HHS Public Access

Author manuscript

Expert Rev Hematol. Author manuscript; available in PMC 2017 December 01.

Published in final edited form as:

Expert Rev Hematol. 2017 December ; 10(12): 1087–1094. doi:10.1080/17474086.2017.1395279.

The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait

Rakhi P. Naik[a] and **Vimal K. Derebail**[b]

[a]Division of Hematology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA

[b]Division of Nephrology and Hypertension, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Introduction—Renal dysfunction is among the most common complication of sickle cell disease (SCD), from hyposthenuria in children to progression to overt chronic kidney disease (CKD) in young adults. Emerging evidence now suggests that sickle hemoglobin-related nephropathy extends to individuals with sickle cell trait (SCT).

Areas covered—This review will highlight the pathophysiology, epidemiology, and management recommendations for sickle hemoglobin-related nephropathy in both SCD and SCT. In addition, it will focus on the major demographic and genetic modifiers of renal disease in sickling hemoglobinopathies.

Expert commentary—Studies have elucidated the course of renal disease in SCD; however, the scope and age of onset of renal dysfunction in SCT has yet to be determined. In SCD, several modifiers of renal disease – such as α-thalassemia, hemoglobin F, APOL1 and HMOX1 – have been described and provide an opportunity for a precision medicine approach to risk stratify patients who may benefit from early intervention. Extrapolating from this literature may also provide insight into the modifiers of renal disease in SCT. Further studies are needed to determine the optimal treatment for sickle hemoglobin-related nephropathy.

Keywords

Sickle cell disease; sickle cell trait; sickle nephropathy; hemoglobinopathy; chronic kidney disease

1. Introduction

Renal manifestations are among the most common complications of sickle cell disease (SCD), from the near universal finding of hyposthenuria in children to progression to end-stage renal disease (ESRD) in adults—a continuum referred to as sickle nephropathy. The

CONTACT: Rakhi P. Naik, rakhi@jhmi.edu, Division of Hematology, Department of Medicine, Johns Hopkins University, 1830 E. Monument Street Suite, 7300, Baltimore, MD 21205, USA.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

hypoxic, acidotic, and dehydrated environment of the renal medulla promotes erythrocyte sickling, ultimately leading to ischemic-reperfusion injury, vasculopathy, and glomerular damage. However, while the relationship between renal impairment and SCD—a term used to describe several genotypes including hemoglobin SS/Sβ°, SC and Sβ+ thalassemia—has long been recognized, the association between chronic kidney disease (CKD) and hemoglobin AS or sickle cell trait (SCT) has only recently been established. This review will highlight the pathophysiology, epidemiology, and management recommendations for sickle hemoglobin-related nephropathy in both SCD and SCT. In addition, we will discuss demographic and major genetic modifiers of renal disease in sickling hemoglobinopathies and the role of precision medicine in identifying individuals who may benefit from early intervention.

2. Pathophysiology of sickle cell nephropathy

The unique physiologic environment of the kidney leads to susceptibility to renal injury in SCD. The renal medulla has particularly low oxygen tension, hyperosmolarity, and low pH, all of which promote hemoglobin S (HbS) polymerization and subsequent sickling of red blood cells in SCD. The typical understanding of SCD-related kidney disease suggests that repetitive episodes of sickling lead to ischemic injury and microinfarction, ultimately resulting in loss of the vascular architecture of the renal medulla [1]. This vaso-occlusion and microinfarction is thought to contribute to several of the noted clinical features of SCD-related kidney disease, including altered urinary concentration, hematuria, and indirectly, hyperfiltration [2,3]. As noted in murine models of ischemic renal injury, transgenic sickle mice demonstrate substantially greater renal injury than wild-type mice and even demonstrate injury in the kidney contralateral to the induced ischemic insult [4].

Glomerular hyperfiltration and renal hyperperfusion are also common features in SCD, occurring as early as infancy [2,5]. While the mechanisms of hyperfiltration are not completely understood, it is thought to be indirectly triggered by medullary hyperperfusion as described above. In response to medullary ischemia, vasodilatory substances, including prosta-glandins, are released leading to reduced renal vascular resistance and increased effective renal arterial blood flow [6]. Further studies have suggested additional mechanisms may also contribute to hyperfiltration. For example, transgenic sickle cell mice exhibit increased expression of heme oxygenase-1 (HO-1) in the kidney and other tissue beds as part of a response to oxidative stress. HO-1, in turn, leads to increased production of carbon monoxide (CO) which is also local vasodilatory properties [5,7].

Endothelial dysfunction has been described in SCD and also likely plays an important role in the pathogenesis of sickle cell kidney disease. Soluble fms-like tyrosine kinase 1 (sFLT-1), a splice variant of vascular endothelial growth factor receptor 1 (VEGFR1) binds circulating VEGF, prevents its interaction with endothelial cells, and ultimately induces endothelial dysfunction. A study of 73 SCD patients demonstrated an association between sFLT-1 and worsening albuminuria suggesting a contribution to sickle cell nephropathy [8]. Endothelin-1 (ET-1), a peptide with potent vasoconstrictive properties, is produced by endothelial cells in response to various insults, including sheer stress, hypoxia, and inflammatory signals. ET-1 mediates endothelial dysfunction by reducing NO bioavailability

and induces direct injury to podocytes via the ETA receptor [9,10]. In sickle cell mouse models, ET-1 has been demonstrated to mediate glomerular injury via reactive oxygen species, and ETA receptor antagonism appears to afford renal protection [11,12]. In patients with SCD, ET-1 has also been demonstrated to be associated with albuminuria and measures of vascular dysfunction [13].

Finally, hemolysis itself may contribute to the development of kidney disease due to the increase in levels of plasma free hemoglobin and subsequent hemoglobinuria. Free heme filtered through the glomerulus is directly cytotoxic to renal tubular epithelial cells, which subsequently induces damaging inflammatory responses [10]. A recent study also found that hemoglobin competes with filtered albumin by binding to megalin and cubilin in the proximal tubule. Albumin resorption is impaired leading to tubular proteinuria (independent of glomerular damage) that likely also induces renal injury [14]. Kidney biopsy specimens of individuals with SCD may demonstrate hemosiderin deposition in glomerular and tubular epithelial cells [15]. Clinical studies have demonstrated an association between hemolysis markers and albuminuria [16,17]. Additionally, data from a combined cohort study confirmed a relationship between hemoglobinuria and progressive CKD [18].

