Hemoglobin Differences by Race in Children With CKD

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Background: There are known racial disparities in the prevalence of anemia in adults with chronic kidney disease (CKD), but these differences have not been well described in children.

Study Design: Cohort study, cross-sectional analysis.

Setting & Participants: The Chronic Kidney Disease in Children (CKiD) Study is a multicenter prospective cohort study of children with mild to moderate CKD. This analysis included 429 children of African American or white race.

Predictor: Race.

Outcomes & Measurements: This study examined the association of race with hemoglobin level. Both multiple linear regression and generalized gamma modeling techniques were used to characterize the association between race and hemoglobin level.

Results: 79% of the cohort was white, 21% was African American. Neither median hemoglobin level nor frequency of erythropoiesis-stimulating agent use differed by race. In multivariate analysis, lower levels of iohexol-measured glomerular filtration rate, African American race, and glomerular disease (vs nonglomerular disease) as the underlying cause of CKD were independently associated with decreased hemoglobin levels; independent of glomerular filtration rate and CKD diagnosis, African American children had average hemoglobin levels that were 0.6 g/dL (95% CI, −0.9 to −0.2 g/dL) lower than those of white children. Generalized gamma modeling showed that differences in hemoglobin levels observed by race become more pronounced when moving from high to low in the overall hemoglobin level distribution.

Limitations: Cross-sectional analysis cannot establish causality, and data for iron stores were not available for all patients.

Conclusions: African American compared with white children have lower hemoglobin values in CKD independent of the underlying cause of CKD. These racial differences in hemoglobin levels appear to increase at the lower end of the hemoglobin level distribution in this population.

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Anemia is a common and treatable comorbid condition in children with chronic kidney disease (CKD). The anemia of CKD is associated with increased risk of the development and progression of left ventricular hypertrophy and accelerated CKD progression.[1,2] In addition, anemia has been associated with lower health-related quality of life and increased risk of hospitalization in children with CKD.[3,4] Despite the widespread use of iron supplementation and erythropoiesis-stimulating agents (ESAs), anemia remains common in both end-stage renal disease and CKD populations.[5]

Racial disparities in hemoglobin (Hb) levels in both adults and children with end-stage renal disease are well established; African American adults typically initiate dialysis therapy with significantly lower Hb levels compared with whites, and African American race has been a significant risk factor for anemia in children and teenagers on dialysis therapy.[6-8] In adults with earlier stages of nondialysis CKD, anemia is more prevalent in African American compared with white patients.[9,10] In children with CKD, differences in Hb values and anemia prevalence by race have

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not been well described. Our objective in this analysis is to examine the associations between race and Hb level in children with CKD.

METHODS

Study Population and Design

We analyzed baseline data collected for participants enrolled in the Chronic Kidney Disease in Children (CKiD) Study, an observational prospective cohort study of CKD in children conducted at 44 pediatric centers in North America.[11] Eligibility criteria for enrollment in CKiD include age of 1-16 years, estimated glomerular filtration rate (GFR) of 30-90 mL/min/1.73 m^2 using the Schwartz formula,[12] no prior organ transplant, and informed consent by a parent or guardian.

Analysis was cross-sectional and restricted to individuals who self-reported their race as only African American or only Caucasian (white). Additional inclusion criteria were valid concomitant measurements of Hb and GFR, self-reported medication use, and known age, sex, ethnicity, and CKD diagnosis.

Measurements

Blood and urine samples are collected at the time of each baseline CKiD study visit. A complete blood count panel, including measurement of Hb, is performed locally. Albumin, urine creatinine, and urine protein measurements are performed by the CKiD central laboratory (University of Rochester, Rochester, NY). GFR is measured directly using iohexol plasma disappearance, details of which have been published previously.[13] Additional data used in this analysis include age, sex, height, weight, blood pressure, primary CKD diagnosis (glomerular or nonglomerular), medication use during the past 30 days, Tanner stage (Tanner stage 1 = prepubertal), and self-reported race, ethnicity, household income, and maternal education ($\geq$12 vs $<$12 years). Age- and sex-specific height and body mass index (BMI) percentiles, as well as normalized scores for age and sex (z scores), are calculated using standard growth charts for US children. Blood pressure is measured using an aneroid sphygmomanometer.[14]

