein thrombosis has been diagnosed in some patients with sickle cell disease and, because Hb-SS predisposes to venous thrombosis, this complication should be considered in all patients with Hb-SS in whom massive proteinuria develops.

**Table 2.** Factors that may induce focal segmental glomerulosclerosis in sickle cell disease.

<table>
<thead>
<tr>
<th>Hyperfiltration of cortical nephrons due to:</th>
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<tr>
<td>- Hypersecretion of vasodilator prostaglandins</td>
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<td>- Increased renal synthesis of nitric oxide</td>
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<tr>
<td>- Cytokines from damaged vascular endothelium</td>
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<tr>
<th>Increased production of reactive oxygen species due to:</th>
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<tr>
<td>- Hypoxia/reoxygenation</td>
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<td>- Recruitment of activated leukocytes</td>
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<td>- Auto-oxidation of sickle hemoglobin</td>
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<tr>
<th>Chronic exposure of tubular epithelium to high levels of filtered plasma proteins due to:</th>
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<tbody>
<tr>
<td>- Cortical nephron hyperfiltration</td>
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<tr>
<td>- Podocyte damage</td>
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<td>- Glomerular tuft adhesions</td>
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<th>Autologous immune-complex nephritis due to:</th>
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<tr>
<td>- Renal tubular epithelial antigens</td>
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<td>- Cryoprecipitable renal tubular antigen-antibody complexes</td>
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ACUTE RENAL FAILURE

Acute renal failure has rarely been described in association with sickle cell disease. Some reports describe a reversible acute oliguric renal failure in the setting of sickle cell crisis [81–83]. In these studies, rhabdomyolysis was suggested as the cause of this acute renal failure. In a study by Sklar et al, volume depletion in the setting of sickle cell crisis was the most common cause [84]. In more recent studies, episodes of acute renal failure were most commonly noted in cases of overwhelming sepsis with high fever [81–83], probably due to diffuse microvascular occlusion and organ ischemia or to non-traumatic rhabdomyolysis [82,83, 85]. Hassell and coworkers described a syndrome of acute multi-organ failure involving the lung, liver, and kidney in 14 sickle cell patients; this occurred during an unusually severe painful crisis [83]. Pham and colleagues described a case of postpartum exacerbation of sickle cell nephropathy manifested by nephrotic syndrome and declining renal function [86], probably due to the hemodynamic stress of pregnancy superimposed on a background of substantial chronic nephron loss.

CHRONIC RENAL FAILURE

Renal function may deteriorate with age in sickle cell disease patients, either as a result of the parenchymal damage due to sickling or because of glomerular disease. The incidence of renal failure in patients with sickle cell disease is 4% to 18% in US adults [41,76]. Data from the US Renal Data System obtained for 1993 to 1997 showed that 0.1% of patients with ESRD had sickle cell disease as a primary cause [87].

Both maintenance hemodialysis and renal transplantation are viable options for patients with sickle cell nephropathy who progress to ESRD. Survival of patients on hemodialysis has been shown to be equivalent to that of other non-diabetic ESRD patients [88]. Although both graft and patient survival after transplantation for sickle cell nephropathy-related ESRD are slightly lower on a long-term basis than in patients undergoing transplant for other causes, there is a tendency towards a better survival of these patients compared with those treated by dialysis [89]. Ojo et al published the results of patient and allograft outcomes in renal transplant recipients with ESRD secondary to sickle cell nephropathy [89]. The study consisted of 22,647 African-American end-stage sickle cell nephropathy patients who received kidney transplants between 1984 and 1996, identified through the United Network of Organ Sharing (UNOS). One-year graft survival in recipients with end-stage sickle cell nephropathy was found to be similar to that in recipients with other causes of ESRD. However, the 3-year cadaveric graft survival was diminished among patients with sickle cell nephropathy (48% vs 60%). Abbott et al analyzed 375,152 patients in the US Renal Data System who were initiated on ESRD therapy between January 1992 and June 1997 in a historical cohort study of sickle cell nephropathy [90]. They found that sickle cell nephropathy patients had an independently increased risk of mortality. However, when renal transplantation was also included in the model, sickle cell nephropathy was no longer significant. Nevertheless, further analysis by Scheinman revealed a trend toward better patient survival with renal transplantation compared with sickle cell nephropathy patients on maintenance hemodialysis [91]. Despite these encouraging results, renal transplantation in sickle cell disease is not without morbidity. An increase in the frequency of crisis has been demonstrated in patients who undergo successful kidney transplantation, which appears to be due to increased endogenous hematopoiesis with a consequent increase in blood viscosity and vaso-occlusive crisis [92–95].