Progressive of kidney damage in SCD is likely driven by a multitude of processes including those described above. Hyperfiltration and its associated hemodynamic changes injure the glomerular endothelium, filtration barrier, and parietal epithelium. These injuries are thought to produce the characteristic lesion of focal segmental glomerulosclerosis (FSGS) most commonly described in SCD [5,19,20]. Ongoing hemolysis, vaso-occlusive injury, endothelial dysfunction, proteinuria, and to a lesser degree, iron deposition likely contribute to continuing renal injury.

The pathophysiology of kidney disease in SCT is thought to have similar, but attenuated, processes as those for SCD although there are limited data to support this. Microangiographic studies of the kidney in SCT individuals demonstrate vascular disruption compared to normal controls, but less severe than patients with SCD [1]. While patients with SCT do exhibit hematuria, impaired urinary concentration, and albuminuria, and the other features of CKD common to SCD have not been examined in detail in SCT [5,21].

3. Epidemiology

3.1. Hematuria and renal papillary necrosis

Perhaps, the most common renal abnormality noted in individuals with SCD and SCT is that of hematuria [21]. The etiology of hematuria is presumed to be due to vaso-occlusive events, microinfarction, and subsequent ischemic parenchymal injury and may present as microscopic or painless gross hematuria. The left kidney is more commonly involved, presumptively due to its slightly larger size and higher venous pressure resulting from compression of the left renal vein by the aorta and superior mesenteric vein [21]. The most profound manifestation of these ischemic events is renal papillary necrosis, with infarction of the renal papillae leading to gross hematuria and potentially even ureteral obstruction due to clot and/or tissue sloughing. Potential additional contributors to papillary necrosis include

analgesic use, concomitant cirrhosis, diabetes mellitus, pyelonephritis, systemic vasculitis, renal vein thrombosis, or urinary tract obstruction [22].

3.2. Impaired urinary concentration

One of the earliest manifestations of renal disease in sickling hemoglobinopathies is impaired concentrating ability (hyposthenuria) [23]. Early studies demonstrated a dose-dependent relationship between concentration of HbS and degree of hyposthenuria, with individuals with hemoglobin SS or Sβ° genotypes (sickle cell anemia, SCA) demonstrating severely impaired concentrating ability (inability to concentrate urine to >450 mOsm/kg with water deprivation) starting in infancy and those with SCT demonstrating a later onset of impairment usually by age 10 [24]. This impaired ability to concentrate urine starting at a young age is thought to relate to the increased prevalence of nocturnal enuresis among children and adolescents with SCD [25], a phenomenon that may persist into adulthood [26].

3.3. Hyperfiltration

In addition to hyposthenuria, hyperfiltration—variably defined as GFR ≥ 90–140 mL/min/1.73 m^2 [27]—is also frequently observed in children with SCD, often as early as infancy. In the BABY HUG study, elevated glomerular filtration rate (GFR) ≥ 110 mL/min/1.73 m^2 as measured directly by plasma clearance of ^{99m}Tc-DTPA was present in over 50% of infants from 9 months to 1 year and demonstrated progressive escalation with increasing age beyond 15–19 months [28]. This increase in GFR appears to continue to progress well into young adulthood with nearly all children >2.5 years of age demonstrating elevated GFR in the HUSTLE study [29], and nearly all adults age 18–30 years also demonstrating high creatinine-based eGFR ≥ 130 mL/min/1.73 m^2 [30]. As the degree of renal clearance declines, however, eGFR levels also appear to drop off, starting around age 30–40 [30]. Whether similar glomerular hyperfiltration occurs in SCT is unknown, although one small study of Congolese children suggested that hyperfiltration defined as creatinine-based eGFR >140 mL/min/1.73 m^2 was more common in SCT than hemoglobin AA controls [31].

As a correlate to glomerular hyperfiltration, increased GFR in SCD results in proximal tubular hyper-functioning and creatinine hypersecretion. Creatinine levels in individuals with SCD have been noted to be lower than controls, suggesting that estimates of creatinine clearance may underestimate renal dysfunction in SCD. In fact, creatinine-based estimation equations for GFR all appear to overestimate kidney function when compared to radionucleotide measures of GFR [32]. Because of this phenomenon, cystatin C has been suggested as a more accurate marker of CKD in both children and adults with SCD with GFR greater than 30 mL/min/1.73 m^2 [27,33]. In SCT, cystatin C-based eGFR was associated with higher prevalence of low eGFR <60 mL/min/1.73 m^2 compared to creatinine-based estimations, but correlations with direct measures of GFR have not been investigated [34].

3.4. Albuminuria

Similar to diabetic nephropathy, hyperfiltration appears to result in progressive glomerular injury in SCD. Baseline hyperfiltration of eGFR >130–140 mL/min/1.73 m^2 is associated with the development of microalbuminuria (urine albumin 30–299 mg/g creatinine) in adults

with SCA [30]. Albuminuria >30mg/g has also been found in over 20% of SCD children, with greater than 60% of patients with SCA demonstrating albuminuria by adulthood [35,36]. Progression to macroalbuminuria >300 mg/g affects nearly 40% of adults with SCA by age 40 [36]. Nephrotic range proteinuria, however, is rare and only occurred in only 12/250 (4%) of SCD patients in one series, with the pathology attributed to progressive sickle glomerulopathy rather than an alternative cause in a majority of cases [37].

In SCT, a study of four population-based United States cohorts found that 31.7% of African American adults with SCT had baseline albuminuria >30 mg/g, with an odds ratio (OR) if 1.86 (1.49–2.31) comparing those with and without SCT [34]. These findings have been further extended to SCT individuals of Hispanic/Latino ancestry [38]. Similar studies in children with SCT have not been performed; therefore, the age at onset of these changes in SCT is unknown.

