Hyperkalemia and Metabolic Acidosis Occur at a Higher eGFR in Sickle Cell Disease

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Key Points
- Hyperkalemia and metabolic acidosis are more common in severe and moderate sickle cell disease compared with age- and sex-matched African Americans from the National Health and Nutrition Examination Survey (NHANES).
- Hyperkalemia and metabolic acidosis occur at higher eGFR thresholds in sickle cell disease compared with age- and sex-matched African Americans from the NHANES.

Abstract
Background People with sickle cell disease (SCD) have an elevated estimated glomerular filtration rate (eGFR) compared with the general population, and this may alter the usual creatinine-based eGFR cutoffs for which physiologic evidence of kidney dysfunction is apparent. This study aimed to identify eGFR thresholds for hyperkalemia and metabolic acidosis in patients with SCD.

Methods This was a cross-sectional analysis of 733 patients with severe (hemoglobin SS or Sβ0-thalassemia) SCD genotype, 238 patients with moderate (hemoglobin SC or Sβ+-thalassemia) SCD genotype, and 1333 age- and sex-matched African Americans from the National Health and Nutrition Examination Survey (NHANES). The prevalence rates of hyperkalemia and metabolic acidosis were compared by eGFR category. Cutoffs for hyperkalemia and metabolic acidosis were determined using generalized additive models.

Results Hyperkalemia and metabolic acidosis were more common in those with severe SCD genotype (13% and 21%, respectively) compared with the NHANES (0.3% and 5%, respectively); the prevalence rates in the moderate SCD genotype were intermediate for hyperkalemia (3%) and metabolic acidosis (11%). The proportion of patients with hyperkalemia and metabolic acidosis progressively increased with lower eGFR category in both SCD genotype groups. The eGFR thresholds for hyperkalemia and metabolic acidosis were higher in the severe (85 and 91 ml/min per 1.73 m², respectively) and moderate (52 and 102 ml/min per 1.73 m², respectively) SCD genotypes compared with the NHANES (34 and 46 ml/min per 1.73 m²).

Conclusions We demonstrate that hyperkalemia and metabolic acidosis are more common and occur at higher eGFR values in patients with SCD compared with age- and sex-matched African Americans, including in eGFR ranges considered to be normal. Future studies using redefined creatinine-based eGFR thresholds for abnormal kidney function may identify high-risk patients for earlier intervention strategies and referral for specialized renal care in SCD.

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Introduction
Sickle cell disease (SCD) is a recessively inherited red blood cell disorder characterized by abnormal hemoglobin polymerization, resulting in vaso-occlusion and hemolytic anemia. The renal system is particularly susceptible to SCD-related damage due to the hypoxic, acidotic, and hyperosmolar environment in the kidney medulla—all conditions that potentiate hemoglobin polymerization (1). These conditions promote red blood cell sickling and lead to diverse pathologic renal manifestations (1).

In the general population, the risks for hyperkalemia and metabolic acidosis increase once the eGFR is <30 ml/min per 1.73 m² (2–4). A high prevalence of metabolic acidosis (42%) and defects in tubular acidification (52%) have been observed in SCD cohorts with

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an eGFR >60 ml/min per 1.73 m² (5,6). The differences in eGFR thresholds may be related to lower serum creatinine levels due to reduced muscle mass, abnormal tubular secretion of serum creatinine, and/or high cardiac output from the hemolytic anemia (7,8). Consequently, we hypothesize that eGFR thresholds for the development of hyperkalemia and metabolic acidosis are higher for patients with SCD compared with individuals without SCD. Evaluating this issue may be clinically important to guide treatment strategies in this population of patients at high risk for kidney dysfunction.

We investigated the eGFR values at which hyperkalemia or metabolic acidosis became evident in patients with severe (Hb SS or Hb Sβ-thalassemia) or moderate (Hb SC or Hb Sβ+-thalassemia) SCD genotypes and in African Americans from the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods

