Height: the missing link in estimating glomerular filtration rate in children and adolescents

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Glomerular filtration rate (GFR) is the most useful indicator of kidney function and kidney disease progression. Measurement of GFR is laborious to perform clinically, as it is time-consuming and costly, with turn-around time for results being too slow for many clinical situations encountered in the hospital and outpatient setting. Thus, there is great interest in developing GFR estimating formulas derived from endogenous biomarkers. This applies also to children in whom performance of GFR studies is likely to be more difficult. There is nearly universal acceptance and application of adult eGFR formulas derived from serum creatinine (Scr) [1, 2], and these formulas incorporate, in addition to Scr, sex, race and age to optimize accuracy. However, such an application is not as useful in children because of the maturational increase in Scr in the setting of normal renal function. As has been shown previously [3–5], Scr increases in pediatrics with growth and development, and after puberty shows a gender-dependent divergence. Thus, the development of GFR-estimating formulas in children has focused on additional parameters to better estimate kidney function.

Previously, we showed that the parameter ‘height/Scr’ could explain more than 70% of the variability of GFR in children (Figure 1a) [6]. Whereas other parameters have been investigated, height/Scr has retained its key place in building GFR estimating equations [6–8]. The proportionality relationship between GFR and height/Scr is subsumed in the coefficient k , which was originally found to be 0.55 mL/min per 1.73 m² [6]. Subsequent studies showed a higher k value for adolescent boys [7, 9] probably due to the higher muscle mass per kg body weight in this group.

These relationships were generated during the era when the colorimetric Jaffe reaction was adapted to an automated chemical analyzer; by incorporating a dialysis step and interposing blanks between samples, there was reduced interference and improved accuracy compared with the rapid kinetic assays [7, 10]. However, with the development of the more accurate enzymatic serum creatinine assay and international isotope dilution mass spectroscopy (IDMS) reference standards [1, 11], the proportionality-constant k was reduced by some 25% to

0.41 in the NIH-supported CKiD study of children with chronic kidney disease and GFRs ranging from 15 to 75 mL/min per 1.73 m² [8]. In this population of children with moderate CKD, growth was limited (median was the 23rd percentile) and nearly 80% of the population was immature as staged by Tanner I to III [8]. Height/Scr still explained 65% of the variability in GFR in CKD (Figure 1b) [8]. In this publication, we indicated the need to validate this formula in children and adolescents with higher GFRs and with normal or higher height percentiles. There has been a major effort to improve on these creatinine-based eGFR formulas in children.

Indeed, Pottel’s group and others [12–14] have utilized medical center-based adjustments in the proportionality-constant k , and confirmed the need for age adjustment in k for males older than 13 years [13, 15]. Recently, this group developed a very simple eGFR equation: $eGFR = 107.3/(Scr/Q)$ [16]. Q was derived from Scr values depending on age and gender or height; databases of Belgian children and adolescents provided anthropometric and Scr data, and regressions were generated to provide these median values. Such Q values from these databases could be accessed in laboratory computers and utilized for an output to the patient’s electronic medical record. However, some of their analyses have shown that height-independent simple eGFR equations did not perform as well as those incorporating height [16, 17]. The fact that height, and possibly race, are not always available to clinical laboratory databases limits the application of superior height-based GFR-estimating formulas and suggests the need for alternative estimates, new approaches to information technology or increased interaction of laboratory databases with the electronic medical record.