3.5. Chronic kidney disease

Progression of glomerular damage ultimately leads to eGFR decline in SCD and SCT patients, even as measured by creatinine-based estimates. In one adult SCD cohort with mean age 31.6 years, nearly 30% had baseline CKD defined as eGFR <60 mL/min/1.73 m^2 and/or albuminuria >150 mg/g, which progressed to a prevalence of 41.8% over 5 years [39]. In SCT, 36.8% of African Americans were found to have CKD by eGFR and albuminuria criteria by a mean age of about 60 years, compared to 25% prevalence in non-SCT adults [40], resulting in about a 1.5–2 fold risk of CKD in SCT carriers of African or Hispanic ancestry compared to noncarriers [34,38]. Studies using directly measured GFR in SCD and SCT patients with late-stage kidney disease, however, have not been performed.

3.6. End-stage renal disease

Advanced CKD and ESRD, though infrequent complications, are associated with significant morbidity and mortality in SCD. In a large cohort of >1000 SCA patients, renal failure was noted in 12% of patients with a median age of onset of 37 years. That study also noted that 14% of SCD deaths were directly attributable to renal disease, second only to chronic lung disease and pulmonary hypertension [41]. Advanced CKD was also demonstrated to be the most common etiology of death in the Cooperative Study of Sickle Cell Disease (CSSCD) among patients with chronic organ failure, comprising 10.5% of total deaths [42]. In SCD patients over the age 60, advanced CKD is a major cause or contributor to death in 43% of patients [43].

Studies investigating the relationship between SCT and ESRD, however, have been conflicting. A cross-sectional analysis of ESRD patients on dialysis demonstrated an increased prevalence of SCT among those with ESRD compared to expected population prevalence [44], but a subsequent case-control of diabetic, hypertension-attributed, and glomerular disease-associated ESRD did not find an association with SCT [45]. More recently, longitudinal data from a large, population-based cohort do suggest a 2-fold increased risk of developing ESRD in SCT compared to noncarrier controls [40]. The influence of this potential increase in ESRD risk among SCT carriers on mortality has not

been determined, though prior studies have demonstrated no increase in overall mortality among individuals with SCT [46].

4. Modifying factors

4.1. Age

Age is by far the most potent modifying factor of sickle nephropathy, as described in the prior section. Progression to overt CKD appears to occur by early adulthood (age 20–30s), and as more individuals with SCD are reaching the fourth to sixth decade of life, the prevalence and risk of CKD is likely to increase as well. In SCT, the age of onset of renal dysfunction is unknown but is expected to be a later age than with SCD.

4.2. Hypertension

The relationship between sickle nephropathy and hypertension has not been well-studied. Several studies have found lower mean blood pressures and prevalence of hypertension among individuals with SCD compared to controls, even among those with renal disease [36,47,48]. It has been hypothesized that this phenomenon may be due to lower urinary concentrating ability and urinary sodium loss in individuals with SCD [49]; however, the pathophysiology is not clear. Interestingly, in patients with SCA, macroalbuminuria and renal insufficiency appear to be associated with resistance to developing hypertension [36] Furthermore, a recent multi-center study of SCD has suggested that pulse pressure, rather than mean arterial pressure, may be more predictive of SCD-related vasculopathy, including in the kidney [50]. Nonetheless, arterial hypertension may be a risk factor for CKD in SCD [51]. For example, nocturnal hypertension, based on age-specific criteria, was associated with a lower mean eGFR in a pediatric cohort of patients with SCA and relative systemic hypertension >120/70 mmHg appears to associate with higher creatinine levels in SCA adults [52,53].

The relationship between hypertension and renal disease in SCT is similarly complicated. Several United States-based population studies have demonstrated that SCT confers a higher risk (2–3 fold) of CKD among African Americans without hypertension compared to an only 1.5 increased risk in hypertensive individuals, despite a similar prevalence of hypertension in SCT and non-SCT carriers at baseline [34,40]. This may suggest that SCT-related nephropathy itself results in relative hypotension; however, further studies will be needed to elucidate this relationship.

4.3. SCD genotype

As with most complications in SCD, genotype is an important modifier of prevalence and severity of CKD. The phenotypic variation observed with sickling genotypes relates to differences in degree of hemolysis, endothelial dysfunction, and viscosity, with hemolytic complications such as pulmonary hypertension and leg ulcers being more common in SCA genotypes and viscosity-related manifestations such as retinopathy and possibly avascular necrosis being more common in sickle variant syndromes [54]. Renal medullary vasculopathy appears to fit into the former category; albuminuria and advanced renal

insufficiency have consistently been found to be more prevalent among individuals with SCA compared to those with SC or Sβ$^+$thalassemia [36,55].

4.4. Alpha-thalassemia

The major determinant of rheologic changes ('sickling') of erythrocytes in sickling hemoglobinopathies is polymerization of sickle hemoglobin. Polymerization is, in turn, facilitated by low oxygen saturation and by higher concentration of HbS and is impaired by high concentrations of hemoglobin F [56,57]. Alpha-thalassemia deletions, the most common of which is the −3.7kb deletion, are found in approximately 30% of African Americans and, in the case of SCT, co-inheritance directly relates to decreased HbS percentage. Specifically, in SCT, co-inheritance of α-thalassemia gene deletions decreases the percentage of HbS in a dose-dependent manner such that individuals with a higher number of α-thalassemia deletions demonstrating the lowest percentage of HbS [58]. This results in a sickle hemoglobin concentration per erythrocyte range of about 25–45%. This phenomenon has been demonstrated to be clinically relevant in the kidney; in one study, α-thalassemia deletions protected against urinary concentrating defects in individuals with SCT in a dose-dependent manner [59]. However, α-thalassemia has not yet been studied in other manifestations of renal disease in SCT, such as albuminuria and decreased GFR; therefore, the impact on renal disease progression in SCT is unknown.

