Glomerular Hyperfiltration in Sickle Cell Disease

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Sickle cell disease (SCD) is a monogenetic, chronic anemia syndrome that is caused by a point mutation in the \( \beta \)-globin gene and affects approximately 100,000 individuals in the United States. Approximately 4 to 5% of these individuals have or will develop stage 5 chronic kidney disease (CKD), and 0.11% of patients who are on long-term maintenance renal replacement therapy have SCD-associated nephropathy (1–3).

Homozygous hemoglobin S leads to severe, chronic, hemolytic anemia and the propensity for hemoglobin polymerization, and red blood cell (RBC) sickling causes small artery occlusions. SCD is a multiorgan syndrome with involvement of the central nervous system (infarcts, strokes), eyes, heart, lungs (pulmonary hypertension), spleen (infarcts), muscle, bone (avascular necrosis), and kidneys. Renal complications include chronic medullary injury and papillary necrosis and transient macrohematuria, which are thought to be caused by vasa recta occlusive disease as a result of RBC sickling. Medullary injury also causes reduced urine-concentrating ability and a mild form of (type IV) distal renal tubular acidosis. Glomerular abnormalities include micro- and macroalbuminuria and the nephrotic syndrome. Histologically, FSGS is the predominant glomerular lesion in patients with SCD and proteinuria (4). Of note, glomeruli are much enlarged in SCD presumably by hypertrophy (5). In young patients with SCD, the GFR is substantially increased but tends to decrease progressively with time (6–8). Glomerular enlargement and early hyperfiltration are thought to play important roles in subsequent chronic glomerular injury and progressive CKD in SCD.

Haymann et al. (9) in this issue of CJASN examine the prevalence of glomerular hyperfiltration and determine potential risk factors in SCD. In 280 adults with SCD, these investigators used the three-variable Modification of Diet in Renal Disease (MDRD) formula to estimate GFR. Estimated GFR was validated in a subgroup of patients with \( ^{51} \)Cr-EDTA renal clearance measurements. Hyperfiltration (MDRD-GFR >130 in women, >140 ml/min per 1.73 m\(^2\) in men) was found in 51% of this population, and chronic renal insufficiency (MDRD-GFR <60 ml/min per 1.73 m\(^2\)) was seen in 8.6 and 3.8% in women and men, respectively. Approximately one half (49%) of the patients with glomerular hyperfiltration did not have proteinuria, 36% had microalbuminuria, and 15% had macroalbuminuria. This distribution of renal glomerular function and proteinuria may suggest a progressive pattern from early glomerular hyperfiltration and hypertrophy to microalbuminuria, CKD with macroalbuminuria, renal insufficiency, and finally stage 5 CKD with advanced renal insufficiency requiring renal replacement therapy. If this assumed chain of renal disease progression indeed occurs in SCD, then it would be important to determine causes and risk factors for glomerular hyperfiltration to develop early interventions.

In SCD increased GFR is associated with increased renal plasma flow, a reduced filtration fraction, and an increased glomerular ultrafiltration coefficient (8,10). This suggests that the glomerular hyperfiltration is driven by increased glomerular perfusion and increased effective glomerular filtration surface area (glomerular enlargement) but not by increased glomerular capillary hydrostatic pressure, which would separate this condition from early diabetic nephropathy. Although it is an attractive hypothesis that glomerular hyperfiltration is an important determinant of FSGS and progressive CKD in SCD, prospective studies are needed to answer this question.

The findings by Haymann et al. (9) also suggest that RBC sickling–induced vaso-occlusion is not causative in glomerular hyperfiltration. This is inferred by their result that typical vaso-occlusive clinical complications of SCD such as osteonecrosis, priapism, leg ulcerations, and pulmonary hypertension do not co-segregate in this population with glomerular hyperfiltration. Instead, in addition to younger age, markers of chronic hemolysis including absence of \( \alpha \)-thalassemia (which reduces hemolysis), lower hemoglobin levels, greater hemoglobin F levels, and higher reticulocyte count each are independent risk factors for glomerular hyperfiltration in SCD.

There may be more than one mechanism by which greater rates of chronic hemolysis could contribute to hyperfiltration in the kidney. More severe anemia raises cardiac output and reduces peripheral (and renal) vascular resistance (11,12). Because glomerular hyperfiltration in SCD is driven primarily by increased renal plasma flow, it is possible that the increased cardiac output as a result of chronic anemia drives high GFR. Alternatively, higher hemolysis rates lead to increased tissue iron deposition. Although the kidney is not a major site for iron accumulation in hemosiderosis, some renal iron accumulation has been reported in SCD, albeit moderate and limited to proximal tubules in most cases and involving few podocytes and mesangial cells in some patients (13–15). The contribution of renal iron deposits to renal pathophysiology, pathology, and
progressive CKD, if any, is not well established. Given that severe transfusional hemosiderosis generally does not cause glomerular functional or structural abnormalities, it is perhaps unlikely that renal iron deposition in SCD plays important roles. Some patients with SCD require regular transfusion of packed RBCs, the recommended treatment for stroke prevention and acute coronary syndrome in SCD. Hence, some patients with SCD will develop hemosiderosis. In the patients who had SCD and were studied by Haymann et al. (9), transfusions were given to approximately 11% of patients, but the incidence of hemosiderosis is not reported. Perhaps this subgroup is too small for meaningful analysis. Although findings by Haymann et al. support that chronic hemolysis confers risks for hyperfiltration, the mechanisms remain elusive. Moreover, it is unknown whether early glomerular hyperfiltration is indeed a determinant for subsequent proteinuria, FSGS, CKD, and progression to advanced renal insufficiency in this patient population. Haymann et al. are encouraged to follow this cohort of patients with SCD prospectively with periodic GFR measurements and assessments of proteinuria to address this important question in the future.

Disclosures
None.

References

See related article, “Glomerular Hyperfiltration in Adult Sickle Cell Anemia: A Frequent Hemolysis Associated Feature,” on pages 756–761.