

# HEMATOLOGY eDIGEST

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## Newsletter: May 2006 | Issue 9 : Volume 1

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<p>➔ <b>Jerry L. Spivak, MD</b> Professor of Medicine and Oncology The Johns Hopkins University School of Medicine</p>	<p>➔ <b>Cage S. Johnson, MD</b> Professor of Medicine Keck School of Medicine University of Southern California</p>	<p>➔ <b>James R. Eckman, MD</b> Professor of Medicine Emory University School of Medicine</p>	
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### In this Issue...

Abnormal kidney function is virtually a universal problem in sickle cell disease patients, and has a lifelong impact on their management. Changes in renal tubular function cause a decreased ability to concentrate the urine and excrete hydrogen and potassium, leading to dehydration, acidosis, and hyperkalemia during sickle cell disease complications. Diagnostic criteria may be ambiguous: while proteinuria appears to be an early manifestation of glomerular damage that may predict future renal insufficiency, serum creatinine and measured creatinine clearance have been found to be insensitive indicators of glomerular filtration. In addition, blood pressure is also normally lower in sickle cell anemia patients.

In this issue, we review recent literature that addresses the causes and treatment of renal disease, an emerging major and under-recognized complication in adults with sickle cell disease.

➔ **Commentary & Reviews by:**  
James R. Eckman, MD

⬇ **Guest Editor of the Month:**



**James R. Eckman, MD**  
Professor of Medicine  
Emory University School of Medicine

## Commentary & Reviews

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## Guest Faculty Disclosures

### → James R. Eckman MD.

Faculty Disclosure: Dr. Eckman indicated a past and current financial relationship for grants, research support and honoraria from Novartis Pharmaceuticals.

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## Commentary

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One of the earliest manifestations of renal involvement in sickle cell disease is a renal tubular defect that prevents concentration of urine and excretion of hydrogen ions and potassium<sup>1</sup>. The renal concentrating defect is of importance in patient management because the obligatory loss of water predisposes the individual with sickle cell anemia to dehydration. Dehydration increases the rate of sickling because small increases in serum osmolality draw water out of the erythrocyte. This increases intracellular hemoglobin concentration, profoundly increasing the rate of sickling<sup>2</sup>. These consequences mandate the universal education of sickle cell patients to avoid dehydration and drink water with the onset of pain and other complications; they also indicate the need for intravenous hydration with D5W or D5W 1/4 NS normal saline during such complications, even though this has been validated only in one very small phase II study<sup>3</sup>. Renal tubular functional changes also result in creatinine secretion, causing the creatinine clearance to overestimate the glomerular filtration rate (GFR) and the serum creatinine to improperly correlate with reduction in GFR<sup>4</sup>. These abnormalities may also affect drug clearance in some patients.

In adult sickle cell patients, glomerular damage becomes a major concern because the onset of renal failure markedly decreases quality of life and has been shown to markedly shorten lifespan. Median life expectancy with renal failure is 27 years as compared to 51 years without renal failure<sup>5</sup>. Increasing anemia may also be an early manifestation of renal disease in sickle cell patients because of loss of erythropoietin production and relative resistance to erythropoietin<sup>6</sup>. Another concern is the potential nephrotoxicity of medications that are commonly used to treat acute and chronic pain in sickle cell patients. Nonsteroidal anti-inflammatory drugs can cause a significant reduction in renal blood flow and GFR<sup>4</sup>. While these agents might protect from glomerular damage in the early stages of renal insufficiency, they will predictably result in reduced GFR, urine flow, and free water clearance, leading to complications in individuals with more advanced renal insufficiency.

Once end-stage renal disease occurs, the prognosis is very poor despite the availability of dialysis<sup>5</sup>. Very few sickle patients have been transplanted, although recent results of kidney transplantation in older children and adults with sickle cell disease are encouraging<sup>7,8</sup>, suggesting that this form of therapy should be applied more aggressively in this patient population<sup>9</sup>.

More studies are needed to define the determinants of glomerular damage in sickle cell disease, the preventive strategies for delaying loss of glomerular function, and optimal treatment once irreversible renal

failure occurs. Recent epidemiologic studies suggest this will become a much more prevalent problem due to the increased number of adults of advanced age with sickle cell disease.