In SCD, the relationship between α-thalassemia and HbS polymerization is likely more complex, but nonetheless, alpha-thalassemia deletions are associated with a decreased risk of hemolysis-associated complications such as leg ulcers and stroke [54], a finding that appears to translate to CKD. Patients with hemoglobin SS disease who co-inherit at least 1 copy of an α-thalassemia deletion have a lower prevalence of macroalbuminuria (13%) compared to those without α-globin deletions (40%) [60]. Similarly, α-thalassemia was significantly associated with the absence of hyperfiltration in a young adult population of SCA patients [61]. Another recent study in a cohort of 413 SCD individuals from Cameroon also demonstrated a 'protective' association between α-thalassemia and macroalbuminuria [62].

4.5. Hemoglobin F

As discussed above, hemoglobin F is also a major determinant of HbS polymerization and phenotype in SCD. Hemoglobin F percentage in SCD can range from <5% to 20%, with several genes being implicated in the variability of levels. Early studies revealed differences in % hemoglobin F between sickle haplotypes, with the Senegal and Arab Indian variants having the highest hemoglobin F levels (10–20%) and the African Benin and Central African Republic (CAR)/Bantu haplotypes having the lowest (~5%) [63]. More recent studies have revealed that 20–50% of this hemoglobin F variation is due to polymorphisms in the β-globin gene cluster, the *HBS1L-MYB* intergenic region on chromosome 6, and *BCL11A* on chromosome 2 [64]. Polymorphisms in these genes can lead to nonspecific hetero-cellular elevations in hemoglobin F. In SCD, hereditary persistence of fetal hemoglobin (HPFH) has been associated with a decreased risk of vaso-occlusive crisis and acute chest syndrome [63,65]. Little evidence links increased fetal hemoglobin and renal dysfunction; in one longitudinal study of 725 SCD patients, the CAR β^s haplotype was

associated with a high risk of renal failure [66], and in another study of 144 children with SCA, higher hemoglobin F levels were associated with lower prevalence of microalbuminuria [67]. A common *BCL11A* polymorphism was also associated with lower albumin/creatinine ratio (ACR) than wild type in an adult cohort of SCD [68]. Studies evaluating the effect of hemoglobin F levels on SCT-related nephropathy, however, have not yet been performed.

4.6. HMOX1

Interest has recently developed in variants of *HMOX1*, the gene encoding for the enzyme heme oxygenase-1—the enzyme responsible for heme catabolism. A study of 221 SCD patients from the University of Illinois at Chicago (UIC) and 487 patients from the Walk-Treatment of Pulmonary Hypertension and Sickle cell Disease with Sildenafil Therapy cohort (Walk-PHaSST) demonstrated an association between the *HMOX1* rs743811 variant with lower eGFR, albuminuria, and CKD stage even after adjusting for *APOL1* variants. In the Walk-PHaSST cohort, this variant also associated with ESRD. The longer *HMOX1* GT-tandem repeat polymorphism in the UIC cohort was associated with lower eGFR [69]. Another smaller study of 152 SCD patients in Europe failed to delineate a relationship between the *HMOX1* rs743811 variant and kidney disease [70]. However, another study of young SCD patients (median age 15 years) from Cameroon demonstrated a trend to association between *HMOX1* rs743811 and macroalbuminuria, although this did not quite reach statistical significance ($p = 0.06$) [62]. While certainly not definitely associated with kidney disease in SCD, these *HMOX1* variants do warrant additional examination, particularly due to their direct influence on heme catabolism and potential pathophysiologic role.

4.7. APOL1

APOL1 high-risk variants (G1/G1, G1/G2, or G2/G2), which are found in about 11–13% of African Americans, are the most widely recognized genetic contributors to renal disease. Similar to SCT, they have been found to confer a ~ 2-fold higher risk of renal disease progression and ESRD among unselected African Americans [40,71]; however, in select populations such as hypertension-attributed, FSGS, and HIV associated nephropathy, *APOL1* variants have been found to confer a significantly greater risk of ESRD, ranging from 7- to 29-fold increased risk depending on etiology [72]. Given this strong relationship to renal disease, the question of whether co-inheritance of APOL1 high-risk variants potentiates the risk of sickle nephropathies has been of considerable interest. Few studies have investigated this relationship. In SCD, *APOL1* high-risk variants were associated with a 3-fold increased risk of proteinuria by dipstick measure but not eGFR in one study of 521 patients [73]. Another study of 262 adults with SCA demonstrated an association of *APOL1* high-risk variants with albuminuria and renal progression (defined as 50% decline in eGFR or ESRD) [68].

In SCT, however, a genetic interaction with *APOL1* has not been verified. In two population-based cohorts with a total of 3,292 African Americans, SCT was associated with a 2.67 (CI 1.13–6.33) increased risk of albuminuria in individuals with *APOL1* high-risk variants compared to an OR 1.40 (CI 1.01–1.95) in those without high-risk variants, but this

interaction was not statistically significant [34]. Nonetheless, among individuals with SCT, 50% (12/24) of those with co-inheritance of *APOL1* high-risk variants demonstrated albuminuria compared to 27% of those without *APOL1*. A similar trend was not observed for CKD defined by eGFR < 60 mL/min/1.73 m^2. Another single cohort study of 9909 self-reported African Americans also demonstrated no significant interaction between *APOL1* and SCT for baseline CKD [40].

4.8. Other genetic modifiers

Additional genetic modifiers have been explored in SCD that may also influence risk of CKD. In a cohort of 237 adult SCA patients, lack of Duffy (Fy) antigen expression was significantly associated with a 3-fold increase in proteinuria by dipstick measurement, possibly due to a loss of inflammatory inhibition [74]. In addition, an exploratory evaluation of 1,140 children and adults from the CSSCD found associations between polymorphisms in the bone morphogenic protein (BMP) 1B gene and eGFR, also hypothesized to be due to impaired inflammatory response [75]. Validation of these studies has yet to be performed. Other genetic modifiers of CKD risk in SCD undoubtedly exist and will need to be investigated in future studies.