The paper by Hoste *et al.* [17] in this issue of NDT proposes a new simple equation to estimate GFR in children, adolescents and young adults. The equation is also based on the concept of a population-normalized serum creatinine (Scr) value Q , but is extended beyond the average healthy child to the adolescent and young adult. Q values specific to age and height were modeled as fourth-degree polynomials from median values of a large database of healthy children and

FIGURE 1: Relationship between height/Scr and measured GFR. (a) shows regression of length or height/Scr times the k coefficient of 0.55 from the modified Jaffe creatinine assay (x axis) versus inulin renal clearance (y axis) [6]. (b) shows height/Scr (x axis) and iothexol plasma disappearance GFR (y axis) from the CKiD population of children with moderate CKD; logarithmic plot is shown. Regression line and non-parametric spline depicted by the dashed curve are superimposed [8].

adolescents in Kortrijk, Belgium. Because the population Q values change with age, gender and height, it is evident that simple creatinine-based estimates of GFR do not accurately depict kidney function throughout childhood [7, 12, 18, 19].

The approach reported by Hoste *et al.* [17] utilized major Belgian databases including discrete national growth curves, enzymatic serum creatinines (IDMS referenced) from AZ Groeninge Hospital and ^{51}Cr -EDTA plasma disappearance clearances from a separate group of over 600 patients with normal function over an age range of 0.1–16 years of age, which were previously performed by Piepsz *et al.* [20, 21]. In this study, the authors concluded that the measured GFR in children stabilized to a median value of 107.3 mL/min per 1.73 m² when corrected for BSA determined using the Du Bois and Du Bois surface area formula [15, 22]. An independent database with over 750 renal inulin clearances in children, adolescents and young adults between 10 and 25 years of age comprised a validation group, previously utilized by Selistre *et al.* [12], which included demographic, anthropometric, Scr and GFR data on each of these individuals. The vast majority of the patients in the validation group were in stages 1 and 2 of CKD.

The authors considered six types of GFR-estimating equations including the updated Schwartz height/Scr formula [8], the Schwartz–Lyon height/Scr formula with a slightly higher k modification for older males [12], a simple height-independent equation recently developed by these investigators for age 1–14 years [16], the Flanders Metadata equation which provides an age-dependent k for a height/Scr formula up to age 14 [15], extended age-based Q -dependent simple eGFR formulas and height-based Q -dependent simple formulas [17]. These equations were generated from the above-noted ‘normal’ databases and then applied to the validation test group. Performance was appraised from the bias and accuracy (P30 and P10) of the different eGFR equations compared with measured GFR by inulin renal clearance. In general, the height/Scr formulas and those using a height-based Q value

outperformed the age-dependent and height-independent Q -based eGFR formulas at all ages and levels of GFR, although the latter group tended to be better for the older subjects at GFRs above 90 mL/min per 1.73 m².

The height-independent formulas were also outperformed in underweighted subjects and in kidney transplant patients. In the underweighted subjects, weight and height are reasonably well correlated confirming our hypothesis that height serves as a good surrogate for muscle mass [6, 7, 23]. The locally adapted height/Scr formulas did better than the updated Schwartz formula. A closer look at the data shows that the Schwartz–Lyon formula works best for GFRs below 90 mL/min per 1.73 m² but the $Q(\text{height})$ formula gives the best results in the young adults. At GFRs above 90 mL/min per 1.73 m², the age-extended simple equation may be slightly better than the height-based Q equation, and this is not surprising since they were derived from the data of normal subjects. Using a scoring system incorporating bias and accuracy, the authors concluded that the $Q(\text{height})$ -based eGFR equation gives the best results overall. It therefore could be used as a screening tool for normality of GFR. These data also suggest that more accurate quantification at GFRs below 60 mL/min per 1.73 m² would be accomplished with the Schwartz or Schwartz–Lyon equations.

It should also be noted that the inclusion of another endogenous biomarker, cystatin C, in GFR-estimating equations appears to improve bias and accuracy in children and adults [2, 8, 24–26]. Cystatin C, a small molecular weight protein, has been considered a potential serum-alternative marker to creatinine for estimating GFR in adults [2]. Cystatin C would be less sensitive to alterations in muscle mass, age, sex, race and diet than is creatinine, and the interindividual variability of cystatin C is much less than that of creatinine [27]. Indeed, the reciprocal of cystatin C is well correlated with GFR and can account for nearly 50% of the variability of GFR [28].

