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Height-Independent Estimation of Glomerular Filtration Rate in Children: An Alternative to the Schwartz Equation

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Objective To compare the diagnostic performance of 2 height-independent equations used to calculate estimated glomerular filtration rate (eGFR), those of Pottel (eGFR-Pottel) and the British Columbia Children's Hospital (BCCH) (eGFR-BCCH), with the commonly used Schwartz equation (eGFR-Schwartz).

Study design We externally validated eGFR-Pottel and eGFR-BCCH in a well-characterized pediatric patient population (n = 152) and compared their diagnostic performance with that of eGFR-Schwartz using Bland-Altman analysis. All patients underwent glomerular filtration rate measurement using the gold standard single-injection inulin clearance method (GFR-inulin).

Results Median GFR-inulin was 92.0 mL/min/1.73 m^2 (IQR, 76.1-107.4 mL/min/1.73 m^2). Compared with GFR-inulin, the mean bias for eGFR-Schwartz was −10.1 mL/min/1.73 m^2 (95% limits of agreement [LOA], −77.5 to 57.2 mL/min/1.73 m^2), compared with −12.3 mL/min/1.73 m^2 (95% LOA, −72.6 to 47.9 mL/min/1.73 m^2) for eGFR-Pottel and −22.1 mL/min/1.73 m^2 (95% LOA, −105.0 to 60.8 mL/min/1.73 m^2) for eGFR-BCCH. eGFR-Pottel showed comparable accuracy to eGFR-Schwartz, with 77% and 76% of estimates within 30% of GFR-inulin, respectively. eGFR-BCCH was less accurate than eGFR-Schwartz (66% of estimates within 30% of GFR-inulin; $P < .01$).

Conclusion The performance of eGFR-Pottel is superior to that of eGFR-BCCH and comparable with that of eGFR-Schwartz. eGFR-Pottel is a valid alternative to eGFR-Schwartz in children and could be reported by the laboratory if height data are not available. *(J Pediatr 2013;163:1722-7)*.

Glomerular filtration rate (GFR) is the best indicator of renal function in children.[1] Gold standard GFR measurement techniques[2] are cumbersome, costly, and often unavailable. As an alternative, current guidelines recommend the use of estimated GFR (eGFR) based on serum creatinine concentration in both adults and children.[3] The most commonly used equation for calculating eGFR in children is the Schwartz equation (eGFR-Schwartz),[4] which is calculated from serum creatinine concentration, height, and an empirical constant, *k*, that adjusts for muscle mass and the creatinine measurement method. A major disadvantage of eGFR-Schwartz is the need for height information, which hampers its use in settings in which height data are not available. This precludes automatic reporting of eGFR in children by most clinical laboratories, which has become common practice in adult patients, because most equations for adults do not require anthropometric data.[5,6] To overcome this problem, Zappittelli et al[7] and Pottel et al[8] recently developed eGFR equations (termed the modified British Columbia Children's Hospital [BCCH] equation [eGFR-BCCH] and eGFR-Pottel, respectively) using different approaches to estimate GFR in children independent of height. In their hands, both equations performed similarly to eGFR-Schwartz. Because a height-independent eGFR can be easily calculated by laboratory reporting software, use of these alternative equations may significantly improve pediatric care and facilitate screening for chronic kidney disease (CKD) in children. eGFR-BCCH and eGFR-Pottel have not yet been validated using inulin clearance, however.

In the present study, we aimed to externally validate both the eGFR-BCCH and eGFR-Pottel equations using measurement of GFR by the single-injection inulin clearance method (GFR-inulin) as the gold standard in a well-defined pediatric cohort with varying degrees of CKD. We also compared the diagnostic performance of the

BCCH	British Columbia Children's Hospital
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
eGFR-BCCH	Estimated glomerular filtration rate according to the British Columbia Children's Hospital equation
eGFR-Pottel	Estimated glomerular filtration rate according to the Pottel equation
eGFR-Schwartz	Estimated glomerular filtration rate according to the Schwartz equation
GFR	Glomerular filtration rate
GFR-inulin	Glomerular filtration rate measured by the single-injection inulin clearance method
IDMS	Isotope dilution mass spectrometry
LOA	Limits of agreement

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height-independent eGFR equations and eGFR-Schwartz. We hypothesized that both equations would perform as well as eGFR-Schwartz.