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## INCIDENCE OF RENAL DISEASE IN OLDER ADULTS WITH SICKLE CELL DISEASE

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Two recent studies document the changing demographics of sickle cell disease in the United States, and show that the sickle population is aging related to improved health care. Powars et al performed a longitudinal observational study of 1056 patients followed at one institution, investigating the interactions of era, sex, age and thirty acute clinical events on eight types of irreversible organ damage in the population. They also compared the causes of death in 232 patients, finding that 46 died at age <20 years and 186 died at age >20 years. The authors found that renal failure developed in 122 patients (11%) at a median age of diagnosis of 37 years. About 9 % of the patients with renal failure also had gall bladder disease, avascular necrosis of the hip, or lung disease. Renal failure was the primary cause of death in 33 of the 232 patients and was thought to contribute to death in a number of other patients.

The study by McKerrell et al compared clinical and laboratory differences in a cross-sectional study of individuals followed at one institution who were <30 or >40 years of age. Among McKerrell's findings were that older patients had a lower hemoglobin level, lower platelets count, increased creatinine and BUN, and reduced creatinine clearance when compared to the younger cohort. In addition, the hemoglobin level significantly correlated with creatinine clearance in this study. Of further interest was the lack of increase in blood pressure in the older patients with sickle cell disease.

Both studies document the changing demographics of sickle cell disease in the United States, and highlight that renal insufficiency is becoming a common problem in adults with sickle cell disease. The findings of Powars et al suggest that renal failure contributes significantly to mortality. McKerrell et al further suggest that the progressive anemia and reduced reticulocyte count observed in older patients may be the result of declining renal function in this population. Both authors appropriately caution that prospective studies will be required to confirm their suggestions.

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## THE NATURE OF SICKLE CELL GLOMERULAR DISEASE

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Falk et al screened 381 patients for proteinuria and renal insufficiency, then performed renal biopsies and function studies in 10 patients. Guasch et al performed a cross-sectional study comparing 10 patients with normal glomerular filtration rate (GFR) and albumin excretion rate (AER); 7 with increased AER and normal GFR; and 17 with low GFR. In a second study, they performed detailed analyses of glomerular function in 12 sickle cell patients with normal renal function and in 17 with renal insufficiency. They reported on GFR with inulin clearance, renal plasma flow with clearance of PAH, selective clearance of IgG and dextrans of varying molecular weights to characterize glomerular pore size and number.

Falk's results document the high prevalence of glomerular disease in sickle patients, finding proteinuria in 26% of patients and elevated creatinine levels in 7%. Biopsy findings showed glomerular enlargement, perihilar focal segmental glomerular sclerosis, and hemosiderosis. The study by Guasch et al found increased renal plasma flow over GFR in all groups, indicating a low filtration fraction. All patients with albuminuria had reduced ultrafiltration coefficients that were further reduced in those with CRF. Physiologic analyses showed that the increase in serum creatinine and creatinine clearance greatly underestimated the reduction in GFR in sickle patients. The glomerular lesion in sickle cell disease appeared unique with increase in effective pore size early, followed by loss in glomerular number and size-selectivity as renal insufficiency progressed.

These studies document that glomerular damage is common in children and adults with sickle cell disease and may be the earliest correlate of the development of renal insufficiency. The Guasch study is of particular importance because it documents that routine screening for either serum creatinine or creatinine clearance will be very insensitive in detecting early renal failure in the sickle population. These reports further imply that screening for albuminuria, or perhaps micro-albuminuria, may be required to detect those with early glomerular damage.

Again, careful longitudinal studies will be required to determine if the occurrence of micro-albuminuria or albuminuria accurately defines individuals who will progress to renal insufficiency. For the hematologist providing longitudinal care to patients with sickle cell disease, screening for albuminuria and careful observation for changes in serum creatinine levels - even within the range of normal - is mandatory. Other preventive strategies such as control of blood pressure are also important for health maintenance.

1. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette J. [Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme](#). New Engl J Med 1992; 326:910-915.



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2. Guasch A, Cua M, Wei Y, Mitch WE. [Sickle cell anemia causes a distinct pattern of glomerular dysfunction](#). Kidney Int 1997; 51:826-833.



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## BLOOD PRESSURE IN SICKLE CELL DISEASE

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Two retrospective studies provide evidence that patients with sickle cell anemia have blood pressure that was lower than age-matched controls. In 1981, Johnson et al compared blood pressures in both outpatients and inpatients with sickle cell anemia to age- and sex- matched African-American controls. In 1997, Pegelow et al reported blood pressure determinations from 3,317 subjects in the Cooperative Study of Sickle Cell Disease and compared them with those in the National Health and Nutrition Examination Survey I and II (NHANES I and II).

