Combination of pediatric and adult formulas yield valid glomerular filtration rate estimates in young adults with a history of pediatric chronic kidney disease

Derek K. Ng[1], George J. Schwartz[2], Michael F. Schneider[1], Susan L. Furth[3,4] and Bradley A. Warady[5]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Department of Pediatrics, Division of Pediatric Nephrology, University of Rochester Medical Center, Rochester, New York, USA; [3]Department of Pediatrics, Division of Nephrology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [4]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; and [5]Division of Pediatric Nephrology, Children's Mercy Kansas City, Kansas City, Missouri, USA

As patients with chronic kidney disease (CKD) transition from pediatric nephrology care to adult care, their kidney function is clinically assessed by estimated glomerular filtration rate (eGFR) using both pediatric and adult equations, which may not be congruent. Here we evaluated commonly used eGFR equations and directly measured iohexol GFR (iGFR) among participants between ages 18 and 26 with a diagnosis of pediatric CKD in the Chronic Kidney Disease in Children (CKiD) cohort. The bedside serum creatinine (SCr)-only equation ($CKiD_{SCr}$), the SCr-only CKD-EPI ($CKD\text{-}EPI_{SCr}$), the cystatin C (Cys)-only CKD-EPI ($CKD\text{-}EPI_{Cys}$) and the combined SCr and Cys CKD-EPI ($CKD\text{-}EPI_{SCr\text{-}Cys}$) were compared with a) 279 measured iGFRs obtained from 187 participants and b) 548 eGFRs from the SCr and Cys-based CKiD equation ($CKiD_{SCr\text{-}Cys}$) obtained from 219 participants. Among emerging adults with a median iGFR of 49 ml/min/1.73m^2, the $CKiD_{SCr\text{-}Cys}$ equation had low bias (+1.5 ml/min/1.73m^2) and high correlation (0.94), while $CKiD_{SCr}$ underestimated iGFR and $CKiD_{SCr\text{-}Cys}$ (–5.6 and –7.4 ml/min/1.73m^2, respectively) and $CKD\text{-}EPI_{SCr}$ had an overestimation bias (+8.2 and +6.1 ml/min/1.73m^2, respectively). However, the $CKD\text{-}EPI_{Cys}$ and $CKD\text{-}EPI_{SCr\text{-}Cys}$ exhibited strong agreement with both iGFR and $CKiD_{SCr\text{-}Cys}$. GFR may also be validly estimated in this population by taking the simple average of $CKiD_{SCr}$ and $CKD\text{-}EPI_{SCr}$ (average bias +1.3 compared to iGFR and -0.6 compared to $CKiD_{SCr\text{-}Cys}$). Clinicians should be aware that individually the pediatric and adult SCr-based estimates of GFR had large discrepancies among emerging adults with pediatric CKD. Thus, when cystatin C is not available, we recommend the average of pediatric and adult SCr-based eGFR as a valid tool for clinical use.

Kidney International (2018) **94,** 170–177; https://doi.org/10.1016/j.kint.2018.01.034

Correspondence: *Derek K. Ng, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 N. Wolfe Street, Room E7642, Baltimore, Maryland 21205, USA. E-mail: dng@jhu.edu*

Received 25 August 2017; revised 19 January 2018; accepted 25 January 2018; published online 5 May 2018

KEYWORDS: chronic kidney disease; clinical nephrology; glomerular filtration rate; pediatric nephrology; young adults

The most commonly used clinical equations to estimate glomerular filtration rate (eGFR) may be categorized as either pediatric-[1,2] or adult-[3,4]specific. While these population-specific equations are considered valid for their respective target populations, they have not been formally compared among emerging adults with a history of pediatric chronic kidney diseases (CKDs).