The study was approved by the Institutional Review Boards of the participating institutions, and the subjects provided written informed consent in accordance with the Declaration of Helsinki. The University of Illinois at Chicago (UIC) cohort included 280 Hb SS or Hb Sβ-thalassemia and 90 Hb SC or Hb Sβ+-thalassemia patients recruited into a registry between August 2010 and March 2016. Baseline clinical data were obtained from the electronic medical charts at the time of enrolment. The Walk-Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (Walk-PHaSST) cohort included 471 Hb SS or Hb Sβ-thalassemia and 153 Hb SC or Hb Sβ+-thalassemia patients from eight U.S. centers and one British center that were recruited between February 2008 and June 2009. UIC was a participating site for Walk-PHaSST, and patients from UIC were excluded from this cohort. The NHANES consisted of data from 1502 African Americans evaluated between 2009 and 2012. The NHANES cohort was selected in a 2:1 manner approximately matched for age and sex to the Hb SS or Hb Sβ-thalassemia cohort. We focused our analyses on those subjects with available serum potassium and bicarbonate values (Hb SS or Hb Sβ-thalassemia: n=733; Hb SC or Hb Sβ+-thalassemia: n=238; NHANES: n=1333).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021), which did not include the race coefficient (9). The following standard definitions were applied: hyperkalemia=serum potassium ≥5 mEq/L (10), metabolic acidosis=serum bicarbonate <22 mmol/L (3).

In a cross-sectional analysis, we compared continuous and categorical variables between the severe SCD genotypes, hemoglobin SS or Sβ-thalassemia, or moderate SCD genotypes, hemoglobin SC or Sβ+-thalassemia, to NHANES controls using the Kruskall–Wallis test and chi-squared test. The associations between the annual frequency of vaso-occlusive crises requiring medical attention (acute care center, emergency room, or hospitalization) with eGFR and between lactate dehydrogenase (LDH) and serum potassium were performed using linear regression analysis. The LDH was log transformed for this analysis.

The association between eGFR category and hyperkalemia or metabolic acidosis was analyzed using Cochran’s linear trend test. These analyses were performed using Systat v13 (Systat Software, Inc., Chicago, IL).

To investigate differences in the nonlinear relationship between eGFR and each binary outcome (hyperkalemia and metabolic acidosis) across the three groups, a series of additive logistic regression models were fit for each outcome (11). In unadjusted models, independent variables included group membership (categorical, three levels) and three separate penalized cubic regression splines for group-specific nonlinear eGFR effects, with a maximum basis dimension of k=10 and evenly placed knots. Models were fit by REML using the mgcv package in R (12). Each model was then adjusted for age, sex, hypertension, and diabetes. In adjusted models, age was fit as a cubic regression spline to permit nonlinear effects. “Variable missing” was treated as a separate category for hypertension and diabetes during model estimation. For each model, group-specific partial effects of eGFR were estimated along a range of plausible eGFR values, with standard errors on the basis of the uncertainty corrected posterior distribution of model coefficients. Approximate 95% credible intervals (CIs) were calculated for partial eGFR effect at each eGFR value. The magnitude of the partial effect at each eGFR value represents the contribution of eGFR to the expected outcome for individuals with that eGFR value. Partial effect terms are centered around zero and represent expected increases or decreases in outcomes relative to the group-specific mean. Partial effects are additive contributors to the linear predictor (log-odds of the outcome); as such, estimates are reported on the log-odds scale. Ranges of eGFR over which the partial effect was found to be significantly different from zero (i.e., 95% CI for the smooth term does not contain zero) were identified. Estimates and intervals were plotted, with nonzero portions of each partial effect smooth highlighted and labeled. These nonzero segments of partial smooths represent ranges of eGFR over which the outcome is expected to be higher or lower than the group-specific mean. We conducted a sensitivity analysis for the potassium and bicarbonate generalized additive models, excluding patients being treated with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) because these classes of medications may affect serum potassium (10) and bicarbonate levels (13).

Results

Patient Characteristics

Baseline characteristics of the patients are provided in Table 1, and the distribution of serum potassium and bicarbonate concentrations in all three groups are provided in Supplemental Figure 1. The eGFR was not associated with the frequency of vaso-occlusive crises in either the severe or moderate SCD genotypes (P≥0.4). Patients with severe SCD genotype (hemoglobin SS or Sβ-thalassemia) had a higher prevalence of hypertension and a lower prevalence of diabetes and were more frequently on renin-angiotensin-aldosterone system blockers or nonsteroidal anti-inflammatory drugs compared with the NHANES controls. Additionally, patients with a severe SCD genotype had a higher serum
potassium concentration and more frequent hyperkalemia, a lower serum bicarbonate level and more frequent metabolic acidosis, a lower hemoglobin and a higher LDH concentration, and a higher eGFR and urine albumin concentration compared with the NHANES.

Patients with moderate SCD genotype (hemoglobin SC or S\textsuperscript{b1}-thalassemia) were older, had a higher prevalence of hypertension and more frequent nonsteroidal anti-inflammatory drug use, and a higher systolic blood pressure compared with the NHANES controls. Additionally, patients with moderate SCD genotype had a higher serum potassium concentration and prevalence of hyperkalemia, a higher prevalence of metabolic acidosis, a lower hemoglobin and a higher LDH concentration, and a higher urine albumin concentration compared with the NHANES.