The Johnson study found that blood pressures in sickle cell patients were significantly lower than age-matched controls, and that there was not the expected increase in blood pressure with age in this group (a result supported by the comparison blood pressure findings in young and older patients reported by McKerrell, cited elsewhere in this issue.) Pegelow reported that sickle anemia patients had lower blood pressures than NHANES I and II subjects at every age for diastolic pressure. Both systolic and diastolic pressure were lower in the subjects older than 25 years of age. While they report that there was an increase in blood pressure with age, that rate of increase was less in patients with sickle cell anemia. Additional important observations were that increased mortality was observed in individuals with high systolic and

diastolic pressures, and that occurrence of stroke increased with elevation of systolic blood pressure.

These observations have a number of important implications in the management of sickle cell patients. One is the need to know the normal blood pressure of individual sickle cell anemia patients, so that their blood pressure can be properly interpreted during acute illnesses. Of potentially even greater importance is the need to realize that modest elevations in systolic and diastolic blood pressure are associated with increased risk for stroke and early mortality. In addition, because of the prevalence of proteinuria and renal insufficiency, Pegelow speculated that a blood pressure of 120/80 may reflect borderline hypertension in young individuals with sickle cell anemia, and that a pressure of 140/90 should be evaluated and treated.

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## ≡ TREATMENT OF PROTEINURIA IN SICKLE CELL DISEASE

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The study by Falk et al (reviewed above in this issue) included a short term trial of the angiotensin converting enzyme (ACE) enalapril in 10 sickle subjects with proteinuria. Baseline daily urinary protein output was determined and repeated after 3 weeks on enalapril 5 or 10 mg/day, and again three weeks after stopping the study drug. Falk reported that 3 weeks of treatment with enalapril significantly decreased daily proteinuria but that levels rapidly returned to baseline after the drug was discontinued.

Fitzhugh et al report a retrospective review of their use of enalapril and hydroxyurea in three children with significant proteinuria. Blood pressure, serum potassium, serum and urine albumin and creatinine were measured. After an average of 3.1 years on enalapril, the three subjects reported by Fitzhugh et al had a significant improvement in urinary protein/creatinine ratio and normalization of serum albumin. After the addition of hydroxyurea for an average of 3.5 years, fetal hemoglobin increased and the urinary protein/creatinine ratio improved further to near normal levels.

Foucan et al report a small randomized double-blind controlled trial of captopril in 22 normotensive subjects with sickle cell and proteinuria. The 24 hour excretion of albumin in the urine was compared at baseline and after six months of observation. Subjects treated with captopril had a 45 mg/day decrease in proteinuria, while the controls had a 18 mg/day increase in proteinuria after 6 months of treatment. There was a slight decrease in blood pressure in the captopril group and one subject developed hyperkalemia.

Clearly further studies will be required before these observations can be translated into definitive clinical management or recommendations for sickle cell disease patients. A longitudinal study of renal function with sickle cell disease will be required to validate the suggestion that micro- or macro- albuminuria predicts future renal failure, and to identify other risk factors for progressive renal disease. Longer phase II or phase III trials of ACE inhibitors or angiotensin II receptor blocking (ARB) agents should be conducted to show that the reduction in proteinuria translates into prevention of progressive renal dysfunction. Lacking such studies, screening for mild elevations in blood pressure and macro-albuminuria should be incorporated into routine health maintenance in sickle cell patients. Patients with mild elevations in blood pressure should be evaluated and treated. When concurrent proteinuria is present, it seems reasonable to start with an ACE inhibitor or ARB with monitoring for hyperkalemia. For patients with isolated proteinuria, hydroxyurea administration should be considered, and currently, based on preliminary studies in sickle cell disease and other causes of proteinuria and renal failure, many clinicians are also treating these individuals with ACE inhibitors.

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### Target Audience

This activity has been developed for Hematologists. There are no fees or prerequisites for this activity.

### Learning Objectives

At the conclusion of this activity, participants should be able to:

- Identify the impact of renal abnormalities on the management of sickle cell anemia;
- Explain the significance of proteinuria in sickle cell patients and why routine management should include screening for albuminuria;
- Discuss the special considerations in diagnosis of hypertension in sickle cell disease patients.

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- Dr. Eckman has indicated a past and current financial relationship for grants, research support and honoraria from Novartis Pharmaceuticals.
- Dr. Johnson has indicated a financial relationship of grant/research support from the NIH and the NHLBI. He has also acted as consultant to Novartis, SuperGen, Thios and Icagen.

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