5. Screening guidelines

Evidence-based recommendations for SCD-related complications were developed by a National Heart Lung and Blood Institute (NHLBI) expert panel in 2014 [76,77]. Although there has been no specific study to guide screening regimens for renal disease in SCD, consensus panel recommendations have been based on considerations of cost and potential benefits. Most recent guidelines state that all children with SCD should be screened for proteinuria annually starting at age 10. If the proteinuria screen is positive by dipstick, a first morning urine albumin-to-creatinine or 24 h urinary albumin should be performed and if positive, consideration should to taken to consult with or refer to a renal specialist [77]. The guidelines additionally state that any patient with macroalbuminuria (>300 mg/24 h) or modest elevations in creatinine (>0.7 mg/dL in children, >1.0 mg/dL in adults) should be referred to a nephrologist [76].

Formal recommendations for screening for CKD in individuals with SCT are not currently available, in part, because evidence of an association of SCT and CKD has only recently been documented. However, because screening for sickle hemoglobin is mandated as part of newborn screening in all 50 states, the need for additional research to guide screening and counseling recommendations in SCT has been increasingly recognized [78].

6. Treatment

The most widely studied treatment for SCD-related nephropathy has been angiotensin-converting enzyme (ACE)-inhibitors. ACE inhibitors dilate the efferent arterioles leading to a decrease in glomerular pressure and albuminuria. Because sickle nephropathy is in part due to vasoconstriction and progressive glomerular hypertension, ACE inhibitors have offered an attractive therapeutic intervention for SCD-related renal dysfunction [79]. In a prospective study of 10 patients with SCD-related proteinuria, enalapril (5–10 mg/day) x 2

weeks was found to decrease 24 urinary protein excretion by a mean of 57% [19]. In another study of eight patients treated with 6 months of enalapril (5 mg daily) therapy, 7/8 achieved normalization of their urinary albumin levels [80]. Given the success of these small studies, one of the few randomized controlled trials in SCD was performed to evaluate the efficacy of captopril in 22 patients with SCA and microalbuminuria. Captopril (dose escalated from 6.25 mg daily to 25 mg daily in the first 3 months for a total 6 months) resulted in a 37% reduction in urinary albumin compared to +17% increase in the placebo group [81]. Based on these results, the NHLBI consensus panel has recommended initiation of an ACE inhibitor for all adult SCD patients with albuminuria >30 mg/g.

SCD-specific therapies such as hydroxyurea and chronic transfusion have not been formally studied for SCD-related renal complications. In the BABY HUG study, hydroxyurea for 24 months did not reduce hyperfiltration in 193 infants (mean age 13.8 months) with SCD, but did show benefit for hyposthenuria and decreased renal enlargement [82]. An evaluation of children in the HUSTLE prospective study, however, did demonstrate an effect of hydroxyurea in reducing hyperfiltration among a cohort of 23 older children (median age 7.5 years) [82]. In a study of 149 adults with SCD, patients on hydroxyurea were only one-third as likely to exhibit albuminuria, although this study was limited by its cross-sectional nature [83]. A small prospective study of 58 patients noted reduction in albuminuria at 6 months after initiation of hydroxyurea, although noted primarily in the microalbuminuria subgroup [84]. Due to the paucity of data, there are no specific recommendations regarding hydroxyurea use for SCD-related nephropathy, although hydroxyurea has been suggested to improve renal disease-associated anemia when used as an adjunct to erythropoiesis-stimulating agents (ESAs) [77].

In SCT, epidemiologic studies have shown that higher doses of ESAs may be required to achieve a hemoglobin response in SCT carriers with ESRD compared to noncarriers [85]. However, no formal studies have specifically investigated potential treatments for CKD in SCT.

7. Expert commentary

Sickle nephropathy is a common complication of SCD and emerging evidence suggests that the spectrum of renal disease extends to SCT. The epidemiology of renal dysfunction in SCD has been evaluated in numerous studies and has verified an early onset of albuminuria and hyperfiltration in children with a progression to overt CKD by early adulthood. Several genetic modifiers of renal disease in SCD have been described and provide an opportunity for a precision medicine approach to risk stratify patients who may benefit from early intervention. Because CKD is associated with significant morbidity and mortality in SCD, the need for effective treatments is essential. ACE inhibitors likely delay progression to CKD in SCD patients; however, continued efforts should be made to identify SCD-specific therapies—such as hydroxyurea, transfusion therapy, and others—which may have benefit in prevention of sickle nephropathy.

Many aspects of the epidemiology of renal disease in SCT have yet to be determined. Genetic counseling and screening guidelines for renal dysfunction in SCT require a more in-

depth knowledge of the scope, age of onset, and rate of progression of renal disease in carriers of SCT. Furthermore, insights about the genetic modifiers of nephropathy in SCD should be extrapolated to and explored in SCT. For example, α-thalassemia has already been shown to be a potent modifier of urinary concentrating ability in SCT, and future research is needed to determine if co-inheritance of SCT and α-thalassemia may protect against development of overt renal dysfunction. Because many of the existing longitudinal cohorts follow a general population with a low prevalence of SCT, a dedicated SCT cohort may be necessary to answer these questions. In addition, similar to in SCD, treatments to delay progression of nephropathy in SCT carriers are critical, and future studies will need to focus on the use of ACE inhibitors and other treatments to delay progression of renal complications in SCT.

8. Five-year view

The recent surge in epidemiologic and genetic research in SCD and SCT is likely to lead to considerable advances in our understanding of sickle hemoglobin-related nephropathy. In particular, we will gain knowledge about the demographic and genetic profile of individuals with sickle hemoglobinopathies who are at high risk for progression of their kidney disease. A precision medicine approach will allow us to tailor counseling, screening, and treatment recommendations for individuals with SCD or SCT and markers of renal dysfunction. We will also gain increasing understanding about the pathophysiology of renal disease in sickling disorders, which will help guide testing and development of effective therapies.

Acknowledgments

Funding

RP Naik is supported in part by National, Heart, Lung, and Blood Institute (NHLBI) [grant K08HL125100].