Potassium

Hyperkalemia, defined as a serum potassium $\geq 5$ mEq/L, was observed in 0.3% of African Americans from the NHANES, in 13% of patients with severe SCD genotype, and in 3% of patients with moderate SCD genotype (Table 1). Progressively higher proportions of patients with hyperkalemia were observed with lower eGFR category in the severe ($P<0.001$) and moderate ($P=0.04$) SCD genotypes (Figure 1A). In the subgroup of patients with urine albumin $<30$ mg/g and eGFR $\geq 60$ ml/min per 1.73 m$^2$, hyperkalemia occurred in 7% and 2% of patients with severe or moderate SCD, respectively, which was higher than the prevalence in the NHANES controls (0.1%; $P<0.001$). Serum LDH was directly associated with serum potassium concentration in both the severe (natural log, $\beta=0.26\pm0.04$; $P<0.001$) and moderate (natural log, $\beta=0.19\pm0.06$; $P=0.003$) SCD genotypes. In the generalized additive models, significantly higher proportions of patients with hyperkalemia were observed at eGFR cutoffs of $<34$ ml/min per 1.73 m$^2$ in the NHANES, $<85$ ml/min per 1.73 m$^2$ in the severe SCD genotype cohort, and $<52$ ml/min per 1.73 m$^2$ in the moderate SCD genotype cohort (Figure 2A). The eGFR ranges for hyperkalemia were similar in the sensitivity analyses, excluding those on ACEi/ARB in the NHANES ($<33$ ml/min per 1.73 m$^2$) and severe SCD genotype ($<85$ ml/min per 1.73 m$^2$) cohorts, whereas no significant eGFR threshold for hyperkalemia was identified in the moderate SCD genotype cohort.

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**Table 1. Patient characteristics**

| Characteristics | National Health and Nutrition Examination Survey (N=1333) | Severe Sickle Cell Disease (N=733) | Moderate Sickle Cell Disease (N=238) |
|-----------------|--------------------------------------------------------|-----------------------------------|-------------------------------------|
| Age, yr         | 35 (14)                                                | 35 (12)                           | 39 (15)*                            |
| Women           | 55%                                                    | 54%                               | 63%                                 |
| Hypertension    | 27%                                                    | 34%*                              | 47%*                                |
| Diabetes        | 7%                                                     | 1%*                               | 4%                                  |
| Hydroxyurea, %  | —                                                      | 46%                               | 17%                                 |
| Diuretic        | 4%                                                    | 3%                                | 7%                                  |
| RAAS blocker    | 4%                                                    | 11%*                              | 6%                                  |
| NSAIDs          | 1%                                                     | 28%*                              | 31%*                                |
| Systolic BP, mm Hg | 121 (16)                                           | 119 (14)                          | 123 (15)*                           |
| Potassium, mmol/L | 3.9 (0.3)                                               | 4.4 (0.5)*                        | 4.2 (0.4)*                          |
| Hyperkalemia    | 0.3%                                                   | 13%*                              | 3%*                                 |
| Bicarbonate, mmol/L | 25 (2)                                                  | 24 (3)*                            | 25 (3)                              |
| Metabolic acidosis | 5%                                                      | 21%*                              | 11%*                                |
| Hemoglobin      | 13.4 (1.5)                                             | 8.7 (1.5)*                         | 11.3 (1.6)*                         |
| LDH, U/L        | 128 (112–147)                                          | 386 (283–542)*                    | 228 (193–291)*                     |
| eGFR, ml/min per 1.73 m$^2$ | 99 (21)                                                | 111 (32)*                         | 99 (27)                             |
| **eGFR by strata** |                                                        |                                   |                                     |
| $\geq 20$       | 18%                                                    | 52%*                              | 21%*                                |
| 90–119          | 49%                                                    | 28%                               | 44%                                 |
| 60–89           | 31%                                                    | 10%                               | 27%                                 |
| $< 60$          | 9%                                                     | 9%                                | 8%                                  |
| Urine ACR, mg/g creatinine | 6 (5–11)                                               | 33 (9–206)*                       | 10 (4–38)*                          |
| **Urine ACR by strata** |                                                    |                                   |                                     |
| $< 30$          | 90%                                                    | 48%*                              | 72%*                                |
| 30–299          | 9%                                                     | 32%                               | 22%                                 |
| $\geq 300$      | 2%                                                     | 20%                               | 6%                                  |
| Vaso-occlusive crises, per year | —                                                      | 2 (0–5)                           | 1 (0–3)                             |

Data shown as percentages, mean (SD), or median (interquartile range). Severe SCD, hemoglobin genotype SS or S\textsuperscript{b0}-thalassemia; moderate SCD, hemoglobin genotype SC or S\textsuperscript{b1}-thalassemia; NHANES, National Health and Nutrition Examination Survey; SCD, sickle cell disease; Hb, hemoglobin; RAAS, renin-angiotensin-aldosterone system; NSAID, nonsteroidal anti-inflammatory; LDH, lactate dehydrogenase; ACR, albumin-to-creatinine ratio.

