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Original Investigation

Relationships of Measured Iohexol GFR and Estimated GFR With CKD-Related Biomarkers in Children and Adolescents

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Background: 2 valid and reliable estimated glomerular filtration rate (GFR) equations for the pediatric population have been developed from directly measured GFR data in the Chronic Kidney Disease in Children (CKiD) cohort: the full CKiD and bedside CKiD equations. Although adult GFR estimating equations replicate relationships of measured GFR with biomarkers, it is unclear whether similar patterns exist among children and adolescents with chronic kidney disease (CKD).

Study Design: Prospective cohort study in children and adolescents.

Settings & Participants: 730 participants contributed 1,539 study visits.

Predictors: Measured GFR by plasma iohexol disappearance (mGFR), estimated GFR by the full CKiD equation ($eGFR_{CKiDfull}$; based on serum creatinine, cystatin C, serum urea nitrogen, height, and sex), and estimated GFR by the bedside CKiD equation ($eGFR_{CKiDbed}$; calculated as 41.3 × height [m]/serum creatinine [mg/dL]) were predictors of CKD-related biomarkers. Deviations of mGFR from $eGFR_{CKiDfull}$ and deviations of $eGFR_{CKiDfull}$ from $eGFR_{CKiDbed}$ from linear regressions (ie, residuals) were included in bivariate analyses.

Outcomes & Measurements: CKD-related biomarkers included values for urine protein-creatinine ratio, blood hemoglobin, serum phosphate, bicarbonate, potassium, systolic and diastolic blood pressure *z* scores, and height *z* scores.

Results: The median age of 730 participants with CKD was 12.5 years, with median mGFR, $eGFR_{CKiDfull}$, and $eGFR_{CKiDbed}$ of 51.8, 54.0, and 53.2 mL/min/1.73 m^2, respectively. $eGFR_{CKiDfull}$ demonstrated as strong or stronger associations with CKD-related biomarkers than mGFR; $eGFR_{CKiDbed}$ associations were significantly attenuated (ie, closer to the null). Residual information in mGFR did not substantially increase explained variability. $eGFR_{CKiDbed}$ estimated faster GFR decline relative to mGFR and $eGFR_{CKiDfull}$.

Limitations: Simple linear summaries of biomarkers may not capture nonlinear associations.

Conclusions: $eGFR_{CKiDfull}$ closely approximated mGFR to describe relationships with CKD-severity indicators and progression in this pediatric CKD population. $eGFR_{CKiDbed}$ offered similar inferences, but associations were attenuated and rate of progression was overestimated. The $eGFR_{CKiDfull}$ equation from 2012 is preferred for pediatric research purposes.

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INDEX WORDS: Pediatric; glomerular filtration rate (GFR); estimated GFR; measured GFR; iohexol; kidney function; kidney measure; chronic kidney disease (CKD); children; adolescents; Chronic Kidney Disease in Children (CKiD); GFR estimating equation; CKD biomarker.

Glomerular filtration rate (GFR) is considered to be the best assessment of kidney health and may be measured directly by the plasma disappearance of an exogenously administered agent. Because direct measurement of GFR is burdensome and invasive, equations developed to determine estimated GFR (eGFR) are part of routine clinical care and are often substituted for measured GFR (mGFR) in research studies. The Chronic Kidney Disease in Children (CKiD) cohort has obtained more than 2,500 iohexol-based mGFRs, which have been used to develop GFR estimating equations. These include the full CKiD equation ($eGFR_{CKiDfull}$) based on values for serum creatinine (Scr), cystatin C, serum urea nitrogen (SUN), and height, introduced in a 2012 publication,[1] and the simple bedside equation[2] ($eGFR_{CKiDbed}$), which is 41.3 times the ratio of height to Scr level. These equations have performed extremely well internally[1,2] and in diverse external special populations using non–iohexol-based

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methods.[3-17] In addition, several publications have used these equations for epidemiologic purposes, including etiologic[18-21] and prospective studies.[22,23]

While published estimating equations are valid, with low bias and good precision, agreement metrics have been primarily comparisons between the proposed eGFR equation and mGFR in terms of bias, accuracy, precision, and correlation. Investigating potential differences between these 2 assessments for epidemiologic inference is another metric of agreement, and recent analyses in adult populations have explored this.[24-29] To our knowledge, describing potential differences in how GFR methods characterize relationships between kidney function and chronic kidney disease (CKD) biomarkers in children and adolescents has not yet been fully characterized.

The objective of this study was, in turn, to compare relationships between different GFR assessment methods and indicators of CKD severity and GFR trajectory in a population of children and adolescents with diverse CKD diagnoses. Using GFR as the predictor, we investigated whether eGFR described the same relationship as mGFR with markers of CKD (eg, proteinuria and metabolic, cardiovascular, and growth variables). For this aim, we not only quantified the strength of the association, but also the variability explained by eGFR and how that was improved by including the information in mGFR that is not present in eGFR. In addition, using GFR as the outcome, we investigated whether the characterization of GFR decline over time by proteinuria level at baseline was different when using mGFR or eGFR. Comparing how mGFR, $eGFR_{CKiDfull}$, and $eGFR_{CKiDbed}$ describe relationships of CKD severity and progression may provide guidance for pediatric CKD study populations external to CKiD and help facilitate simple and standardized assessments of GFR for research to improve reproducibility.