Patients with sickle cell disease have a relative erythropoietin deficiency. Steinberg described good results when patients with sickle cell disease and chronic renal failure used higher doses of epoetin-α than are needed in patients with other forms of ESRD [96]. However, the results obtained by Roger et al with this drug in similar situations were disappointing [97].

Bone marrow transplantation has recently emerged as a novel treatment for sickle cell disease. As this procedure is associated with high morbidity and mortality, it has been indicated in a relatively small number of patients [98]. Whether bone marrow transplantation can stop the progression of sickle cell nephropathy is unknown [2].

THERAPEUTIC ASPECTS

Treatment of hematuria

Efforts are needed to prevent or reverse sickling, to prevent clot retention in the urinary tract, to increase tissue oxygenation, and to reduce acidosis and hypertonicity in the medulla. In this regard, the maintenance of a high urinary flow is useful both for elimination of blood clots and for reduction of renal medullary osmolality, which in turn reduce RBC sickling in the vasa recta. The fluid for infusion should be hypotonic; up to 4 L/1.73 m²/day may be used. Urinary alkalinization and blood transfusion when necessary may reduce medullary sickling [99]. Drugs such as hydroxy-carbamide (hydroxyurea) and recombinant human erythropoietin increase the percentage of HbF in patients with sickle cell disease, and may reduce sickling. Some studies report an increase of about 15% in HbF with the use of hydroxyurea [100]. Conflicting
results, however, have been reported about its effect on the number of sickling crises [101,102].

**Nonsteroidal anti-inflammatory drugs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often considered to be benign and preferable to opioids for the treatment of pain in sickle cell disease. However, particular risks of NSAID use do exist in these patients. Blood loss from occult gastritis, although often unnoticed in other patients, may destabilize precarious hemodynamic compensation in chronic anemia. Since NSAIDs and acetaminophen are used throughout life, the risk of analgesic nephropathy must be considered, especially in patients who are already at risk of renal failure from sickle cell disease [103,104]. On the other hand, isolated reports show no consistent benefits of NSAIDs or immunosuppressive drugs such as steroids and/or cyclophosphamide in the management of sickle cell nephropathy [2,75].

**Angiotensin-converting enzyme inhibitors**

In the renal ablation animal model of FSGS, characterized by glomerular hyperfiltration and hypertension, angiotensin-converting enzyme (ACE) inhibitors decrease glomerular hyperfiltration and hypertension and reduce the risk for subsequent development of FSGS [105]. This observation encouraged investigators to test the efficacy of these drugs in reducing both proteinuria and the likelihood of renal failure in patients with sickle cell disease.

Foucan et al evaluated the effect of captopril on microalbuminuria in sickle cell disease patients and concluded that ACE inhibitors delay progression of sickle cell nephropathy [106]. In their study of 381 patients with sickle cell disease, Falk et al found that the mean 24-hour urinary protein excretion decreased by about 57% below the baseline value ($p < 0.001$) during the administration of enalapril in sickle cell disease patients with nephropathy [67]. Longer-term studies are needed, however, to determine whether this ACE inhibitor-induced reduction in urinary albumin excretion translates into a reduced risk of renal failure.

Interventions that reduce oxidant stress mediated by reactive oxygen species might also reduce the risk of nephropathy in sickle cell disease. Anti-oxidant therapy, therefore, might retard FSGS progression in such patients [69].

**Management of tubular dysfunction**

It is not usually necessary to treat tubular dysfunction. Preventive measures, such as encouraging patients to increase fluid ingestion in situations of greater water loss, can be used to avoid complications. Diarrhea and dehydration should be treated promptly, keeping in mind that these patients have a lower ability to concentrate urine and, hence, become dehydrated more easily. Because tubular sodium reabsorption is increased, possibly causing cardiac insufficiency, physicians must avoid prescribing large volumes with standard sodium content for water repletion in these patients [99]. Hyperuricemia can be aggravated by the use of diuretics, particularly thiazides. During hemolytic crises, the physician should be alert to the increase in serum potassium. In these cases, the use of β-blockers or ACE inhibitors can aggravate hyperkalemia. A β-stimulant, on the other hand, may be important to move this ion into cells [99]. Although indomethacin reduces ammonia excretion [107], decreases sodium tubular reabsorption, and improves the response to diuretics [39], its use is not recommended because of the significant fall in GFR and effective renal plasma flow after indomethacin administration to Hb-SS patients [24,25].

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