As clinical management of pediatric CKD improves, a higher proportion of children with CKD now reach adulthood prior to end-stage renal disease and transition to adult nephrology and urology care.[5–9] One clinical challenge of characterizing CKD progression is interpreting serial measurements of eGFR from different equations during the transition from pediatric to adult specialty care. A study by Selistre *et al.*[10] examined these estimations of GFR in children and young adults (10 to 25 years of age), and they demonstrated that among those over 18, the adult formulas overestimated measured GFR, and pediatric formulas underestimated measured GFR. Given the fundamental differences between the populations used to develop the pediatric and adult equations and the paucity of data in this unique age range, we sought to compare and contrast these equations among emerging adults with a history of pediatric CKD enrolled in the Chronic Kidney Disease in Children (CKiD) study.

For pediatric patients, the CKiD study published a simple bedside estimating equation utilizing only height and serum creatinine (SCr) in 2009,[1] which we refer to as $CKiD_{SCr}$ (and has been previously denoted as $eGFR_{CKiDbed}$[11]). An updated equation using CKiD data was published in 2012[2] utilizing SCr, cystatin C (Cys), blood urea nitrogen (BUN), height and sex, which we denote as $CKiD_{SCr\text{-}Cys}$ (and has been previously denoted as $eGFR_{CKiDfull}$[11]). Similarly, for adults (i.e., age ≥18 years) the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium published an equation using only SCr

in 2009 (CKD-EPI$_{SCr}$[3]), and in 2012 published 2 equations using Cys only (CKD-EPI$_{Cys}$[4]) and combined SCr and Cys (CKD-EPI$_{SCr-Cys}$[4]). The CKiD$_{SCr}$ and CKiD$_{SCr-Cys}$ equations were developed in children <18 years of age (mean age = 11 ± 4) with mild to moderate CKD (mean GFR = 45 ± 16 ml/min per 1.73 m^2). In contrast, the CKD-EPI equations were developed in adults (mean age = 47 ± 15 years), with a higher GFR (mean GFR = 68 ± 39 ml/min per 1.73 m^2).

Our objective was to describe the similarities and differences in these commonly used clinical tools using directly measured GFR by iohexol plasma disappearance as the reference, and in turn, with the CKiD$_{SCr-Cys}$ equation. Given the good agreement metrics for equations based on SCr and cystatin C previously reported in children[11–18] and adults,[19–21] we expected the equations using both to be preferable to SCr alone. However, the most common current clinical scenario is having only SCr available. Therefore, we explored a simple method to validly estimate GFR when cystatin C is not available in this older adolescent–young adult population with a pediatric diagnosis of CKD.

RESULTS

A total of 219 CKiD participants contributed 548 annual study visits at which they were at least 18 years of age with data to estimate GFR from pediatric and adult equations. Of these, 187 individuals contributed 279 person-visits with directly measured iGFR, corresponding to the original CKiD study design with iGFR measured every other year. Table 1 presents the demographic and clinical characteristics of the first available visit after age 18 years among those contributing estimated GFR data and the subset who contributed iGFR data. The average body size was typical for mature adults (median height = 1.69 m and median weight = 68 kg). Approximately one-half of the participants had CKD onset at birth and 27% had CKD onset after 10 years of age; 63% had an underlying nonglomerular form of CKD characterized as structural abnormalities of the kidney and urinary tract. Of the person-visits, 95% of the observations were between 18 and 23 years of age, with the maximum age being 26 years. Participant characteristics were similar between the 219 contributing eGFR data and the subset of 187 who contributed iGFR data.

Figure 1 displays and Table 2 quantifies the agreement between CKiD$_{SCr-Cys}$ (mean level = 50.7 ± 21.1 ml/min per 1.73 m^2) and directly measured iGFR (mean level = 49.2 ± 22.5 ml/min per 1.73 m^2) among 279 person-visits. The CKiD$_{SCr-Cys}$ had minimal overall bias (+1.5 ml/min per 1.73 m^2), similar dispersion (ratio of SDs = 0.94), and a high correlation with iGFR (r = 0.94). The proportion of CKiD$_{SCr-Cys}$ within 30% of iGFR was 90%, which was essentially the same as the results from the validation dataset (91%) from the original equation development that did not include any of these person-visits.[2] Since we were primarily interested in discrepancies in commonly used clinical instruments, we additionally used CKiD$_{SCr-Cys}$ as the reference for the subsequent analyses in Table 3.