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1•. Statius van Eps LW, Pinedo-Veels C, de Vries GH, et al. Nature of concentrating defect in sickle-cell nephropathy. Microradioangiographic studies. Lancet. 1970; 1(7644):450–452. Important early studies on renal vascular changes in SCD and SCT. [PubMed: 4189754]

2. Becker AM. Sickle cell nephropathy: challenging the conventional wisdom. Pediatr Nephrol. 2011

3. Ataga KI, Derebail VK, Archer DR. The glomerulopathy of sickle cell disease. Am J Hematol. 2014; 89(9):907–914. [PubMed: 24840607]

4. Nath KA, Grande JP, Croatt AJ, et al. Transgenic sickle mice are markedly sensitive to renal ischemia-reperfusion injury. Am J Pathol. 2005; 166(4):963–972. [PubMed: 15793278]

5. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015; 11(3):161–171. [PubMed: 25668001]

6. de Jong PE, Statius van Eps LW. Sickle cell nephropathy: new insights into its pathophysiology. Kidney Int. 1985; 27(5):711–717. [PubMed: 3894760]

7. Nath KA, Grande JP, Haggard JJ, et al. Oxidative stress and induction of heme oxygenase-1 in the kidney in sickle cell disease. Am J Pathol. 2001; 158(3):893–903. [PubMed: 11238038]

8. Ataga KI, Brittain JE, Moore D, et al. Urinary albumin excretion is associated with pulmonary hypertension in sickle cell disease: potential role of soluble fms-like tyrosine kinase-1. Eur J Haematol. 2010; 85(3):257–263. [PubMed: 20491879]

9. Ramzy D, Rao V, Tumiati LC, et al. Elevated endothelin-1 levels impair nitric oxide homeostasis through a PKC-dependent pathway. Circulation. 2006; 114(1 Suppl):I319–26. [PubMed: 16820593]

10. De Miguel C, Speed JS, Kasztan M, et al. Endothelin-1 and the kidney: new perspectives and recent findings. Curr Opin Nephrol Hypertens. 2016; 25(1):35–41. [PubMed: 26625864]

11. Heimlich JB, Speed JS, O'Connor PM, et al. Endothelin-1 contributes to the progression of renal injury in sickle cell disease via reactive oxygen species. Br J Pharmacol. 2016; 173(2):386–395. [PubMed: 26561980]

12. Kasztan M, Fox BM, Speed JS, et al. Long-term endothelin-a receptor antagonism provides robust renal protection in humanized sickle cell disease mice. J Am Soc Nephrol. 2017

13. Ataga KI, Derebail VK, Caughey M, et al. Albuminuria is associated with endothelial dysfunction and elevated plasma endothelin-1 in sickle cell anemia. PLoS One. 2016; 11(9):e0162652. [PubMed: 27669006]

14. Eshbach ML, Kaur A, Rbaibi Y, et al. Hemoglobin inhibits albumin uptake by proximal tubule cells: implications for sickle cell disease. Am J Physiol Cell Physiol. 2017; 312(6):C733–C740. [PubMed: 28356267]

15. Lusco MA, Fogo AB, Najafian B, et al. AJKD atlas of renal pathology: sickle cell nephropathy. Am J Kidney Dis. 2016; 68(1):e1–3. [PubMed: 27343810]

16. Day TG, Drasar ER, Fulford T, et al. Association between hemolysis and albuminuria in adults with sickle cell anemia. Haematologica. 2012; 97(2):201–205. [PubMed: 21993677]

17. Hamideh D, Raj V, Harrington T, et al. Albuminuria correlates with hemolysis and NAG and KIM-1 in patients with sickle cell anemia. Pediatr Nephrol. 2014; 29(10):1997–2003. [PubMed: 24890337]

18. Saraf SL, Zhang X, Kanias T, et al. Haemoglobinuria is associated with chronic kidney disease and its progression in patients with sickle cell anaemia. Br J Haematol. 2014; 164(5):729–739. [PubMed: 24329963]

19••. Falk RJ, Scheinman J, Phillips G, et al. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. N Engl J Med. 1992; 326(14):910–915. High impact study detailing the pathologic changes of sickle nephropathy and response to ACE-inhibitor therapy. [PubMed: 1542341]

20. Maigne G, Ferlicot S, Galacteros F, et al. Glomerular lesions in patients with sickle cell disease. Medicine (Baltimore). 2010; 89(1):18–27. [PubMed: 20075701]

21. Key NS, Derebail VK. Sickle-cell trait: novel clinical significance. Hematology Am Soc Hematol Educ Program. 2010:418–422. [PubMed: 21239829]

22. Henderickx MMEL, Brits T, De Baets K, et al. Renal papillary necrosis in patients with sickle cell disease: how to recognize this 'forgotten' diagnosis. J Pediatr Urol. 2017; 13(3):250–256. [PubMed: 28341428]

23•. Sharpe CC, Thein SL. How I treat renal complications in sickle cell disease. Blood. 2014; 123(24):3720–3726. Good review on existing treatments for sickle nephropathy. [PubMed: 24764565]

24. Francis YF, Worthen HG. Hyposthenuria in sickle cell disease. J Natl Med Assoc. 1968; 60(4): 266–270. [PubMed: 5661193]

25. Wolf RB, Kassim AA, Goodpaster RL, et al. Nocturnal enuresis in sickle cell disease. Expert Rev Hematol. 2014; 7(2):245–254. [PubMed: 24617333]

26. Anele UA, Morrison BF, Reid ME, et al. Overactive bladder in adults with sickle cell disease. Neurourol Urodyn. 2016; 35(5):642–646. [PubMed: 25871445]

27. Alvarez O, Zilleruelo G, Wright D, et al. Serum cystatin C levels in children with sickle cell disease. Pediatr Nephrol. 2006; 21(4):533–537. [PubMed: 16491413]

28••. Ware RE, Rees RC, Sarnaik SA, et al. Renal function in infants with sickle cell anemia: baseline data from the BABY HUG trial. J Pediatr. 2010; 156(1):66–70e1. Comprehensive study of renal dysfunction in children with SCD. [PubMed: 19880138]