*P<0.01 compared with NHANES subjects; hyperkalemia defined as potassium $\geq 5$ mEq/L; metabolic acidosis defined as $\text{HCO}_3^-$ $<22$ mmol/L.
Serum Bicarbonate

Metabolic acidosis, defined as a serum bicarbonate $< 22$ mmol/L, was observed in 5% of African Americans from the NHANES, in 21% of patients with severe SCD genotype, and in 11% of patients with moderate SCD genotype (Table 1). Progressively higher proportions of patients with metabolic acidosis were observed with lower eGFR category in the severe ($P < 0.001$) and moderate ($P = 0.008$) SCD genotypes (Figure 1B). In the subgroup of patients with urine albumin $< 30$ mg/g and eGFR $\geq 60$ ml/min per 1.73 m$^2$, the prevalence of metabolic acidosis was 18.1% and 13.3% in patients with severe or moderate SCD, respectively, which was higher than in the NHANES controls (4%; $P < 0.001$). In the generalized additive models, significantly higher proportions of patients with metabolic acidosis were observed at eGFR cutoffs of $< 46$ ml/min per 1.73 m$^2$ in the NHANES, $< 91$ ml/min per 1.73 m$^2$ in the severe SCD genotype cohort, and $< 102$ ml/min per 1.73 m$^2$ in the moderate SCD genotype cohort compared with group-specific averages (Figure 2B). The eGFR ranges for metabolic acidosis were similar in the sensitivity analyses for all three cohorts (NHANES: $< 51$ ml/min per 1.73 m$^2$; severe SCD genotype: $< 92$ ml/min per 1.73 m$^2$; moderate SCD genotype: $< 103$ ml/min per 1.73 m$^2$).

Discussion

We demonstrate that there is a greater prevalence of hyperkalemia and metabolic acidosis in SCD patients compared with age- and sex-matched African Americans from the NHANES. Furthermore, hyperkalemia and metabolic acidosis occurs at eGFR values that are higher in SCD patients compared with the NHANES and above the standard eGFR thresholds currently used to define CKD in the general population (14).

Hyperkalemia is a risk factor for adverse cardiovascular events or discontinuation of kidney protective renin-angiotensin-aldosterone blockers in the general population (15). Higher serum potassium concentrations have been recently described in people with severe SCD genotypes compared with those with moderate SCD genotypes or healthy controls from Ghana (16). Hyperkalemia in SCD may be due to impaired distal tubular function (1) and was previously...
described in a small cohort of SCD patients with a mean GFR of 47.8±12.5 ml/min per 1.73 m² (17). Potassium is an intracellular cation and hemolytic anemia could result in hyperkalemia. The degree of intravascular hemolysis, as assessed by serum LDH, was associated with higher serum potassium concentrations in both the severe and moderate SCD genotypes. We demonstrate that hyperkalemia is present in 13% of patients with severe SCD genotype and 3% of patients with moderate SCD genotype and that the proportion of SCD patients with hyperkalemia increases with lower eGFR.

Metabolic acidosis has been linked to more rapid progression of CKD (18,19), bone buffering leading to osteopenia (20), protein-energy malnutrition (21), reduced cardiac contractility and congestive heart failure (22), and early mortality in the general population (23). Metabolic acidosis may be particularly relevant in the pathobiology of SCD because the degree of acidosis alters oxygen affinity, precipitates hemoglobin polymerization, and promotes red blood cell sickling (24). A high prevalence of metabolic acidosis has been observed in other cohorts of severe SCD genotype (5,25,26). For example, a serum bicarbonate of <23 mmol/L was observed in 42% and ≤20 mmol/L in 16% of patients with severe SCD genotype (5). The prevalence of metabolic acidosis in patients with moderate SCD genotype is less clear. Etiologies for metabolic acidosis in SCD may include impaired ammonium availability, hyporeninemic hypoaldosteronism, or impaired distal tubular acidification capacity (5,6,25,27). Consistent with the literature, we observed a higher prevalence of metabolic acidosis in patients with severe SCD genotype (21%) and a higher prevalence of metabolic acidosis in patients with moderate SCD genotypes (11%) compared with African Americans from the NHANES (5%). Furthermore, the prevalence of metabolic acidosis increased with lower eGFR in both SCD genotype groups.