There are several limitations to these combined estimating formulas that use cystatin C. First, the assays are not yet consistently referenced to international IDMS standards [29], and the effect of standardization of the cystatin C measurement is not completely determined for the various available analyzers. Second, the agreement between different assays is not consistently strong, despite the measurement of the same analyte [28, 30]. Third, in many hospitals and laboratories, this assay is still a send-out, requiring additional paperwork, cost and time for results to be returned to the physician. Fourth, cystatin C determination is roughly 10 times more expensive than enzymatic serum creatinine. Accordingly, the improvements in pediatric eGFR formulas should be deserving of the extra time, money and effort to obtain standardized cystatin C measurements.

When both serum creatinine and cystatin C values are readily available, Grubb as well as our CKiD *et al.* [28, 31] have suggested that the clinician estimate GFR with univariate height/Scr- and cystatin C-based formulas. If they agree within 10–15%, the combined formulas can yield a GFR value that would likely be close to that obtained with a measured GFR. On the other hand, if there is significant disagreement between eGFR values obtained with the two types of estimating equations, and there was no obvious explanation for the discrepancy, a measured GFR would be indicated. In support of this approach, Inker *et al.* [2] recently reported that, for adults, the combined creatinine–cystatin C CKD EPI equation performed better than equations based on either marker alone.

There are a few additional concerns regarding the article by Hoste *et al.* [17]. The reference clearances relied on a single point taken at 120 min after injection of Cr EDTA. The uncertainty of a single point could result in a substantial variability in the determination of GFR despite the published correlation with two-point blood sample clearance methods [32]. In addition, the Brochner-Mortensen correction for a single-slope clearance was not used, but rather the Chantler linear correction, which tends to artificially elevate the computed GFR more than the former correction [32–35]. The recommendation of the British Nuclear Medicine Society is to utilize the Brochner-Mortensen correction [36]. Also, the clearances were not performed on those whose Scr values were used, nor on those whose height and weight were determined. Methods to assess the precision and accuracy of height determinations were not discussed in the paper or in the growth chart database.

Additionally, the validation group and the studies by Bachetta *et al.* and Selistre *et al.* [12, 13] utilized a compensated Jaffe technique to measure serum creatinine. While the regression line appears to be rather tight in Figure 1 of Bachetta *et al.* [13], there is a significant negative bias at the lower end of serum creatinine values in the Bland–Altman plot wherein the values for normal children can be found. Without further studies, it may not be possible to utilize compensated Jaffe creatinine values in formulas generated from enzymatic creatinines, and Q values may need to be recalibrated, particularly for the younger children. Indeed the raw values for Scr in the first decade of life are nearly as large as the corrections used in the compensated Jaffe creatinine determination [15].

Another analysis that should be considered is how well the screening test stages the patient. For example, we do not know

how many subjects with a measured GFR of 90 or above were identified as having eGFR below 90 (CKD stage 2), or how many subjects with measured GFR below 60 were identified as having a eGFR above 60. Some would consider this analysis to be at least as important as the standard bias, P30, and P10 determinations. The prediction would be that height-based eGFR formulas might fail less frequently to accurately stage the CKD.

These comments notwithstanding, the Pottel group in Belgium has provided novel and useful information to assist clinicians and researchers in estimating GFR from serum creatinine. Their approach provides the basic format for screening children, adolescents and young adults for the presence of kidney disease. Whereas this approach should be applicable universally, in the presence of standardized serum creatinine values, it would be important to validate these parameters in other countries and racial populations, and to ensure that Jaffe creatinines closely approximate enzymatic values in the lower range of detection.

CONFLICT OF INTEREST STATEMENT

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(See related article by Hoste *et al.* A new equation to estimate the glomerular filtration rate in children, adolescents and young adults. *Nephrol Dial Transplant* 2014; 29: 1082–1091.)

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