29. Aygun B, Mortier NA, Smeltzer MP, et al. Hydroxyurea treatment decreases glomerular hyperfiltration in children with sickle cell anemia. Am J Hematol. 2013; 88(2):116–119. [PubMed: 23255310]
30. Vazquez B, Shah B, Zhang X, et al. Hyperfiltration is associated with the development of microalbuminuria in patients with sickle cell anemia. Am J Hematol. 2014; 89(12):1156–1157. [PubMed: 25132221]
31. Aloni MN, Ngiyulu RM, Nsibu CN, et al. Congolese children with sickle cell trait may exhibit glomerular hyperfiltration: a case control study. J Clin Lab Anal. 2017 [Epub ahead of print].
32. Asnani MR, Lynch O, Reid ME. Determining glomerular filtration rate in homozygous sickle cell disease: utility of serum creatinine based estimating equations. PLoS One. 2013; 8(7):e69922. [PubMed: 23894560]
33. Asnani M, Reid M. Cystatin C: a useful marker of glomerulopathy in sickle cell disease? Blood Cells Mol Dis. 2015; 54(1):65–70. [PubMed: 25300191]
34••. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. JAMA. 2014; 312(20):2115–2125. First comprehensive study of CKD in SCT. [PubMed: 25393378]
35. McPherson Yee M, Jabbar SF, Osunkwo I, et al. Chronic kidney disease and albuminuria in children with sickle cell disease. Clin J Am Soc Nephrol. 2011; 6(11):2628–2633. [PubMed: 21940843]
36. Guasch A, Navarrete J, Nass K, et al. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006; 17(8):2228–2235. [PubMed: 16837635]
37. Bakir AA, Hathiwala SC, Ainis H, et al. Prognosis of the nephrotic syndrome in sickle glomerulopathy. A retrospective study. Am J Nephrol. 1987; 7(2):110–115. [PubMed: 3605231]
38. Kramer HJ, Stilp AM, Laurie CC, et al. African ancestry-specific alleles and kidney disease risk in hispanics/latinos. J Am Soc Nephrol. 2017; 28(3):915–922. [PubMed: 27650483]
39. Gosmanova EO, Zaidi S, Wan JY, et al. Prevalence and progression of chronic kidney disease in adult patients with sickle cell disease. J Investig Med. 2014; 62(5):804–807.
40. Naik RP, Irvin MR, Judd S, et al. Sickle cell trait and the risk of ESRD in blacks. J Am Soc Nephrol. 2017; 28(7):2180–2187. [PubMed: 28280138]
41•. Powars DR, Chan LS, Hiti A, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005; 84(6):363–376. Large longitudinal study of end-organ damage in SCD. [PubMed: 16267411]
42. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994; 330(23):1639–1644. [PubMed: 7993409]
43. Serjeant GR, Serjeant BE, Mason KP, et al. The changing face of homozygous sickle cell disease: 102 patients over 60 years. Int J Lab Hematol. 2009; 31(6):585–596. [PubMed: 18644042]
44. Derebail VK, Nachman PH, Key NS, et al. High prevalence of sickle cell trait in African Americans with ESRD. J Am Soc Nephrol. 2010; 21(3):413–417. [PubMed: 20056747]
45. Hicks PJ, Langefeld CD, Lu L, et al. Sickle cell trait is not independently associated with susceptibility to end-stage renal disease in African Americans. Kidney Int. 2011; 80(12):1339–1343. [PubMed: 21849968]
46. Heller P, Best WR, Nelson RB, et al. Clinical implications of sickle-cell trait and glucose-6-phosphate dehydrogenase deficiency in hospitalized black male patients. N Engl J Med. 1979; 300(18):1001–1005. [PubMed: 431593]
47. Johnson CS, Giorgio AJ. Arterial blood pressure in adults with sickle cell disease. Arch Intern Med. 1981; 141(7):891–893. [PubMed: 7235808]
48. Grell GA, Alleyne GA, Serjeant GR. Blood pressure in adults with homozygous sickle cell disease. Lancet. 1981; 2(8256):1166.
49. Pegelow CH, Colangelo L, Steinberg M, et al. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. Am J Med. 1997; 102(2):171–177. [PubMed: 9217567]