Methods

Data from all patients who consecutively underwent a gold standard GFR measurement at the Pediatric Renal Center of the VU University Medical Center between March 2008 and September 2012 were analyzed retrospectively. GFR measurements were performed based on clinical indication. Anthropometric data were obtained by chart review. All patient data were recorded in an anonymous manner such that subjects could not be identified directly or through identifiers linked to the subjects. The study was therefore exempted from institutional review board review. Anthropometric data values are expressed as SDSs (*z*-scores) away from the mean using the growth data of the Fourth Dutch Growth Study.[9] The reference standard and the index test were performed at the same time. Because muscle mass influences serum creatinine levels and thus the performance of creatinine-based equations, malnourished patients (ie, children with a body mass index SDS <-3) and patients with spina bifida were excluded from this study.

GFR was measured by single-injection inulin clearance, a validated method for accurately determining GFR in children.[10] The GFR-inulin studies were performed at the pediatric outpatient clinic after an overnight fast. Clinical hydration status of all patients was assessed before measurement. Before and during GFR measurement, patients had free access to water or tea without sugar. GFR measurements were performed exclusively in patients with normal hydration status as assessed by the supervising physician. All patients received a single intravenous dose (5000 mg per 1.73 m^2 of body surface area, with a maximum dose of 5000 mg) of inulin (Inutest; Fresenius, Bad Homburg, Germany) administered over 1 minute. Dedicated nurses assessed for extravasation of inulin during administration.

Serial blood samples were obtained at 10, 30, 90, and 240 minutes after injection. After sampling, blood was centrifuged for 5 minutes at 1800 × *g* and then stored at −20°C until measurements. Inulin was measured within 14 days using an enzymatic method based on the determination of fructose concentration after acid hydrolysis of inulin, as described by Jung et al[11] with minor modifications.[12] GFR-inulin was calculated using a 2-compartmental model with MW/Pharm 3.5 software (Mediware, Groningen, The Netherlands), a pharmacokinetic program using Bayesian estimates from patient and population data.[10]

Immediately before the GFR-inulin clearance study, blood was drawn for measurement of serum creatinine, using an enzymatic method (Modular Analytics <P>; Roche Diagnostics, Mannheim, Germany), which is traceable to an isotope dilution mass spectrometry (IDMS) standard.[13]

eGFR Equations

All 3 equations are based on IDMS-traceable standards for creatinine measurement. eGFR-Schwartz is calculated as:

$$eGFR\text{-}Schwartz\left(\mathrm{mL/min1.73\ m^2}\right) = 41.3 \times \frac{height(m)}{serum\ creatinine\ (mg/dL)}$$

eGFR-BCCH, by Zappittelli et al,[7] estimates GFR based on serum creatinine concentration and age:

$$inverse\ \ln(eGFR - BCCH)(\mathrm{mL/min/1.73\ m^2})$$

$$= 8.067 + (1.034 \times \ln(0.011/(serum\ creatinine(mg/dL))) + (0.305 \times \ln(age(years)))) + 0.064 \quad \text{if male.}$$

eGFR-Pottel uses median serum creatinine reference values:

$$eGFR-Pottel\left(\mathrm{mL/min/1.73\ m^2}\right) = 107.3/\left(\frac{serum\ creatinine\ (mg/dL)}{Q}\right)$$

where Q is the median serum creatinine concentration for children based on age and sex (Table I).[14]

Renal function was classified according to the National Kidney Foundation's Kidney Disease Outcome Quality Initiative guidelines for CKD.[3] Underclassification was considered if the CKD stage based on GFR-inulin was higher than that based on eGFR, and overclassification was considered if the CKD stage based on GFR-inulin was lower than that based on eGFR.

Statistical Analyses

All analyses were performed using SPSS 20.0 (IBM, Armonk, New York). Continuous variables are presented as mean (SD) for variables with a Gaussian distribution and as median (IQR) for variables with a non-Gaussian distribution. Differences between continuous variables between patients aged ≤14 years and those aged >14 years were analyzed using the Student *t* test. Nonnormally distributed variables were naturally log-transformed before analysis. Differences in bias between the tested equations were analyzed using the paired-samples *t* test. Qualitative variables are shown as counts (proportion) and were compared using the χ^2 test or McNemar test. The analytical performance of the different eGFR equations was assessed in compliance with the Standard for the Reporting of Diagnostic Accuracy studies criteria.[15] Using Bland-Altman analysis,[16] we calculated bias (ie, mean difference between GFR-inulin and eGFR) and the limits of agreement (LOA; mean bias ± 1.96 × SD). Accuracy was determined as the proportions of patients with an eGFR value within 30%, 20%, and 10% of that measured by GFR-inulin. Differences were considered statistically significant at a *P* value <.05 and a trend of *P* values of .05-.10 in all analyses.