Table 1 | Demographic and clinical characteristics of young adults with a history of pediatric CKD at time of first GFR after age 18 years

Variable	Participants contributing estimated GFR n = 219	Participants contributing iohexol GFR n = 187
Age, yr	18.5 (18.2, 18.9)	18.7 (18.3, 19.3)
Female sex	41 (89)	42 (78)
African American race	21 (46)	19 (36)
Body size		
Height, m	1.69 (1.61, 1.77)	1.69 (1.61, 1.77)
Weight, kg	68 (57, 84)	67 (57, 84)
Body mass index, kg/m^2	24 (20, 29)	23 (20, 29)
Body surface area, m^2	1.8 (1.6, 2.0)	1.8 (1.6, 2.0)
CKD characteristics		
Nonglomerular form of CKD	63 (137)	61 (115)
CKD onset at birth	51 (111)	51 (93)
CKD onset >0 and ≤5 years old	12 (26)	13 (23)
CKD onset >5 and ≤10 years old	10 (21)	11 (20)
CKD onset >10 and <16 years old	27 (58)	26 (48)
Urine protein:creatinine, mg/mg Cr	0.7 (0.2, 1.6)	0.7 (0.2, 1.6)
Nephrotic range proteinuria (>2 mg/mg Cr)	19 (40)	16 (29)
Biomarkers of kidney function		
Serum creatinine, mg/dl	1.6 (1.2, 2.2)	1.6 (1.2, 2.1)
Height/serum creatinine, m/mg per dl	1.0 (0.8, 1.4)	1.1 (0.8, 1.4)
Cystatin C, mg/l (IFCC calibrated)	1.6 (1.2, 2.3)	1.6 (1.2, 2.2)
Blood urea nitrogen, mg/dl	23 (17, 33)	24 (17, 33)
Number of GFR observations[a]		
1	32 (71)	63 (118)
2	26 (56)	26 (48)
3	42 (92)	11 (21)
Total number of observations	548	279

CKD, chronic kidney disease; Cr, creatinine; GFR, glomerular filtration rate; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine. Median (interquartile range) or percentage (frequency).
[a]By study design, estimated GFR was measured annually and iohexol-based GFR was measured every 2 years.

Table 2 presents the agreement metrics for various GFR estimating equations using iGFR as the reference, among 279 person-visits. CKiD$_{SCr}$ substantially underestimated iGFR (average bias = −5.6 ml/min per 1.73 m^2) and had smaller dispersion (ratio of SDs = 0.89) with a correlation of 0.89. In contrast, CKD-EPI$_{SCr}$ substantially overestimated iGFR (average bias = +8.2 ml/min per 1.73 m^2) and had more variability (ratio of SDs = 1.39), with a correlation of 0.91. Both CKiD$_{SCr}$ and CKD-EPI$_{SCr}$ had relatively low proportions within 30% of iGFR, at 71% and 66%, respectively. Agreement was substantially better for CKD-EPI equations that included cystatin C. On average, there was less overestimation of iGFR by CKD-EPI$_{Cys}$ and CKD-EPI$_{SCr-Cys}$ (average biases = +2.7 and +3.3, respectively). Both CKD-EPI$_{Cys}$ and CKD-EPI$_{SCr-Cys}$ equations had larger variability than iGFR (ratios of SDs = 1.32 and 1.31, respectively). The CKD-EPI$_{Cys}$ equation had good correlation (r = 0.90) and accuracy (74% within 30% of CKiD$_{SCr-Cys}$). However, the CKD-EPI$_{SCr-Cys}$