50. Novelli EM, Hildesheim M, Rosano C, et al. Elevated pulse pressure is associated with hemolysis, proteinuria and chronic kidney disease in sickle cell disease. PLoS One. 2014; 9(12):e114309. [PubMed: 25478953]
51. Asnani M, Serjeant G, Royal-Thomas T, et al. Predictors of renal function progression in adults with homozygous sickle cell disease. Br J Haematol. 2016; 173(3):461–468. [PubMed: 27018388]
52. Lebensburger JD, Cutter GR, Howard TH, et al. Evaluating risk factors for chronic kidney disease in pediatric patients with sickle cell anemia. Pediatr Nephrol. 2017
53. Gordeuk VR, Sachdev V, Taylor JG, et al. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. Am J Hematol. 2008; 83(1):15–18. [PubMed: 17696198]
54. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev. 2007; 21(1):37–47. [PubMed: 17084951]
55. Drawz P, Ayyappan S, Nouraie M, et al. Kidney disease among patients with sickle cell disease, hemoglobin SS and SC. Clin J Am Soc Nephrol. 2016; 11(2):207–215. [PubMed: 26672090]
56. Noguchi CT, Schechter AN. The intracellular polymerization of sickle hemoglobin and its relevance to sickle cell disease. Blood. 1981; 58(6):1057–1068. [PubMed: 7030432]
57. Poillon WN, Kim BC, Castro O. Intracellular hemoglobin S polymerization and the clinical severity of sickle cell anemia. Blood. 1998; 91(5):1777–1783. [PubMed: 9473246]
58. Steinberg MH, Embury SH. Alpha-thalassemia in blacks: genetic and clinical aspects and interactions with the sickle hemoglobin gene. Blood. 1986; 68(5):985–990. [PubMed: 3533181]
59••. Gupta AK, Kirchner KA, Nicholson R, et al. Effects of alpha-thalassemia and sickle polymerization tendency on the urine-concentrating defect of individuals with sickle cell trait. J Clin Invest. 1991; 88(6):1963–1968. Experimental study of the effect of alpha-thalassemia on hyposthenuria in SCT. [PubMed: 1752955]
60. Guasch A, Zayas CF, Eckman JR, et al. Evidence that microdeletions in the alpha globin gene protect against the development of sickle cell glomerulopathy in humans. J Am Soc Nephrol. 1999; 10(5):1014–1019. [PubMed: 10232687]
61. Haymann JP, Stankovic K, Levy P, et al. Glomerular hyperfiltration in adult sickle cell anemia: a frequent hemolysis associated feature. Clin J Am Soc Nephrol. 2010; 5(5):756–761. [PubMed: 20185605]
62. Geard A, Pule GD, Chetcha Chemegni B, et al. Clinical and genetic predictors of renal dysfunctions in sickle cell anaemia in Cameroon. Br J Haematol. 2017 [Epub ahead of print].
63. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun. 2010; 1:104. [PubMed: 21045822]
64. Thein SL, Menzel S. Discovering the genetics underlying foetal haemoglobin production in adults. Br J Haematol. 2009; 145(4):455–467. [PubMed: 19344402]
65••. Lettre G, Sankaran VG, Bezerra MA, et al. DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proc Natl Acad Sci US. 2008; 105(33):11869–11874. Comprehensive analysis of key regulators of hemoglobin F in SCD.
66. 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(8):614–620. [PubMed: 1892333]
67. Lebensburger J, Johnson SM, Askenazi DJ, et al. Protective role of hemoglobin and fetal hemoglobin in early kidney disease for children with sickle cell anemia. Am J Hematol. 2011; 86(5):430–432. [PubMed: 21523807]
68. Saraf SL, Shah BN, Zhang X, et al. APOL1, alpha-thalassemia, and BCL11A variants as a genetic risk profile for progression of chronic kidney disease in sickle cell anemia. Haematologica. 2017; 102(1):e1–e6. [PubMed: 27658436]
69. Saraf SL, Zhang X, Shah B, et al. Genetic variants and cell-free hemoglobin processing in sickle cell nephropathy. Haematologica. 2015; 100(10):1275–1284. [PubMed: 26206798]
70. Kormann R, Jannot AS, Narjoz C, et al. Roles of APOL1 G1 and G2 variants in sickle cell disease patients: kidney is the main target. Br J Haematol. 2017 [Epub ahead of print].

71••. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013; 369(23):2183–2196. High impact analysis of progression of CKD in African Americans with APOL1 risk variants. [PubMed: 24206458]

72. Dummer PD, Limou S, Rosenberg AZ, et al. APOL1 kidney disease risk variants: an evolving landscape. Semin Nephrol. 2015; 35(3):222–236. [PubMed: 26215860]

73••. Ashley-Koch AE, Okocha EC, Garrett ME, et al. MYH9 and APOL1 are both associated with sickle cell disease nephropathy. Br J Haematol. 2011; 155(3):386–394. Well-analyzed study of APOL1 risk variants in sickle nephropathy. [PubMed: 21910715]

74. Afenyi-Annan A, Kail M, Combs MR, et al. Lack of Duffy antigen expression is associated with organ damage in patients with sickle cell disease. Transfusion. 2008; 48(5):917–924. [PubMed: 18248572]

75. Nolan VG, Ma Q, Cohen HT, et al. Estimated glomerular filtration rate in sickle cell anemia is associated with polymorphisms of bone morphogenetic protein receptor 1B. Am J Hematol. 2007; 82(3):179–184. [PubMed: 17034027]

76••. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014; 312(10):1033–1048. Expert panel consensus report for the management of SCD complications. [PubMed: 25203083]

77. Expert Panel NHLBI. [Accessed on 21 Jun 2017] Evidence-based management of sickle cell disease. Available from: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf. Published 2014

78. Naik RP, Haywood C Jr. Sickle cell trait diagnosis: clinical and social implications. Hematology Am Soc Hematol Educ Program. 2015; 2015(1):160–167. [PubMed: 26637716]

79. Sasongko TH, Nagalla S, Ballas SK. Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease. Cochrane Database Syst Rev. 2013; 3:CD009191.

80. Aoki RY, Saad ST. Enalapril reduces the albuminuria of patients with sickle cell disease. Am J Med. 1995; 98(5):432–435. [PubMed: 7733120]

81. Foucan L, Bourhis V, Bangou J, et al. A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia. Am J Med. 1998; 104(4):339–342. [PubMed: 9576406]

82. Alvarez O, Miller ST, Wang WC, et al. Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. Pediatr Blood Cancer. 2012; 59(4):668–674. [PubMed: 22294512]

83. Laurin LP, Nachman PH, Desai PC, et al. Hydroxyurea is associated with lower prevalence of albuminuria in adults with sickle cell disease. Nephrol Dial Transpl. 2014; 29(6):1211–1218.

84. Bartolucci P, Habibi A, Stehle T, et al. Six months of hydroxyurea reduces albuminuria in patients with sickle cell disease. J Am Soc Nephrol. 2016; 27(6):1847–1853. [PubMed: 26586692]

85. Derebail VK, Lacson EK Jr, Kshirsagar AV, et al. Sickle trait in African-American hemodialysis patients and higher erythropoiesis-stimulating agent dose. J Am Soc Nephrol. 2015; 25(4):819–826.

Key issues

- Sickle nephropathy is a common complication of sickle cell disease, and early markers of renal dysfunction can be found in children with sickle cell disease.
- Overt chronic kidney disease occurs by early adulthood in patients with sickle cell disease.
- End-stage renal disease is a rare complication but is associated with high mortality in sickle cell disease.
- Genetic modifiers of sickle nephropathy in sickle cell disease include sickle cell genotype, α-thalassemia, hemoglobin F, *APOL1*, and *HMOX1*.
- Annual screening and treatment with angiotensin-converting enzyme (ACE)-inhibitors may delay renal disease progression in sickle cell disease.
- The spectrum of sickle hemoglobin-related nephropathy extends to sickle cell trait, with sickle cell trait conferring ~2 fold increased risk of chronic kidney disease compared to non-carriers.
- Further research is needed to elucidate the epidemiology, genetic modifiers, and potential treatment for renal disease in sickle cell trait.