METHODS

Study Population

As of 2016, the CKiD cohort study had enrolled 891 children and adolescents aged 1 to 16 years from the United States and Canada, representing diverse CKD diagnoses with eGFRs between 30 and 90 mL/min/1.73 m^2. Details of the study design have been previously described.[30] The iohexol-based mGFR was obtained at the first 2 annual visits and every other annual visit thereafter. Blood chemistry, including Scr, cystatin C, SUN, and urine data, were collected at each annual visit. The study design and conduct were approved by the internal review boards for each participating center and by an external advisory committee appointed by the National Institutes of Health. Written informed consent/assent was obtained from all participants/families according to local institutional review board requirements.

Glomerular Filtration Rate

mGFR was calculated from a 2-compartment model for visits occurring from 2005 to 2011 and from a universal equation for a 1-compartment model from 2011 to 2015.[31] Iohexol concentrations from November 2006 to March 2016 were increased by 12% as part of a multilaboratory assay recalibration (Schwartz et al, manuscript in preparation). Equations for eGFR included: (1) a full equation published in 2012,[1] referred to hereafter as $eGFR_{CKiDfull}$ and defined as $39.8 \times (\text{height [m]/Scr [mg/dL]})^{0.456} \times (1.8/\text{cystatin C [mg/dL]})^{0.418} \times (30/\text{SUN [mg/dL]})^{0.079} \times 1.076$ (if male) $\times (\text{height [m]}/1.4)^{0.179}$; and (2) the 2009 bedside equation[2] (referred to hereafter as $eGFR_{CKiDbed}$), which is commonly used clinically and is simply $41.3 \times$ height [m]/Scr [mg/dL].

Biomarkers Related to CKD Severity

Biomarkers as outcomes were urine protein-creatinine ratio (UPCR; in milligrams per milligram of creatinine; measured as a portion of first morning void), blood hemoglobin (grams per deciliter), serum bicarbonate (milliequivalents per liter), potassium (milliequivalents per liter), and phosphate (milligrams per deciliter).[27] For the assessment of cardiovascular and growth markers, systolic (SBP) and diastolic blood pressure (DBP) z scores (adjusted for age, sex, and height[32]) and height z scores (adjusted for age and sex[33]) were included as outcomes.

Statistical Methods

The first approach of the analyses used 3 separate univariate regression models for each biomarker (as the dependent variable) and mGFR, $eGFR_{CKiDfull}$, and $eGFR_{CKiDbed}$ as separate independent variables (in the log scale to provide measures of percent change) for each model. Biomarkers, with the exception of z scores, were log transformed (to achieve normality), and the slope from this model was expressed as the change in biomarker value associated with a 50% lower GFR. To account for the correlation of repeated measurements within individuals, generalized estimating equations were used to appropriately adjust standard errors for all models. To compare whether estimates by $eGFR_{CKiDfull}$ and $eGFR_{CKiDbed}$ were statistically different from those of mGFR, we used bootstrap methods and sampled at the individual level to preserve the within-person correlation of biomarkers and of repeated measurements. Specifically, 500 data sets were created from children and adolescents in our analytic data set who were sampled with replacement.

The objective of the second approach was to quantify the putative additional information that is in mGFR, but not in $eGFR_{CKiDfull}$ (ie, obtaining mGFR deviations from $eGFR_{CKiDfull}$ based on the regression of mGFR on $eGFR_{CKiDfull}$; ie, residuals). Specifically, we expanded the model including $eGFR_{CKiDfull}$ in the first approach to the following:

$$\text{Biomarker} = \gamma_0 + \gamma_1 \log\left(eGFR_{CKiDfull}\right) + \gamma_2 \text{mGFR deviations from } eGFR_{CKiDfull} + \text{error}$$

where the error term is normally distributed with mean 0 and standard deviation (SD) σ. This model allows for a comparison of R^2 values in which the null model assumes γ_2 equals 0 (ie, first approach) and the test model allows γ_2 to be estimated from the data. This provides an estimate of the explanatory power of information in mGFR not present in $eGFR_{CKiDfull}$.

As part of the second approach, we also carried out similar analyses in which the primary predictor was $eGFR_{CKiDbed}$. That is, we quantified how much more explained variability is added by including the deviations of mGFR from $eGFR_{CKiDbed}$, and those of $eGFR_{CKiDfull}$ from $eGFR_{CKiDbed}$ to the third univariate model in the first approach (ie, using only $eGFR_{CKiDbed}$). The summary measures were the comparisons of the R^2 values for the univariate and bivariate models. Statistical significance was determined by the same bootstrapping method described for the first approach.

The third approach in the analyses used longitudinal data to determine changes in GFRs over time. In addition to the overall