Statistical Analyses

Hb levels, prevalence of Hb level less than the 5th normative percentile for age and sex (based on the Second National Health and Nutrition Examination Survey [NHANES III] data in healthy children),[15] and current ESA and iron supplement use were reported for African American and white participants. Continuous data were characterized using median values and 25th and 75th percentiles; categorical data were described using percentages and frequencies. Differences in the prevalence of categorical variables were tested using Fisher exact tests, and for continuous variables, Wilcoxon rank-sum tests.

A log-scale scatter plot of Hb levels by measured GFR (mGFR) and race was developed and overlaid with race-specific linear regression curves. Race-specific uni- and multivariate modeling using linear ordinary least squares regression was performed. Piecewise linear models allowing for effect modification of the Hb-mGFR relationship by race were tested. Potential covariates in the final model included race, log-(mGFR), age, sex, CKD diagnosis, maternal education, BMI z score, pubertal status, iron supplement use, and ESA use. Model parameters were evaluated using Wald test. Statistical significance was evaluated at the level of $\alpha = 0.05$.

To further characterize differences in the distribution of Hb levels between racial groups, we used percentile plots and generalized gamma models in a classic 2-sample problem: African American versus white participants. Percentile plots are an extension of the classic box plot, highlighting additional quantiles beyond the 25th, 50th, and 75th (we show the 5th, 10th, 90th, and 95th, as well as individual observations that sit outside of the 5th and 95th quantile values, respectively).[16] The width of the percentile plot decreases in proportion to departures from the 50th percentile. Thus, in comparison to the width of the plot at the median (50th percentile), the plot is half as wide at the 25th and 75th percentiles and one-fifth as wide at the 10th and 90th percentiles.

Generalized gamma models draw upon the family of generalized gamma distributions that are characterized by 3 parameters: location (β), scale (Φ), and shape (λ).[17] This family includes commonly used distributions (eg, log normal characterized by $\lambda = 0$) and is particularly useful for describing effects of exposures not just at the mean, but at all percentiles (eg, effects on the tails of the distribution). Differential effects of an exposure at different percentiles is accomplished by allowing the exposure to modify not only the location (β), but also the scale (Φ) and/or shape parameters (λ). Using results from the generalized gamma models, we plotted race-specific probability density functions of Hb and calculated relative Hb percentiles. Relative percentiles are simply the ratios of the pth percentile of Hb in African American children to the pth percentile of Hb in white children for each value of p between 1 and 100. If relative percentiles are equal to 1, this will correspond to the null hypothesis of no association with race; if they are less than 1, this will indicate that African American children have lower Hb levels, even in children with similar values of other covariates present in the model. An attractive feature of the model is that it allows for heterogeneity of the relative percentiles across different values of P. As such, it is possible that the lower half of the Hb values may show stronger differences by race than the upper half of the race-specific Hb level distributions. To allow race to have differential effects at different percentiles, generalized gamma models with unique Φ and 8 estimates for each racial group were tested. To account for the effect of ESA therapy on Hb level, individuals currently receiving an ESA had their Hb value left censored or considered to be equal to or less than the value measured, but greater than zero. To achieve this, the model redistributes the Hb levels of treated individuals to values equal to or lower than their observed Hb level by looking at other participants with similar covariates who are not using ESAs.[18] Valid analyses allowing for left-censoring of Hb values by ESA use assume that ESA use is at random within racial groups and the measured covariates (ie, 2 individuals with the same race and covariate values are equally likely to use ESA). Inclusion of parameters in the final model was based on the comparison of nested models using the Akaike information criterion.[19] Confidence intervals for the relative percentile curves were calculated using the delta method.

All analysis was performed using SAS 9.2 (SAS Institute Inc, www.sas.com). Figures were produced using S Plus 8.0