The clinical implications for identifying patients at risk for hyperkalemia or metabolic acidosis include earlier referral to a nephrologist and implementation of prevention and treatment strategies, such as dietary potassium restriction, initiating sodium bicarbonate replacement therapy, and patient and provider behavior modification (e.g., avoiding nonsteroidal anti-inflammatory drugs). In patients with non-SCD-related CKD, metabolic derangements from tubular dysfunction are usually a late manifestation that occur when the eGFR is <30 ml/min per 1.73 m² (2–4). The eGFR cutoffs for hyperkalemia and metabolic acidosis in SCD are less clear. We demonstrate that hyperkalemia and metabolic acidosis occur at higher eGFR values, often considered in the normal eGFR range, in SCD patients compared with the general NHANES population. In patients with severe SCD genotype, the risks of hyperkalemia and metabolic acidosis increased once the eGFR was <85 and 91 ml/min per 1.73 m², respectively. These eGFR cutoffs are much higher than in the NHANES controls. Our findings highlight the need for close monitoring of serum potassium and bicarbonate once the eGFR is <120 ml/min per 1.73 m² and to consider initiating more aggressive measures once the eGFR is <90 ml/min per 1.73 m². A more stringent cutoff for kidney dysfunction (serum creatinine of >0.9 g/dl in men and >0.77 g/dl in women) in severe SCD genotypes has been recommended in the literature (28), and our data strongly supports this practice, relative to actionable decrements in tubular function. The higher eGFR cutoffs were also consistent for metabolic acidosis in those with moderate SCD genotype.

There are several limitations to our study. This is a cross-sectional analysis, and future studies longitudinally monitoring changes in eGFR, serum potassium, and serum bicarbonate are needed. Metabolic acidosis was defined by serum bicarbonate <22 mmol/L, and we lacked blood pH measurements. Our definition may have included compensatory metabolic acidosis due to respiratory alkalosis, a known feature of SCD (29), although a prior study demonstrated that low serum bicarbonate in patients with SCD is associated with a low pH but not with a low arterial partial pressure of carbon dioxide (5). We did not have

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**Figure 2.** Generalized additive models for the association of eGFR ranges with hyperkalemia and metabolic acidosis. Blue and red shaded regions represent statistically significant eGFR ranges when the prevalence of abnormal tubular function was higher or lower, respectively, compared with the group-specific averages.
measurements of urine anion gap or NH₄ excretion, and this will also need to be investigated in prospective studies. Another limitation is that the GFR was estimated and not directly measured, although prior studies have shown that the 2009 CKD-EPI formula without race correlates relatively well with measured GFR in SCD patients (7,30). We applied the 2021 CKD-EPI formula for eGFR, determined using serum creatinine and without race, which is a commonly available clinical tool, and our eGFR cutoffs can be readily applied to most clinical settings. Although the frequency of vaso-occlusive crises was not associated with eGFR, AKI may accelerate the rate of eGFR decline in SCD (31). Assessing the relationship between AKI, hyperkalemia, and metabolic acidosis should be evaluated in future studies.

In conclusion, hyperkalemia and metabolic acidosis are common and occur at eGFR cutoffs that are much higher, including eGFR values considered to be in the normal range, in patients with SCD. Future studies using redefined eGFR thresholds for abnormal kidney function may help identify high-risk patients for earlier intervention strategies, avoidance of potential nephrotoxins, and earlier referral for specialized renal care.

Disclosures
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Author Contributions
V.K. Derebail, V.R. Gordeuk, J.P. Lash, J. Little, R.F. Machado, S.L. Saraf, and X. Zhang were responsible for the investigation; V.R. Gordeuk, J.P. Lash, S.L. Saraf, and X. Zhang were responsible for the formal analysis; J.P. Lash and S.L. Saraf were responsible for supervision; S.L. Saraf and X. Zhang curated the data; S.L. Saraf was responsible for funding acquisition, project administration, and resources; and all authors were responsible for conceptualization, methodology, writing the original draft of the manuscript, and reviewing and editing the manuscript.

Supplemental Material
This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.00068020/-/DCSupplemental.

Supplemental Figure 1. Distribution of serum potassium and bicarbonate concentrations.

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