blood advances

TO THE EDITOR:

Sex differences in the trajectory of glomerular filtration rate in pediatric and murine sickle cell anemia

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Chronic kidney disease (CKD) is a frequent concomitant complication of sickle cell anemia (SCA) and constitutes an independent risk factor for death in the adult sickle cell population.[1,2] Structural and functional changes in the kidney begin in children with SCA and are evidenced by whole kidney hyperfiltration and hyposthenuria.[3-6] It is postulated that persistent single nephron hyperfiltration contributes to the development of sclerosis; over time, continued glomerulosclerosis contributes to a decrease in renal reserve and progression to CKD.[6,7] However, few data track progression from hyperfiltration during pediatrics to the development of CKD in adulthood in order to identify risk for earlier progression to CKD. Therefore, longitudinal natural history studies to monitor estimated glomerular filtration rate (eGFR) in children and adults are vital so that risk factors can be elucidated and interventions initiated prior to the decline in whole nephron glomerular filtration rate (GFR). Recent evidence suggests that the prevalence and rate of progression of renal disease are sex dependent. Insights into sex disparity in renal involvement present a new perspective as emerging data suggest there may be a sex difference in renal outcomes in SCA.

The recent paper published in *Blood Advances* by Kasztan et al identified significant findings related to sex differences in measured GFR using a humanized SCA mouse model.[8] First, they demonstrated that male SCA mice experience a significantly higher measured GFR than female SCA mice starting at 12 weeks of age. Second, in males, but not females, the magnitude of the increase in GFR experienced early in life (from 8 to 12 weeks of age) was significantly correlated to a lower measured GFR at 32 weeks of age. These data for the first time show that in the male SCA murine model, hyperfiltration early in life predicts the development of a more rapid decline in GFR and lower GFR later in life. In addition, this early hyperfiltration was significantly associated with the development of renal damage presented with albuminuria and proteinuria at 32 weeks of age. To complement the murine data, we also have data providing evidence that hyperfiltration in the first decade of life precedes the development of CKD defined by albuminuria in childhood.[3]

To further evaluate sex differences in GFR early during childhood, we attempted to replicate the data from our prior murine study in children with SCA from our Institutional Review Board–approved University of Alabama at Birmingham Pediatric SCA Nephropathy cohort.[1] We identified 168 participants with hemoglobin sickle cell (HbSS) or hemoglobin sickle β0n (HbSB0) thalassemia who had 687 cystatin C levels (mean: 4.1 cystatin C levels per patient) measured from 6 to 17 years of life. eGFR was calculated from cystatin C as previously described.[9] We fit a general linear mixed regression model with random intercept to accommodate correlations among readings from the same subject to evaluate the relationship between eGFR and age stratified by sex. We obtained the 95% confidence intervals (CIs) and used them to form a band around the fitted lines. We also reanalyzed the data from the Kasztan et al paper to fit a mixed regression model for the 18 humanized SCA male and 12 humanized SCA female mice that underwent transcutaneous fluorescein isothiocyanate–labeled sinistrin GFR measurements (ie, sinistrin clearance) every 4 weeks from 8 to 32 weeks as previously described.[1]

We present fitted models for pediatrics and mouse model of SCA data (Figure 1A-B). We identify no significant difference in eGFR from 6 to 12 years of age, but by age 13, male pediatric SCA participants begin to demonstrate a significantly lower eGFR than female SCA participants. Next, using generalized linear modeling, we demonstrate that age is negatively associated with GFR for males (slope = −1.66; 95% CI, −2.46, −0.86) but positively associated with GFR for females (slope = 1.4923; 95% CI, 0.74, 2.25). This finding mirrors the murine data in which the humanized male SCA mice have a higher GFR at 12 weeks, but by 28 weeks of age have a significantly lower GFR (Figure 1B). Using generalized linear

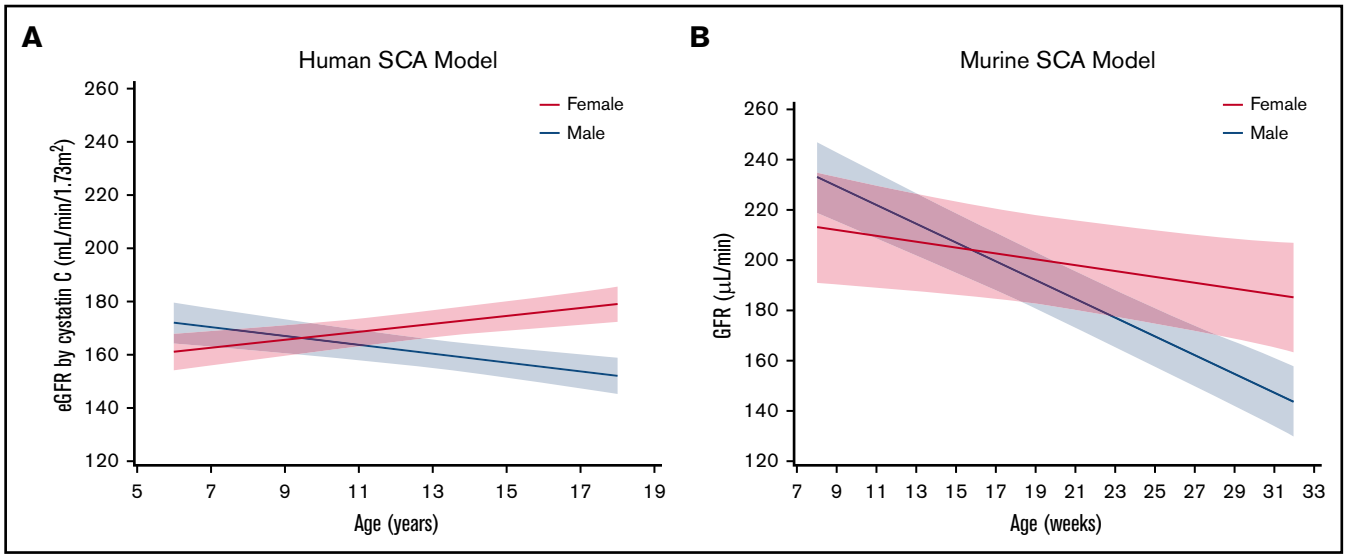

Figure 1. Trajectory of GFR by sex in pediatric and murine SCA. Trajectory of eGFR (human) (A) and GFR (murine) (B) changes over time in sickle cell anemia by sex.

modeling, we demonstrate that age is negatively associated with GFR in the SCA murine model, but has a stronger correlation for males (slope = −3.73; 95% CI, 4.46, −3.01) than for females (slope = −1.16: 95% CI, −2.23, −0.10).

Although the rate of progression for many renal diseases, regardless of etiology, is affected by sex,[10,11] there are very limited data regarding the contribution of sex to the onset and progression of SCA-associated nephropathy. The limited adult SCA data that are available are contradictory. Some adult studies have shown no sex differences in eGFR using a single time point, on the progression of sickle cell nephropathy or performing sex-adjusted analyses; however, a few studies reported greater prevalence of hyperfiltration and progression of SCA-associated nephropathy in males.[12-18] Data from the Jamaica Sickle Cell Cohort Study, over the 15-year observation period, demonstrated that young adult SCA males present with greater decline in eGFR and steeper increase in serum creatinine when compared with age-matched females.[13] These data points were replicated in a Duke adult cohort of 193 participants that demonstrated that men had a significantly higher rate of decline in eGFR than women.[16] A third study, which included 280 young adult SCA patients from France, showed significantly greater frequency of SCA-associated nephropathy as well as hyperfiltration status in men than in woman.[12] Considering that the greater prevalence of hyperfiltration is associated with a younger age,[6,12] data are now accumulating to support the sex disparity in young SCA patients. Potential mechanisms underlying sex differences in renal involvement in SCA are available from both rodent and human studies. Animal studies suggest that greater degree of hypoxia,[8] vascular stasis,[8] and ultrastructural glomerular in glomerular filtration barrier[19] or sex hormones[20] may account for sex differences in SCA-associated nephropathy with greater susceptibility to renal injury in males. In humans, anemia status, degree of hemolysis,[21,22] or fetal hemoglobin levels[22] present the main possibilities explaining sex-related differences in the onset of renal disease and renoprotective phenotype in females with SCA.

These data points expose some of the neglected sex-specific discrepancies in SCA and encourage more comprehensive prospective clinical studies in order to explore this phenomenon. SCA-associated nephropathy depicts exceptional challenges from diagnostic and therapeutic standpoints. It is of great importance to identify the risk factors for renal complications in SCA, as we need to tailor our diagnostic tools to precisely target SCA-associated nephropathy. Therefore, a critical step is to recognize novel contributors that would help us with early and effective interventions to modify disease advancement. Current data suggest that, similar to the murine data, sex differences do occur in pediatric sickle cell patients. Future research needs to explore sex differences in GFR and its impact on progression to sickle cell nephropathy.

In compliance with this policy, data collected in this study will be made available to other researchers, after the goals have been met and primary aims have been published. Disclosure of sensitive health and behavior data presents a potential risk to human subjects, and we will take all steps to ensure that this does not happen when data are shared. Furthermore, all identifying information related to the individual participants will be removed when data are shared, and our study ID number will be replaced by a new ID number selected at random. In addition, we will strongly recommend that all recipient groups ensure that every member of the staff sign a Confidentiality Agreement. We will develop a data and resource sharing agreement with the legal advice from the Compliance Office of the University of Alabama at Birmingham and ensure that we follow National Institutes of Health guidelines with respect to data sharing. Before data are shared with researchers, we will require that researchers enter into a data and resource sharing agreement. This agreement will ensure that (1) data are used only for research purposes; (2) data do not identify any individual participant; (3) data are secure, using appropriate computer technology; and (4) there is a commitment to destroy or return data after analyses are completed.

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